

**DISSERTATION SUBMITTED FOR THE MASTER'S
DEGREE IN MEDICAL MICROBIOLOGY**



TITLE

**NIPAH VIRUS – EPIDIOLOGY AND CURRENT STATUS
AT NATIONAL & INTERNATIONAL LEVEL – META –
ANALYSIS**

SUBMITTED

BY

ANAND KUMAR

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**DEPARTMENT OF MICROBIOLOGY
INTEGRAL INSTITUTE OF MEDICAL SCIENCES & RESEARCH
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DASULI, KURSI ROAD, LUCKNOW-226026, U.P.**

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A

DISSERTATION

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Medical Microbiology

By

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DEDICATED TO
“TEACHERS”
“FAMILY”
&
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INTRODUCTION

INTRODUCTION-

The recent pandemic threat of viral pathogens such as corona virus, influenza virus, nipah virus, etc. It implies that the occurrence and spread of diseases are not limited by geographical borders. In many cases, it turns out that animals are the source of human infection. Only 87 out of 1,399 human pathogens were first reported in humans in the years after 1980 [1,1]. The rapid growth of India's population and consequent increased animal-human interactions, combined with changing environmental conditions and inadequate sanitation and regulation, have made India one of the world's major hotspots for farm animal diseases, including zoonosis, to be transmitted from animal to human and that accounts for 75% of all human diseases. Controlling zoonosis is particularly important in developing countries, where the absolute burden of these diseases is up to 130 times higher than in developed countries [2].

Emerging zoonoses are the result of anthropogenic and socioeconomic changes in the environment. The expansion of the road network, the opening up of agricultural land and the intensification of the wildlife trade have led to the emergence of new pathogens from the wild, with Nipah virus (NiV) being one of the prime examples of emerging zoonoses[3]. Nipah virus infection is a rare zoonosis caused by Nipah virus of the Paramyxoviridae family. Pteropus bats (fruit-eating species popularly known as flying foxes) are believed to be the natural hosts of the virus[4]. Among the genus Pteropus, the Indian flying fox (*Pteropus giganteus*) and the relatively smaller short-nosed flying fox or Indian short-nosed flying fox (*Cynopterus sphinx*), which are widespread and very common species in South Asia, have been identified as the main reservoir. To date, Nipah virus has not been isolated from insectivorous bats. There is no obvious disease in flying foxes. Bats have also been recognized as important reservoirs for other zoonotic viruses, including Ebola, Marburg, SARS, and Melaka viruses[5]. It is an enveloped, single-stranded, non-segmented, negative-

sense RNA virus with helical symmetry. The RNA genome 3 to 5 contains a sequential arrangement of six genes namely nucleocapsid (N), phosphoprotein (P), matrix (M), fusion glycoprotein (F), binding glycoprotein (G) and long polymerase. (L). N, P and L combined with the viral RNA and formed the viral ribonucleoprotein (vRNP). The F and G proteins are responsible for virion cell attachment and subsequent entry into the host cell[6].

Further analysis of the deduced amino acid sequences of the porcine NV seremban isolate showed that they were identical to the CDC and UMMC2 human NV isolates. In contrast, the deduced amino acid sequences of the porcine isolate NV-Sungai Buloh were identical to those of the human NV isolates UMMC1 and UM-0128. NV-Seremban differed from NVSungai Buloh at only one amino acid position (1645) within the polymerase (L) protein. However, both isolates differed from the NV isolate Flying Fox, NV-Flying Fox, at three positions of amino acids, residues 30, 206 and 348 in the nucleoprotein (N), phosphoprotein (P) and fusion protein (F) coding regions.

In contrast, the NV-Tambun pig isolate showed a distinct distinctive sequence compared to all other NVs. NV-Tambun differed from all known NVs at 47 nucleotide positions; 28 of these differences occurred within the coding regions of the virus. Nucleotide differences translated into amino acid changes at 11 positions; residues 274, 304, and 378 of protein P, residues 147 and 250 of matrix protein (M) and protein F, respectively, residues 20 and 272 of glycoprotein (G), and residues, 223, 1645, 1753, and 2039 of protein L.

The amino acid changes observed in the heavily phosphorylated P protein at positions 274 and 304 resulted in residue changes from serine to arginine and from threonine to alanine, respectively. These changes can reduce potential phosphorylation sites on protein P, since serine, threonine, tyrosine, and histidine residues are the usual targets for protein

phosphorylation. Amino acid substitutions at positions 223 (threonine → asparagine), 1645 (serine→phenylalanine), and 2039 (histidine→ asparagine) in protein L may also decrease the number of predicted potential phosphorylation sites in L. A substitution of the amino acid isoleucine by asparagine at position 20 of the G protein added a potential glycosylation site in addition to the eight identified N-linked glycosylation sites[7].

Nipah virus can survive in some fruit juices or mango for up to 3 days and in artificial date palm juice (13% sucrose and 0.21% BSA in water, pH 7.0) at 22 °C for at least 7 days with a urinary half-life of 18 hours of flying foxes. NiV is relatively stable in the environment and remains viable at 70 C for 1 h (only virus concentration is reduced).It can be completely inactivated by heating to 100 C for more than 15 min[8]. However, the viability of the virus in its natural environment may vary depending on different conditions. NiV can be easily inactivated with commercially available soaps, detergents and disinfectants such as sodium hypochlorite[9].

The host range-

I have confirmed that the Malaysian fruit bats (commonly known as flying foxes), *P. vampyrus* and NiV's natural reservoir hosts are *P. hypomelanus*[10,11]. The virus is thought to have been introduced into the pig population from *Pteropus* bat species. Malaysia has a diverse bat fauna with at least 13 species of fruit bats including two species of flying foxes (pteropid bats) and more than 60 species of insectivorous bats[12]. A serological study during the 1999 outbreak showed neutralizing antibodies in 5 bat species, 4 fruit bat species and 1 insectivorous bat species. These included 31% positive antibodies to *Pteropus hypomelanus* (island fruit bats) and 17% positive antibodies to *Pteropus vampyrus* (Malaysian fruit bats) in Peninsular Malaysia[13].

TRANSMISSION OF VIRUS-

In Pteropus bats, Nipah virus has been repeatedly found in urine, and viral RNA has rarely been detected in oropharyngeal and rectal swabs from naturally or experimentally infected bats. It has also been found in fruits that have been partially eaten by bats. Despite high seroprevalence rates, only a few bats in a colony can shed virus at any one time, and shedding from the colony can be sporadic. Nipah virus is highly contagious in pigs, which act as amplifying hosts and can shed this virus in respiratory secretions and saliva. Experimental infections indicate that shedding can begin as early as 2 days after infection and last up to 3 weeks. During the Malaysian outbreak, it appeared that the Nipah virus was spread within a farm via aerosols and direct contact between pigs. The spread of the virus between farms has generally been associated with pig transport.

Although this virus has not previously been reported in pig urine, it can occur in the kidneys and exposure to pig urine is a risk factor for human infection. Anecdotal evidence suggests that vertical transmission can occur across the placenta. Transmission in semen is possible, and reused vaccination needles may have helped spread the virus among pigs in Malaysia. Cats can be experimentally infected by intranasal and oral inoculation and shed Nipah virus in respiratory secretions and urine. Cats and a dog that recently died in the Philippines had eaten meat from infected horses. Intrauterine transmission has been demonstrated in cats, with the virus being detected in the placenta and in embryonic fluid. Although no experimental studies in dogs have been published, serological studies in Malaysia suggest that Nipah virus did not spread horizontally in dogs during this outbreak. Humans can be infected through direct contact with infected pigs, probably through mucous membranes but possibly also through skin abrasions.

During a current Nipah-like outbreak with inside the Philippines, maximum sufferers have been concerned in slaughtering un-well horses or had eaten undercooked horsemeat from un-well horses. In Bangladesh, human instances had been related to ingesting unpasteurized date palm sap (juice). Oral transmission, the use of synthetic palm sap spiked with Nipah virus, and breathing transmission have been each verified in a hamster model. Person-to-individual transmission can arise after near direct touch, and has been not unusual place in the course of a few outbreaks in Bangladesh and India. Humans can shed Nipah virus in breathing secretions, saliva, and urine, and speak to with breathing secretions is idea to be the primary path of spread. Some human beings additionally have become unwell after unprotected touch with deceased sufferers, along with in the course of coaching of the corpse for burial. Nosocomial transmission has been documented in hospitals wherein contamination manipulate measures are inadequate; however, the danger to healthcare employees seemed to be low in Malaysian hospitals.

How lengthy Nipah virus can stay feasible with inside the preferred surroundings is uncertain; however, it may live to tell the tale for up to a few days in a few fruit juices or mango fruit, and for at the least 7 days in synthetic date palm sap (13% sucrose and 0.21% BSA in water, pH 7.0) held at 22°C. This virus is pronounced to have a half-lifestyles of 18 hours with inside the urine of fruit bats.

EPIDEMIOLOGY AND DISEASE OUTBREAKS –

In Singapore and Malaysia, febrile encephalitis due to NiV was reported in 246 patients between 1998 and 1999 and in breeding pigs as an epidemic with neurological and respiratory symptoms during the same period[14,15,16]. Farm and slaughterhouse workers belonged to the high-risk group and human mortality was around 40% (Lo and Rota, 2008). NiV infection has not been directly reported in humans or pigs in Indonesia, but exposure of *Pteropus vampyrus* bats to NiV has been reported. Therefore, in Indonesia, there is every possibility that the disease could spread from carrier bats to pigs or humans[17,18,19]. The presence of anti-NiV antibodies in the serum indicated early exposure of the bats to the virus. In India, a serological surveillance study of 41 flying foxes in the northern region of India showed sero-positivity in twenty bats[20].

In 1999, human cases of Nipah viral encephalitis in Malaysia were misdiagnosed as Japanese encephalitis or Hendra-like viral encephalitis. However, the Ministry of Health confirmed that NiV was the causative agent of infection in pigs and humans and that morbidity was higher in the Negri Sembilan region of Malaysia (231 cases out of 283 reported cases). The NiV genome was sequenced at the CDC, Atlanta, Georgia, USA. The Department of Health reported a total of 101 human deaths and approximately 9 million pigs were culled[21]. Researchers confirmed that Nipah infections in pigs and humans that occurred in Peninsular Malaysia in 1998-1999 were transmitted by bats [22]. A three-year epidemiological study was conducted in Peninsular Malaysia to determine the seroprevalence of anti-NiV antibodies and the presence of viruses in *Pteropus vampyrus* and *P. hypomelanus* bats of different ages and physiological status [including adults, particularly pregnant ones, lactating and juvenile bats (6–24 months)]. Between the two bat species, the NiV risk and seroprevalence were higher for *P. vampyrus* (33%) than for *P. hypomelanus* (11%). The seroprevalence and distribution

of NiV showed variation (1–20%) in *P. hypomelanus* bats and also between the years 2004–2006 independent of seasons[23]. The surveillance study was conducted to assess the spread of henipavirus in Southeast Asia, Australasia, Papua New Guinea, East Timor, Indonesia and neighbouring countries. NiV RNA was detected in *P. vampyrus* bats of the family Pteropodidae and in non-pteropid bats *Rousettus amplexicaudatus* from East Timor[24]

Bangladesh The epidemiology of NiV is considerably exclusive in Bangladesh. Since 2001, seasonal outbreaks of NiV have happened in Bangladesh within the iciness months, normally in 20 districts[25] in valuable and north-western Bangladesh (the ‘Nipah belt’), wherein the bulk of spillover activities arise[26]. *Pteropus* bats had been diagnosed because the reservoir[27]. Though touch with pigs has been stated from a majority of sufferers in Bangladesh, near touch with pigs changed into observed to be a hazard thing in a single outbreak[28]. Transmission in Bangladesh can also additionally arise thru numerous routes. Drinking uncooked date palm sap is the maximum not unusual place shape of transmission of contamination from bats to humans[29]. Outbreaks coincide with sap harvesting season (December–May). *Pteropus* bats had been observed to go to date palm bushes and lick the sap streams getting used for series. Bats may contaminate the sap series pots with urine or faeces [30]. Domestic animals may function a direction of transmission from bats to humans. Pigs display excessive seroprevalence towards NiV in Bangladesh[31] aleven though they have got now no longer been implicated in outbreaks there. This is because of variations in animal husbandry in Bangladesh and Malaysia. Rather than massive slaughterhouses, in Bangladesh, man or woman humans personal animals in small organizations and there's little danger of animal to animal spread. Other animals which includes farm animals and goats have additionally been observed to be inclined with the aid of using seroprevalence studies[32].

Human-to-human transmission is a major transmission route in Bangladesh and has been identified in all outbreaks. The largest human-to-human outbreak occurred in Faridpur in 2004[33]. NiV is transmitted by droplet infection[34] and NiV RNA has been detected in the saliva of patients[35]. Other possible routes include living under a bat nest, where bat urine can infect the surrounding area. However, no evidence was found to support this hypothesis [36]. Eating fruit, bitten by the bat has also been suggested as a possible route of transmission, although no definitive evidence is available as yet. It has been established that the main transmission routes in Bangladesh are consumption of date palm sap and person-to-person transmission[37].

In India there was a large outbreak (66 probable cases and 45 fatalities) in Siliguri, West Bengal in 2001 and a smaller outbreak (five cases, 100% mortality) in 2007 in Nadia district, West Bengal. These eruptions occurred beyond the border of the Nipah Belt in Bangladesh. In May 2018, a NiV outbreak was reported in the Kozhikode and Malappuram districts of Kerala, a southern west coast state geographically separated from previously affected areas. Consumption of date palm juice is not common in this area. As of June 1, 2018, there were 18 confirmed cases and 17 deaths [38]. All cases belonged to the working age group, without differentiation by gender[39]. In 2001, the index case in Siliguri remained unidentified but was admitted to Siliguri District Hospital and infected 11 secondary cases, all hospital patients. These patients were transferred to other hospitals and subsequent transmission infected 25 staff and eight visitors[40]. The 2007 outbreak consisted of one person who contracted the disease from consuming date palm-based alcohol and everyone else, including a health worker, contracted the disease from the first case[41]. At least one healthcare worker also contracted the disease in a healthcare setting during the most recent outbreak in 2018 [42]. All Indian outbreaks have been transmitted from person to person. Although the

epidemiology of NiV in India is similar to that in Bangladesh, with only three outbreaks reported to date, there is no definitive evidence.

Philippines In 2014, an outbreak of NiV infection occurred in the Philippines. Seventeen cases were confirmed and the mortality rate was 82%. Ten patients had a history of close contact with horses or consumption of horse meat. The deaths of 10 horses were reported during the same period, nine of which showed neurological symptoms. However, the horse samples were not tested for NiV. Five patients, including two members of the medical staff, acquired the disease through human-to-human transmission. This strain was closely related to the Malaysian strain, for which clear human-to-human transmission had not previously been established[43]. This suggests the possibility of co-evolution of different NiV strains in bats or strain mutation, as the mutation probability increases with each spillover event.

Clinical features –

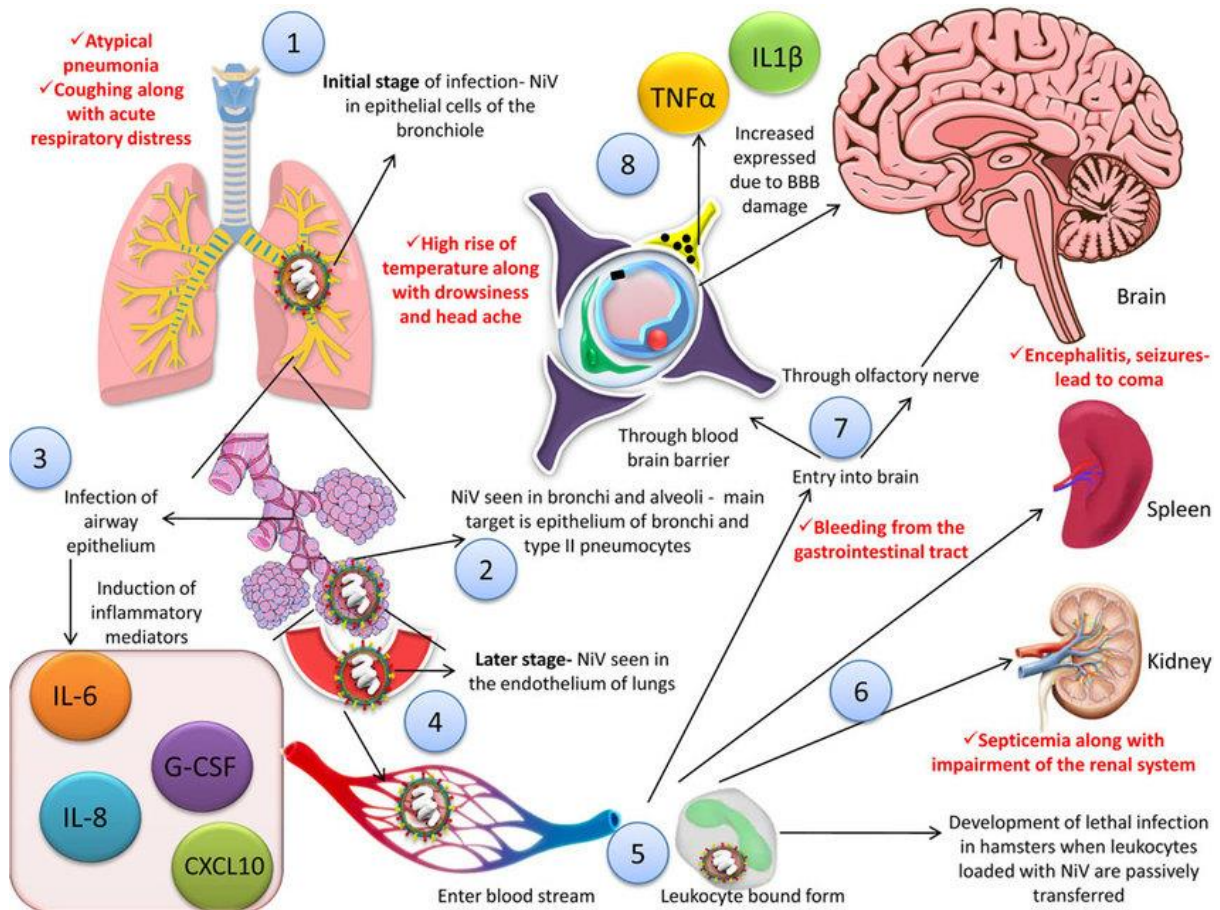
The incubation period for NiV varies from 4 to 21 days. NiV mainly causes acute encephalitis and respiratory diseases and is highly lethal. A small percentage of those infected are asymptomatic[44]. A short incubation period is followed by prodromal signs and symptoms such as febrile headache and myalgia[45]. Characteristics of encephalitis develop within a week, with the most common symptoms being altered mental status, areflexia, hypotension, segmental myoclonus, gaze palsy, and limb weakness. The patients' condition deteriorates rapidly, and coma and death follow within days. Residual neurological deficits are observed in 20% of survivors and range from fatigue to focal neurological deficits and depression[46]. A few cases of recurrent or late-onset NiV encephalitis have been described [47]. There are some differences in the clinical features observed in the Malaysian and Indian outbreaks. A higher mortality rate was observed in India and Bangladesh (70%) compared to

Malaysia (40%). Respiratory diseases occur in 70% of patients in India and Bangladesh[48], while no significant respiratory involvement was observed in Malaysia[49]. Airway involvement can manifest as cough, shortness of breath, and atypical pneumonia[50]. Risk factors for a poor prognosis are advanced age, comorbidities, thrombocytopenia and elevated aminotransferases on admission, brainstem involvement, and seizures.

PATHOGENESIS-

In the early stages of the disease in humans, NiV can be detected in epithelial cells of the bronchioles[51]. Viral antigens can be detected in experimental animal models in the bronchi and alveoli; the main targets are the epithelium of the bronchi and type II pneumocytes[52]. Inflammatory cytokines are induced due to infection of the airway epithelium. This recruits immune system cells, ultimately leading to the development of a disease resembling Acute Respiratory Distress Syndrome (ARDS). Significant inflammatory mediators, namely interleukin (IL)-1a, IL-6, IL-8; Granulocyte colony stimulating factor (G-CSF), C-X-C motif chemokine 10 (CXCL10), etc. are induced when the epithelium of the airways (the smaller ones) become infected[53]. From the breathing epithelium, the virus is disseminated to the endothelial cells of the lungs with inside the later level of the disease. Subsequently, the virus can benefit access into the blood circulate accompanied via way of means of dissemination, both freely or in host leukocyte sure form. Apart from lungs, spleen and kidneys along side mind may also act as goal organs main to a couple of organ failure. There is improvement of deadly contamination in hamsters whilst leukocytes loaded with NiV are passively transferred[54]. In pigs, there's effective contamination of monocytes, herbal killer (NK) cells along side CD6 p CD8p T lymphocytes[55]. In the process of viral entry into the central nervous system and the #40;CNS and#41; namely hematogenous (via the choroid plexus or blood vessels of the brain) and/or anterograde via the olfactory nerves[56]. The blood-brain

barrier (BBB) is disrupted and IL-1b is expressed along with tumor necrosis factor (TNF)-a due to CNS infection by the virus, ultimately leading to the development of neurological symptoms. Inclusion bodies may be present in the infected human CNS. Plaques along with necrosis may be evident in both gray and white matter. It is noteworthy that in various animal models the virus can enter the CNS directly via the olfactory nerve. The turbinate olfactory epithelium is infected by NiV in such animal models. The viral infection then spreads through the lamina cribrosa into the olfactory bulb. Ultimately, the virus spread through out the ventral cortex along with the olfactory tubercle[57].



NiV pathogenesis. 1. In the early stages of infection, NiV can be seen in the epithelial cells of the bronchiole. 2. NiV antigen has been found in the bronchi and alveoli. 3. Inflammatory mediators are activated as a result of airway epithelial infection. 4. In the later stages of the disease, the virus spreads to the endothelial cells of the lungs. 5, 6 Virus enters the bloodstream and spreads, either freely or in host leukocyte bound form, to the brain, spleen, and kidneys. 7. The process of viral entry into the central nervous system (CNS) involves two pathways: hematogenous and anterograde via olfactory nerve nerves. 8. The blood brain barrier (BBB) is disrupted, and IL-1 and tumour necrosis factor (TNF)- are expressed as a result of virus infection of the CNS, leading to the development of neurological symptoms. The symptoms in humans are shown in red font.

**REVIEW
OF
LITERATURE**

REVIEW OF LITERATURE

In study by RK SINGH et al, Over the past two decades, the pathogenesis of Nipah virus along with transmission has become much better understood due to extensive research. This understanding will continue to advance over the next decade. In addition, such an understanding will be of great help in developing techniques along with therapies to treat infected individuals to reduce morbidity as well as mortality. The prevention of such zoonoses in agricultural and health workers should be a priority. Scientists have come forward from a platform such as the Global Outbreak Alert and Response Network (GOARN), particularly following the outbreaks in Bangladesh and India, citing the need to create a communication network between medical and veterinary services regarding this disease. By involving several sectors and with a multidisciplinary approach, precise and concrete prevention strategies can be planned and implemented.

The One Health approach is also paramount. Coordination between institutes and internationally between medical and veterinary virologists and ecologists is needed to fully understand the timing and mechanism of virus shedding by bats. Inspection of all imported animals upon arrival and also prior to travel to the point of origin is essential. Adequate isolation, quarantine and disinfection protocol should be in place, including infrastructure facilities and trained personnel in protective clothing, to respond quickly to the identification of new cases. To prevent future NiV outbreaks, continuous surveillance of human health, animal health and reservoir hosts should be conducted to determine prevalence and predict risk of transmission of the virus in human and swine populations. The successful accelerated development of preventive vaccines and therapeutic or antiviral antibodies is a current need to control spread and treat infected patients during an outbreak. Collaborative efforts like

CEPI and biotech companies will accelerate the development of vaccines or treatments for NiV[58].

In study by sai kit lam and kaw bing chua,at el The Nipah virus encephalitis outbreak in Malaysia, a developing country, has taught us many important lessons. The initial assumption that JE virus was the cause of the disease was wrong, and much time and effort was wasted on controlling associated vectors and vaccination against JE virus. The rapid identification of the new virus required the support of international organizations, which was greatly appreciated by the Malaysian government.

We now have a good case definition for Nipah virus encephalitis, not only in humans but also in swine. This will greatly facilitate monitoring of the disease in the future. The measures taken to combat the spread of the disease proved effective and this information will also prove useful. As with other zoonotic infections, culling may be the quickest and least expensive measure to stop the spread of the disease.

A surveillance system has been put in place on pig farms to provide early warning of disease recurrence. The discovery of the virus' natural reservoir will be of great help in restructuring swine farms to avoid reintroduction of Nipah virus into swine populations[59].

In study by Thomas B Chandra et al, Human-to-human transmission is the main epidemiological feature of the outbreak in Kerala. Transmission was primarily in healthcare settings, and the mortality rate was high. The outbreak has been contained through case isolation, early initiation of barrier care, infection control practices, contact surveillance and home quarantine[60].

In study by G Arunkumare et al, We have reported an outbreak of NDV in southern India, which has resulted in extensive nosocomial transmission. We also provide a detailed description of transmission events that shed light on the nosocomial transmission of NiV. The outbreak was contained due to early laboratory confirmation and an immediate public health response. To institutionalize this success, we must promote early detection and response to outbreaks, a culture of laboratory confirmation, including access to leading laboratories, and improved infection control practices[61].

In study by Breed AC et al, This study showed clear evidence for the presence of NiV east of the Wallace line in East Timor, although it was not detected in individuals from Sulawesi, Sumba, or New Guinea. This extends the range of areas where NiV has been detected by PCR from Peninsular Malaysia by more than 2,500 km southwest to the island of Timor. However, the results from Sulawesi and Sumba suggest that NiV may not be present throughout the intervening area. Rather, the distribution of NiV may be related to the occurrence of certain species of fruit bats, particularly *P. vampyrus*. We also found clear evidence for the presence of henipa viruses in species other than *Pteropus* in Australasia: *Acerodon celebensis* in Sulawesi and *Rousettus amplexicaudatus* in East Timor. A single seropositive result in *Dobsonia magna* from Papua New Guinea complements several other detections of henipavirus antibodies in bats of this genus. An important result of this study was the detection of neither NiV nor HeV henipaviruses in the region. We found molecular tests for such viruses in Sulawesi and Sumba, with samples positive in a generic henipavirus PCR assay but not in specific NiV or HeV assays. In addition, we found serological evidence for such viruses in these two locations and also in Australia, PNG and to a lesser extent East Timor, with samples showing equivocal neutralizing antibody titers against NiV and HeV. Although HeV and NiV are the only recognized pathogenic henipaviruses, there is increasing evidence that other henipaviruses exist. As with other

emerging infectious diseases of wildlife, serological and virological diagnostic options are limited due to the incomplete understanding of the diversity and relatedness of these pathogens (e.g. degree of cross-reactivity). Further studies using improved genome detection methods in areas with inconclusive serological results are needed to elucidate the risk of henipaviruses[62].

IN study by VA Aranklle et al, NiV caused a family outbreak with a 100% mortality rate, confirming human-to-human transmission. The NiV strains from India and Bangladesh were closer than the viruses from Malaysia. Although the outbreaks occurred in neighboring geographic areas, the NiV outbreaks in Bangladesh and India were not caused by the same virus strain or by contagion[63].

In study by Aditi,sheriff M et al, , NiV has become a deadly zoonosis. Bats, the natural reservoir of the virus, spread the virus effectively and outbreaks in humans continue to be reported regularly. Due to the worldwide distribution of bats, outbreaks in new areas are to be expected. The high mortality rate and the acute course of the disease make it difficult to diagnose the infection. Add to this the lack of readily available, inexpensive diagnostic tests and facilities equipped to handle virus samples. Effective treatment and prophylaxis is not available due to a lack of human studies, since the number of cases is small overall and the course of infection is acute. The recent outbreak in India highlights the possibility of potential indirect events in areas where no known risk factors currently exist. Monitoring systems for NiV need to be put in place, particularly in South and Southeast Asia. Countries in South and Southeast Asia urgently need to work together to strengthen surveillance systems to monitor indirect events and prevent transmission. A better understanding of bat ecology and the causes of indirect events, the development of effective treatments and prophylaxis for

humans and animals, and the strengthening of surveillance systems to prevent outbreaks are needed to contain the NiV threat[64].

In study by Massimo Gaingaspero Knowledge and awareness of the disease needs to be improved and disseminated among health services, veterinarians, farmers and consumers. Like other zoonotic agents, Nipah virus could be included in surveillance plans, particularly for wildlife. Prioritization can draw attention to other pathogens that, for example, have a higher incidence in the population. However, field investigations can reveal radical and unexpected epidemiological changes. For example, the discovery of a new filovirus similar to Ebola virus in Spanish microbats has shown that the potential for such indirect events is not limited to Africa or Asia. Therefore, it is important to improve our preparedness to counteract possible future introductions of exotic pathogens such as henipaviruses into non-endemic areas by conducting active pre-emergency investigations. Monitoring the evolution of the epidemiology of a dangerous pathogen like Nipah virus is paramount to be able to quickly adjust control plans should it become a new public health priority[65].

In study by Ang Bsp et al ,NiV emerged as a new virus exactly 20 years ago, causing severe disease and death in humans and animals, devastating the pig farming industry in Malaysia and continuing to cause outbreaks in Bangladesh and India. Because the reservoir host Pteropus bat is widespread and NiV has been found in bats in several countries, the potential for outbreaks in new regions remains significant[66].

In study by Sazaly Abubakar et al , The results reported here provide, for the first time, molecular evidence that at least two major strains of porcine NV were circulating in Malaysia during the 1998 NV outbreak, one strain from the first northern outbreak (NV-Tambun) and the other strain from the subsequent outbreak about 4 months later in the south (NV-Seremban and NV-Sungai Buloh). The NV-Seremban and NV-Sungai Buloh pig isolates had

identical sequences to those reported from human infections, confirming that all human infections during the southern outbreak were from infected pigs. There are no records of isolation of NV-Tambun from patients from the first Tambun outbreak or later outbreaks. Isolation of NV-Seremban and NV-Sungai Buloh from the Tambun eruption has not been reported. It is therefore not possible to determine whether the two main strains came from the same original focus of infection Tambun. Alternatively, the NV Tambun could be the basal ancestral tribe from which the later Southern tribe evolved. Two findings supported this hypothesis: the tambun outbreak occurred at least 4 months before the seremban outbreak, and the sequence differences between NV-seremban and NV-sungai buloh occurred as a result of genetic drift, a common phenomenon in tambunviruses. On the other hand, this occurrence is unlikely given that the genome sequence of NV-Tambun differs from NV-Flying Fox, putatively the original source of sNV infections. In addition, the NV sequences are of both human and porcine origin, sequenced independently in different laboratories were virtually identical, the sequence differences were unlikely to be due to errors inherent in the polymerase chain reaction or adaptation to tissue culture conditions. Therefore, the NV Tambun strain is the most likely causative agent of the first outbreak in pigs in Tambun, resulting from infection originating from a source that has yet to be identified. In contrast, subsequent outbreaks in the south were due to porcine NV isolates with the highest sequence similarity to Tioman Island NV flying fox. This result implies that the 1998 Malaysian NV outbreak is unlikely to be due to a single transmission of NV from Tioman Island fruit bats to pigs, but suggests the possibility of at least two different origins of NV infection[67].

In study by Sayantan Banerjee et al, An outbreak of Nipah virus should be suspected in relevant epidemiological situations (eg, traveling to or staying in geographic areas with known Nipah transmission or contact with pigs or bats) in patient populations with acute encephalitis with or without ARDS, high secondary attack rate and very high mortality.

These patients should be treated with appropriate infection control measures. Until newer drugs are developed for its effective treatment, the role of drugs like ribavirin needs to be clearly established with the help of properly designed studies. Effective Community control measures should be put in place to prevent transmission from animals (bats/pigs) to humans in disease-prone areas. In the fight between virus and human, it is to be hoped that the latter will emerge victorious in the long term[68].

In study by Emmie de wit and Vincent J.munster , Almost two decades have passed since the first appearance of the Nipah virus. Nipah virus continues to cause annual outbreaks in Bangladesh with low case numbers but high death rates. Although human-to-human transmission has been relatively limited so far, adaptation of the virus could lead to more efficient human-to-human transmission, potentially leading to large-scale human outbreaks. Effective therapeutic or prophylactic treatment options are still lacking; However, even if they are available, their implementation in resource-poor outbreak areas in Bangladesh can be difficult. Therefore, efforts should focus on developing cost-effective intervention strategies aimed at preventing zoonotic and human-to-human transmission. Detection of Nipah virus in flying foxes, animals with a large geographic range that partially overlaps areas with very high human population densities, suggests that Nipah virus could potentially cause outbreaks in Southeast Asia and potentially affect much larger areas stocks than before. The discovery of henipaviruses, which are closely related to Nipah virus, in bats in Africa and South and Central America further suggests that with increased contact between bats and humans as a result of habitat destruction and climate change, we may be faced with more in the future Transmission events may face[69].

In study by Emily S. Gurley et al, An outbreak of encephalitis in Faridpur District, Bangladesh between April and May 2004 was investigated to determine the cause of the

outbreak and risk factors for the disease. Biological samples were tested for Nipah virus. Nipah virus contamination on surfaces was assessed by reverse transcription-PCR (RT-PCR). 36 cases of Nipah virus disease were identified; 75% of the case patients died. Several peaks in disease occurred and 33 case patients had close contact with another Nipah virus patient prior to their illness. The results of a case-control study showed that contact with 1 patient carries the highest risk of infection (odds ratio 6.7, 95% confidence interval 2.9-16.8, $p < 0.001$). RT-PCR testing of environmental samples confirmed Nipah virus contamination of hospital surfaces. This research provides evidence of human-to-human transmission of the Nipah virus. The ability for human-to-human transmission increases the potential for further spread of this highly lethal pathogen and underscores the need for infection control strategies for resource-poor settings[70].

In study by Birgit Nikolay et al, Increasing age and respiratory symptoms were indicators of Nipah virus infectivity. Measures to control human-to-human transmission should aim to reduce exposure to body fluids[71].

In study by Jean-Marc et al, In 2000 we conducted a study in Cambodia on henipavirus infections in various species of bats, including fruit bats, and humans exposed to these animals. Among 1,072 bat serum samples analyzed by an enzyme-linked immunosorbent assay, antibodies reactive to Nipah virus (NiV) antigen were detected only in *Pteropus lylei* species; *Cynopterus sphinx*, *Hipposideros larvatus*, *Scotophilus kuhlii*, *Chaerephon plicata*, *Taphozous melanopogon* and *T. theobaldi* species were negative. Serum neutralization applied to, a subset of 156 serum samples, confirmed these results. None of the 8 human serum samples were seropositive for NiV in the serum neutralization assay. An isolated virus showing cytopathic effect with syncytia was obtained from 769 urine specimens collected from roosts of *P. lylei* specimens. Partial molecular characterization of this isolate showed

that it was closely related to NiV. These results support the hypothesis that fruit bats may be the natural hosts of NiV. Surveillance of human cases should be introduced[72].

In study by Supaporn Wacharapluesadee et al, This study reports evidence of NV infection in Thai fruit and insectivorous bats, detected by IgG antibodies to NV in serum samples and NV RNA in urine and saliva. Antibodies against NV have been found in *P. hypomelanus*, *P. vampyrus*, *P. lylei* and *H. Larva*. NV infections in the first two species were similar to those reported in Malaysia. *P. lylei* was the only bat species infected with NV among the 14 species tested in Cambodia. A previous report showed a correlation between the ELISA and the neutralization tests with a sensitivity of 87% and a specificity of 99%. These data support our ELISA results as a first-line screening tool to investigate NV infection in countries that do not have a BSL-4 facility to perform neutralization assays. The finding of unusually high antibody titers against *P. lylei* indicates that NV is primarily found in this bat species in Thailand and Cambodia.

Southern blot analysis is also useful for PCR confirmation; however, sensitivity may not be significantly improved as previously reported for rabies. We used a nested PCR method because of the initial need for less RNA and shorter turnaround time. Confirmation was achieved by direct sequencing of the amplified products. Our current ELISA and PCR data, taken together, are sufficient to conclude that Thai bats were naturally infected with NV. Larger number of positive PCR samples at *P. lylei* could be the result of a bias in species collection. Alternatively, in the serological study, *P. lylei* could be the most common infected species. Sequence analysis of the short 181 nt sequence suggests that >2 strains of NV circulate in Thai bats. Further sequence data are required to confirm this hypothesis. Finding NV RNA in the saliva of *H. larvatus* may indicate that the insectivorous bat is another reservoir, or it may just be an accidental spill.

We believe that NV infection is widespread in Thai fruit bats, as previously reported in Malaysia and Cambodia. Nationwide surveillance is required to clarify the epidemiology of NV infection in Thailand in terms of geographic, seasonal and host attributes[73].

In study by Supaporn Wacharapluesadee , Siriporn Ghai et al, The high degree of similarity between the NiV genomes of Thai bats and the Bangladeshi patient highlights the potential for an outbreak of NiV in Thailand. The findings of the NiV cross-sectoral surveillance were communicated to national authorities and villagers, resulting in preventive control measures, increased surveillance of pigs and humans in the vicinity of known NiV-infected roosts, and increased vigilance and risk behaviours at the community level. This proactive One Health approach to NiV surveillance is a success story, demonstrating that increased collaboration among the human, animal, and wildlife sectors is critical for staying ahead of a zoonotic disease outbreak[74].

In study by Shahana Parveen et al, For high-lethal outbreaks, instead of one-way communication, an interactive strategy, communicated by a team of trained experts, in plain language with supporting evidence such as informative photos, the biomedical model of disease transmission, and the prevention messages can make credible the affected community even those that may at first evoke supernatural causal explanations.

Building relationships and trust with residents of the affected community is essential to understanding local perceptions of the outbreak and a critical first step in emergency response. Particularly during an outbreak, the central health authority should suggest that local health authorities explain the need for treatment or diagnostic procedures to families during care. This can help avoid misunderstandings and potential distrust between affected communities and healthcare professionals[75].

In study by Vijay K.chattu et al, NiV is currently an emerging infectious disease of public health concern in the countries of the Southeast Asian region, which is a natural habitat for fruit bats. Because NiV can be transmitted through a variety of methods, it poses a potential threat to public health worldwide. Since NiV is an issue that needs to be addressed by multiple stakeholders to promote the health of all citizens, the concept of global health diplomacy holds great promise to meet the needs of global health security through its instruments mandatory or non-binding regulations, applied by global governance institutions. Health ministries and stakeholders (e.g. CEPI, CIDRAP) must work together to develop a vaccine and ensure the safety of this bat-borne disease. There is a great need to strengthen intersectoral coordination, review treatment procedures and infection control practices, and ensure the use of PPE and the availability of medicines to better treat suspected cases[76].

In study by Vincent P.Hsu et al, We retrospectively reviewed two encephalitis outbreaks in Meherpur and Naogaon, Bangladesh, which occurred in 2001 and 2003. We collected serum samples from diseased individuals, their household contacts, randomly selected residents, hospital staff, and various animals. Cases were classified as laboratory-confirmed or probable. We identified 13 cases (4 confirmed, 9 probable) in Meherpur; 7 were in people in two households. Patients had close contact with other patients or with a sick cow more frequently than non-patients. In Naogaon, we identified 12 cases (4 confirmed, 8 probable); 7 were in individuals grouped in 2 households. Two Pteropus bats had antibodies to Nipah virus. Samples from hospital workers tested negative for Nipah virus antibodies. These outbreaks, the first since 1999, suggest that transmission may occur through close contact with other patients or through contact with a common source. Monitoring and improving the diagnostic capacity to detect Nipah virus infection is recommended[77].

In study by Fatema Wahed et al, Nipah virus is a recent life-threatening infectious agent in this region. This situation can be worsened by the mutation in the virus with the spread and progression of the infection in the human population with irrational, insufficient or inappropriate therapeutic measures. The main strategy is to prevent human Nipah virus infection before it grows beyond manageable levels. Appropriate surveillance systems need to be put in place so that outbreaks of Nipah virus can be quickly identified and appropriate control measures implemented[78].

In study by Jiarong yu et al, Ribavirin has been confirmed to inhibit Nipah virus replication in vitro, showing a therapeutic effect in a small number of patients and hamster model infection experiments. Animal models are currently used to simulate the pathogenesis and transmission mechanisms of NiV. Susceptibility to high-risk human-to-human transmission is determined by specific human behaviours and interactions between patients and caregivers. This is difficult to simulate in animal models, so animal models cannot be used for direct human propagation studies. Based on the NiV spread route and the NiV risk analysis in China, a spread model that can be applied to human spread research is to be established in the future. Furthermore, based on research published worldwide, there is a need to develop and implement an internationally standardized indirect ELISA kit and IgM capture ELISA to enable the detection of NiV antibodies and eliminate the risk of disease outbreak[79].

IN study by ,A. CHAKRABORTY , H. M. S. SAZZAD et al, During the 2010–2011 Nipah season in Bangladesh, as in preceding Nipah seasons, ingesting uncooked date palm sap and having touch with a case of Nipah encephalitis had been recognized as the 2 maximum not unusualplace danger elements for Nipah contamination and 72% of instances pronounced this type of exposures at some point of their incubation period. We additionally recognized a brand new capability pathway of NiV transmission, ingesting fermented date

palm sap. In the absence of different recognized capability danger elements, ingesting fermented date palm sap seemed to be the maximum conceivable capability pathway of transmission for 3 probably instances with inside the Rangpur cluster. However, in a cluster of NiV contamination pronounced from India at some point of 2007, the index case evolved NiV contamination following ingesting conventional liquor crafted from date palm sap. Paramyxoviruses are considered susceptible to alcohol, but the alcohol concentration required to act as a disinfectant is 60-70%, while the alcohol concentration of conventional spirits in the Indian subcontinent is reported to be around 4%. This suggests that NiV can remain viable in the fermented juice and be transmitted to people who drink that juice. We identified one case of apparent cadaver-to-human transmission. The frequent isolation of NiV from respiratory secretions of Nipah cases and evidence of cadaver-to-human transmission in this outbreak investigation suggest that contact with secretions or body fluids from deceased Nipah cases poses a significant risk of transmission. Messages should emphasize covering the face when in close contact with the deceased and washing hands with soap after the ritual bath. However, such reactive strategies will remain unable to prevent human-to-human transmission of infection from primary cases, as these cases often go undiagnosed in hospital unless they are part of a cluster or are detected late, when secondary cases occur. Therefore, research should be conducted to identify systemic barriers in the implementation of interventions in hospitals to reduce overall human-to-human or cadaver-to-human transmission, such as: B. Respiratory protection and hand washing, and ways to overcome these barriers.

The isolated case from Comilla district is the first confirmed case of Nipah encephalitis in eastern Bangladesh. Although the reasons for the relative non-occurrence of NiV infection in the Eastern Districts are unknown, the detection of this isolated case of Nipah encephalitis, who had a history of drinking raw date palm juice, suggests that other clusters of undetected

NiV may occur outside of the 'Nipah belt' described above. However, given the routine reporting and investigation of disease outbreaks across the country, it is unlikely that a large number of cases will go undetected in this part of the country. This is consistent with findings from previous Nipah outbreaks in Bangladesh, where cases who developed the disease after human-to-human transmission had a lower mortality rate than those who contracted it from eating Nipah date palm. Similarly, in experimental studies in golden hamsters exposed to a higher dose of NiV, additional deaths occurred. Therefore, a higher proportion of surrogate respondents in cases compared to controls may have weakened the association between risk factors and outcome. The apparent protective effects of eating plums, which are a common fruit during winter, may be the result of this bias. This finding could also be coincidental as no plausible biological mechanism supporting a protective effect is known[80].

In study by Michael K. Lo et al, We performed a comprehensive molecular phylogenetic analysis of the currently available complete NiV gene ORFs at the nucleotide and amino acid levels, including recently obtained sequence data from the NiV outbreaks in Bangladesh in 2008 and 2010. Analysis of the combined sequence data from Bangladesh and India in the last decade led us to propose a genotyping scheme based on a 729 nt window of the NiV N ORF. This genotyping scheme provides a simple and accurate way to classify current and future NiV sequences[81].

In study by Stephen P. Luby et al, Human Nipah outbreaks are recurring in Bangladesh in a specific region and season. Fruit bats are the reservoir host for Nipah virus in human populations in central and north-western Bangladesh from 2001 to May, but not every year. We discovered 122 cases of Nipah infection in humans. The mean age of the case patients was 27 years, 87 died. In 62 patients infected with Nipah virus, the disease developed between 5 and 15 days after close contact with another Nipah case. Nine 7% of patients with

Nipah cases transmitted the virus to others. Nipah 12% vs 0%, $p=0.03$. Although a small minority of infected patients transmit Nipah virus, more than half of identified cases result from human-to-human transmission from bat-to-human[82].

In study by Khean Jin Goh, M.R.C.P.et al, Nipah virus causes severe, rapidly progressive encephalitis with a high mortality rate and features suggestive of brainstem involvement. Infection is associated with recent contact with pigs[83].

In study by Medelein H.L et al.,From March 10th to 19th, 1999, 11 workers in 1 out of 2 slaughterhouses in Singapore fell ill with Nipah virus-associated encephalitis or pneumonia, resulting in 1 death. A case-control study was carried out in order to identify occupational risk factors for infection. The case patients were slaughterhouse A workers who had IgM anti-Nipah antibodies; Control subjects were randomly selected workers from Slaughterhouse A who tested negative for anti-Nipah IgM. The 13 patient cases versus 26 (63%) of 41 controls reported contact with live pigs ($p=0.01$).On March 3, 1999, imports of pigs from Malaysian states coexisting with an outbreak of the Nipah virus were banned; On March 19, 1999, imports of pigs from Malaysia were banned and the slaughterhouses closed. No unusual diseases were reported in the pigs processed in February and March. Contact with live pigs appeared to be the most important risk factor for human infection with Nipah virus. Direct contact with potentially infected live pigs should be minimized to prevent transmission of this potentially fatal zoonosis to humans[84].

In study by Joel M. Montgomery et al, Climbing trees, a behavior commonly performed by young children, was associated with an increased risk of NiV infection; although the exact route of transmission is unclear. If human-to-human transmission were extremely efficient, the conditions and population density of Bangladesh ($\approx 1,000$ inhabitants/km²; total population 141 million/144,000/km²) could have resulted in a much larger outbreak. In fact, a study of health workers in Bangladesh found no evidence of chance transmission among people caring for hospitalized patients with Nipah-related diseases. The most likely route of transmission was from bat to human on Goalando; however, some undetermined intermediate or secondary hosts cannot be excluded. Periodic introduction of NiV into human populations in this region may continue due to the overlapping nature of human and pterosaur bat habitats.

In addition, interactions between bats and humans are likely to increase due to the loss of bat habitats, as the few remaining fruit trees are likely to be found in close proximity to human habitation[85].

In study by James G Olson et al, Several species of the genus *Pteropus* show serological evidence of Nipah or HeV infection. Attempts by various groups to recover virus from tissues of serologically positive bats were unsuccessful, as were immunohistochemical tests to detect infection in tissues. Several possible reasons can explain the inability to recover the virus from serologically positive bats. Antibody-positive bats can represent the proportion of those infected who survived and cleared the virus. Experimental inoculation in of a small number of Australian *Pteropus* bats with a related paramyxovirus resulted in the virus replicating, causing microscopic lesions, and being shed; the virus appears to disappear when the antibody response occurs.

We see no evidence of direct transmission of HeV or Nipah viruses from bats to humans. However, during the outbreak of Nipah virus encephalitis in Malaysia, several laboratory-confirmed Nipah cases were identified that had no contact with infected pigs. In Cambodia, the distribution of *Pt. lylei* restricted to places where they are protected from hunting, including urban areas and temples, where human-bat interaction may increase. The fact that these large bats are captured and used for food in further increases the risk of human exposure and infection[86].

In study by Mazrura Sahani et al, Nipah infection was not widespread among slaughterhouse workers in Malaysia and was associated with exposure to pigs. Because it can be difficult to identify Nipah-infected pigs that can transmit the virus based on clinical symptoms, use of personal protective equipment, monitoring for Nipah infection on pig farms supplying slaughterhouses, and avoidance of handling and processing are potential infected pigs present the best strategies to prevent transmission of Pf Nipah virus in slaughterhouses [87].

In study by C.P Girish kumar et al, Although NiV is known to cause subclinical infections, the extent of these infections varies among close contacts during outbreaks. For example, no subclinical infections were reported in outbreaks in Bangladesh, but in outbreaks in Malaysia, between 1% and 15% of infections were subclinical. Parashare et al. reported clinically undetected NiV infection in 6% of 166 community farm controls and 11% of 178 case farm controls. Another study of household contacts of hospitalized NiV-patients showed that 8% had subclinical infections. In an outbreak in Singapore, infections were reported in 2 (4.6%) of 43 asymptomatic slaughterhouse workers. Another study conducted in Singapore among 1,460 healthcare professionals who had contact with NiV patients identified NiV-specific antibodies in 22 (1.5%) of whom 10 were asymptomatic. These studies suggest that infection

with the Malaysian NiV strain causes less severe disease, A lower mortality rate and a higher prevalence of asymptomatic infections compared to outbreaks associated with the Bangladesh strain .Studies in the NiV strain responsible for the outbreak in Kerala were closer and more pathogenic to the strain from Bangladesh. Although previous studies did not show subclinical infections during NiV outbreaks involving the Bangladesh strain, our study suggests that the NiV strain from the Kerala outbreak caused asymptomatic infections. Our study also found that IgM could be detected ≤ 2 months after NiV infection and class switching from immunoglobulin to IgG could occur beyond 2 months[88].

In study by Michael K.Lo,Paul .Rota, Since its emergence in Malaysia, NiV has been a recurring threat to human health in Southeast Asia. The comparative deterioration in clinical findings and CFR in the outbreaks in Bangladesh and India compared to the outbreak in Malaysia underscores the need to improve prevention measures against NiV infection wherever possible. Expanding surveillance and laboratory capacity to diagnose encephalitis in outbreak-prone areas is critical to early detection and containment of outbreaks[89].

In study by A.B. Sudeep et al, NiV positivity in *Pteropus medius* during the current outbreak (2019) suggests the likely role of bats in NiV transmission in Ernakulam, Kerala state. The authors would like to present the proposal for the distribution of the new NiV strain “India (I)” in the southern part of India, which differs from the NiV strains from NE India and Bangladesh. Further studies are needed to understand the disease involvement of this new strain of NiV in humans, along with the development of new diagnostic and treatment modalities[90].

In study by Laura T Mazzola, Cassandra Kelly-Cirino In addition to playing a central role in detecting and controlling outbreaks, diagnostic testing can provide a more nuanced understanding of the positivity window and duration of infection, risk of transmission, and

risk factors for the severity of NiV, one of the most prevalent pathogens. of febrile encephalitis. In particular, diagnoses to support early detection will be crucial for interventions and containment of "hot spots". However, some of the gaps identified in the 2016 WHO R and D plan remain, including a lack of routine EQA, understanding of NiV antibody and viral kinetics, well-characterized and up-to-date performance panels, and close monitoring. Target product profiles for NiV should be refined to include the need to identify all known NiV lineages and the benefits of RDT POC diagnostic and syndrome panels. Because diagnostics are a key element in achieving the R and D plan goals, WHO coordinates research and funding through product development partnerships with groups like FIND to ensure the development, evaluation and delivery of affordable and high-quality diagnostics for NiV[91].

In study by Pragya D. Yadav et al, In this outbreak, NGS helped identify circulating NiV in Kerala as genotype B. We found the highest similarity between the full-length human NiV sequences from Kerala and the NiV N gene sequences from Pteropus spp. Fruit bats (99.7%-100%) compared to NiV sequences from Malaysia, Cambodia and Bangladesh (85.14%-96.fifteen%). This finding indicates that Pteropus spp. Bats were likely the source of human infections in this outbreak.

The clear accumulation of Kerala sequences suggests that this strain may be circulating locally in bats and that there may be some evolution that distinguishes it from the North Bangladesh/West Bengal strain. It may also indicate that the bat colony sampled in this outbreak had an active infection, but additional epidemiological studies in bats may be needed to substantiate this. Freezing and thawing of organs, failure to collect fresh tissue

samples in the field, or preservation of tissues in virus transport medium could be the reasons why the full genome of bats could not be recovered.

Due to the lack of effective specific treatments or prophylactic vaccines against NiV infection, the focus should be on containing this virus. Strict isolation; biological risk reduction; and infection control policies in hospitals should be strengthened, including the explicit use of personal protective equipment as part of risk reduction by healthcare workers. Effective surveillance of close contact and suspected NiV cases aids in early detection and isolation, thereby preventing secondary transmission.

Eating fruit that comes in contact with bat saliva or inhaling small droplets produced by infected urine or saliva from bats that are in the tree canopy can be an important route of transmission of NiV to humans. Although the index patient's route of infection in this outbreak was unknown, more research is needed to determine how contaminated fruit could be a route of transmission for NiV. The high positivity in bats shows the animal epidemic of a NiV infection. Breaking the chain of transmission of NiV requires health education and community awareness raising[92].

In study by S.B. Kasloff et al, In 1998, an outbreak of fatal encephalitis among workers on pig farms in Malaysia and Singapore led to the discovery of Nipah henipavirus (NiV), a new paramyxovirus closely related to Hendra henipavirus with a fatality rate of nearly 40%. After its initial emergence, outbreaks of NiV in Bangladesh have occurred almost annually with a different genotype, NiV Bangladesh, in which the role of pigs in its transmission is unknown. The present study provides the first report on the susceptibility of domestic pigs to NiV Bangladesh after experimental infection, characterizing the acute and long-term phases of the disease and the pathogenesis. All pigs were successfully infected

with NiV Bangladesh after oro-nasal inoculation with virus shedding confirmed by novel genotype-specific qRT-PCR in oral, nasal, rectal and upper airway shedding to the brain, lungs and associated lymphoid tissue. In contrast to previous NiV-Malaysia results in pigs, clinical signs were absent, viraemia was undetectable throughout the study, and only low neutralizing antibody titers were measured 28/29 days after NiV challenge. The results obtained underscore the need for continued and improved NiV surveillance in pigs in endemic and risk areas and raise questions about the applicability of current serological tests to detect animals previously exposed to NiV-B[93].

In study by Jan felix Drexler et al, The new viruses were detected in wild *E. helvum* occupying trees in a zoological garden in central Kumasi, Ghana's second largest city with 1.5 million people. Large colonies of *E. helvum* are widespread in urban areas of sub-Saharan Africa. At the site studied here hundreds of visitors and staff enter the zoo every day and may be exposed. The forms of exposure can be key features in understanding the origin of epidemics of bat-borne viruses such as Ebolavirus, Henipavirus or Coronavirus. It has been suggested that humans may be exposed to viruses from fruit bats, which chew fruit and spit out the pulp at feeding sites. However, it appears that *E. helvum* only roosts in urban areas and rarely feeds there. Detailed studies of the foraging behavior of *E. helveum* missing. Another way of exposure can be through contact with bat urine or feces. In this study, we collected faeces from bats, which are abundant under trees in urban roosts for *E. helvum*. Interestingly, the virus RNA levels observed in faeces were quite low compared to enteric viruses transmitted by the faecal-oral route in humans. It has been widely reported that bat urine contained henipavirus. Despite the timely collection of faecal samples from plastic foil in this study, contamination of these samples with bat urine cannot be completely ruled out. Overall, our data suggest a limited risk of virus exposure from bat faeces. It is important to keep this in mind to avoid hasty measures aimed at eradicating flying foxes as potential virus

hosts as this can disrupt important ecological functions i.e., seed dispersal and pollination *E. helvum* is known to be one of the favorite bat species for wildlife in Africa. Future studies should focus on whether there is a relevant virus concentration in the organs or meat of bats and whether people who regularly consume bat meat may show signs of previous infection[94].

In study by Brain H. Harcorte et al, This first look at strain variation in NV shows that viruses circulating in different areas have unique genetic signatures and suggests that strains may have co-evolved within local natural reservoirs. Until 2004, identification of NV outbreaks in Bangladesh was based solely on serological testing. The isolation and genetic characterization of NV-B confirms that NV was the etiologic agent responsible for these outbreaks[95].

In the study of Paola Kaitrina G. Ching et al, the most common route of transmission of the virus to humans was direct contact with infected horses, exposure to contaminated body fluids during slaughter of diseased horses, and/or the consumption of raw meat from infected horses. However, in at least 5 cases, clinical and epidemiological evidence points to direct human-to-human transmission of the virus. Evidence of human-to-human transmission in this outbreak confirms the need for preventive public health and home care interventions.

Although the source of infections in horses is unclear, fruit bats (family Pteropodidae) are the most likely source based on the known ecology of henipaviruses. Bats from this family have been reported near at least one of the two villages[96].

**AIMS
AND
OBJECTIVE**

AIM AND OBJECTIVES

AIM- TO THE STUDY NIPAH VIRUS-EPIDEMIOLOGY AND CURRENT STATUS AT NATIONAL & INTERNATIONAL LEVEL

OBJECTIVES- TO ANALYZE THE EPIDEMIOLOGY CLINICAL PRESENTATION AND PREVALENCE OF NIPAH VIRUS INFECTION.

MATERIALS
AND
METHODS

MATERIALS ND METHOD

TYPE OF STUDY:- Meta-analysis

DATA TYPE: - Data for this meta-analysis were collected from following sources.

- a) Data from various publications in indexed journals.
- b) Data from recent editions of textbooks.
- c) Online data from various literature reviews.
- d) Data from websites of CDC, NCDC, WHO.

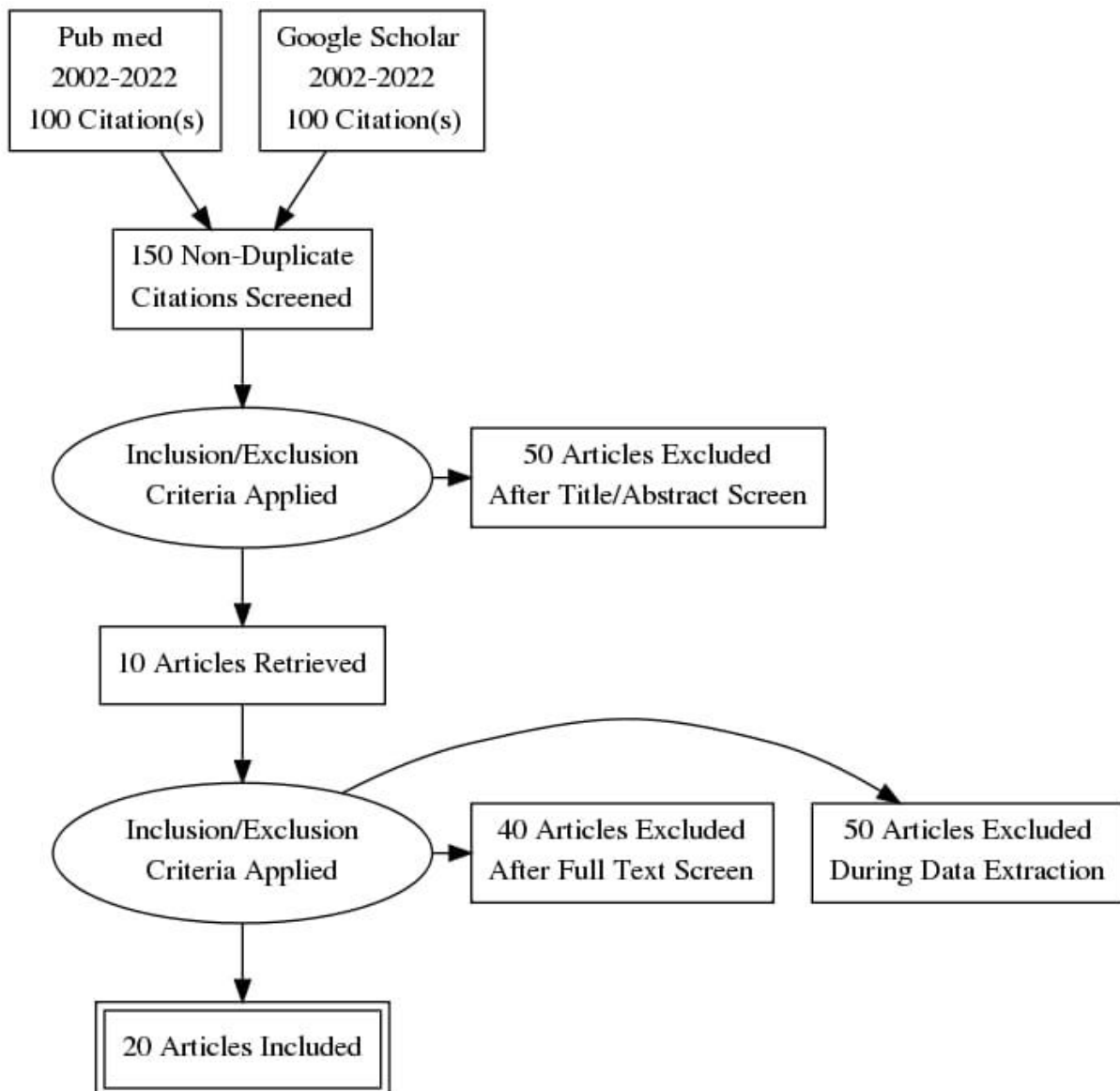
SEARCH STRATEGY: - This meta-analysis followed the PRISMA guidelines.

Articles were searched on PubMed, Google scholar, Web of Science, Science Direct, and Scopus using terms related to Nipah virus were used. Boolean AND, OR and NOT were used.

INCLUSION CRITERIA: -Article titles and abstracts were screened to include relevant articles. Nipah virus, epidemiology Current status of Nipah virus , risk factor of nipah virus Epidemiology, treatment and prevention of pandemic nipah virus.

EXCLUSION CRITERIA: -Article titles and abstracts were screened by researchers independently to exclude irrelevant articles.

Prisma Flow chart-



**OBSERVATION
AND
RESLUTS**

OBSERVATION AND RESULTS-

S.NO	AUTHOR	YEAR	COUNTRY	STUDY FINDING
1.	Raj kumar singh et al.	2019	India	Various types of enzyme-linked immunosorbent assays have been developed along with molecular methods based on polymerase chain reactions for diagnostic purposes. Due to the expensive nature of antibody drugs, the identification of broad-spectrum antivirals along with a focus on small interfering RNAs (siRNAs) is critical. The high pathogenicity of NiV in humans and the lack of vaccines or therapies to combat this disease has attracted the attention of researchers around the world to develop effective vaccines and treatment regimens against NiV.
2.	Sai kit lam and kaw Bing chua	2002	Malaysia	The clinical presentation includes segmental myoclonus, areflexia, hypertension, and tachycardia, and histological evidence includes endothelial damage and vasculitis of the brain and other major organs. Magnetic resonance imaging has demonstrated the presence of discrete high signal intensity lesions scattered throughout the brain.
3.	Thomas b, chandran P,	2019	India	Of the 18 confirmed cases, 16 died (mortality rate 88.8%). The mean incubation period was 9 days. Transmission was person-to-person, with the main case serving as a point source for 15 other cases, including 2 healthcare workers. The median age of the affected cases was 41 years with male predominance. More than 2,600 contacts were monitored. The outbreak was contained within 3 weeks and declared over in July of the same year.

4.	G.Arunkumar et al.	2018	India	From May 2 to May 29, 2018, 23 cases were identified, including the index case; 18 were confirmed in the laboratory. The NiV line responsible for this outbreak was closer to the line from Bangladesh. The median age of the cases was 45 years; the sex of 15 (65%) was male. The median incubation period was 9.5 days (range 6-14 days). Of the 23 cases, 20 (87%) had respiratory symptoms. The mortality rate for was 91%; 2 cases survived. Risk factors for infection included proximity (i.e., touching, feeding, or breastfeeding a NiV-infected person), which enabled droplet infection. The public health response has included isolating cases, contact tracing and adopting infection control practices at the hospital.
5.	Breed AC et al	2013	USA	We found molecular evidence of such viruses in Sulawesi and Sumba, with samples being positive in a generic henipavirus PCR assay but not in NiV or HeV specific assays. In these two places and also in Australia we found serological evidence of such viruses. Although HeV and NiV are the only recognized pathogenic henipaviruses, there is increasing evidence that other henipaviruses exist.
6.	VA Arankalle et al.	2011	India	NiV caused a family outbreak with a 100% mortality rate, confirming human-to-human transmission. A family outbreak in West Bengal, India, with 5 deaths and human-to-human transmission has been attributed to Nipah virus. The complete genome sequence of Nipah virus (18,252 nt) amplified from lung tissue showed 99.2% nt and 99.8% identity with the Bangladesh-2004 isolate, suggesting a common source of the virus.

7.	Aditi and M. Shariff	2019	India	The recent outbreak in India highlights the possibility of potential indirect events in areas where no known risk factors currently exist. Monitoring systems for NiV need to be put in place, particularly in South and Southeast Asia. A better understanding of bat ecology and the causes of indirect events, the development of effective treatments and prophylaxis for humans and animals, and the strengthening of surveillance systems to prevent outbreaks are needed to contain the NiV threat.
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8.	Massimo Giangaspero	2013	Italy	Knowledge and awareness of the disease needs to be improved and disseminated among healthcare providers, veterinarians, farmers and consumers. Prioritization can draw attention to other pathogens that, for example, have a higher incidence in the population. Field investigations can reveal radical and unexpected epidemiological changes. Monitoring the evolution of the epidemiology of a dangerous pathogen like Nipah virus is paramount to be able to quickly adjust control plans in Case , which could become a new public health priority.
9.	Sazaly abubakar et al.	2004	Malaysia	The NV-Seremban and NV-Sungai Buloh pig isolates had sequences identical to those reported from

				<p>human infections, confirming that human infections during the southern outbreak originated from infected pigs. Two findings indicated at least 4 months before the Seremban outbreak. Therefore, the NV Tambun strain is the most likely causative agent of the first outbreak in pigs in Tambun, resulting from infection originating from a source that has yet to be identified. This finding implies that the 1998 Malaysian NV outbreak is unlikely to be due to a single transmission of NV from Tioman Island fruit bats to pigs, but points to the possibility of at least two distinct origins of NV infection.</p>
10	Sayantana Banerjee et al.	2019	India	<p>An outbreak of Nipah virus should be suspected in relevant epidemiological situations (eg, traveling to or staying in geographic areas with known Nipah transmission or contact with pigs or bats) in patient populations with acute encephalitis with or without ARDS, high secondary attack rate and very high mortality. Effective Community control measures should be put in place to prevent transmission from animals (bats/pigs) to humans in disease-prone areas. In the fight of the virus vs. Man, hopefully the latter will prove to be the winner in the long run.</p>
11.	Emily S.Gurley et al.	2007	Bangladesh	<p>36 cases of Nipah virus disease were identified; 75% of the case patients died. Several peaks in disease occurred and 33 case patients had close contact with another Nipah virus patient prior to their illness. The results of a case-</p>

				control study showed that contact with 1 patient carries the highest risk of infection (odds ratio 6.7, 95% confidence interval 2.9-16.8, $p < 0.001$)
12.	Birgit Nikolay et al.	2019	Bangladesh	Of the 248 identified Nipah virus cases, 82 were caused by human-to-human transmission, which corresponds to a reproductive number (i.e., the average number of secondary cases per patient case) of 0.33 (range 95% confidence interval [CI], 0.19) corresponds to 0.
13.	Jean-marc Reynes et al.	2005	Cambodia	Among 1,072 bat serum samples analyzed by an enzyme-linked immunosorbent assay, antibodies reactive to Nipah virus (NiV) antigen were detected only in <i>Pteropus lylei</i> species; <i>Cynopterus sphinx</i> , <i>Hipposideros larvatus</i> , <i>Scotophilus kuhlii</i> , <i>Chaerephon plicata</i> , <i>Taphozous melanopogon</i> and <i>T. theobaldi</i> species were negative. Serum neutralization applied to a subset of 156 serum samples confirmed these results. None of the 8 human serum samples were seropositive for NiV in the serum neutralization assay. A virus isolate showing cytopathic activity with syncytia was obtained from 769 urine samples collected in roosts of <i>P.Lylei</i> specimens. Partial molecular characterization of this isolate showed that it was closely related to NiV.
14.	Suaporn Wacharapluesadee et al	2021	Thailand	NiV RNA (mainly strain from Bangladesh) was detected in fruit bats by RT-PCR every year from 2002 to 2020. The full NiV genomic sequence sequenced directly from bat urine in 2017

				showed 99.17% identity with NiV from a Bangladeshi patient in 2004. No To date, NiV-specific RNA or IgG antibodies have been reported in healthy subjects, encephalitis patients or pigs found. During the sample collection trips, 100 community members were trained in the safe handling of bats.
15.	Shahana paeveen et al.	2016	Bangladesh	Residents initially believed the outbreak was caused by supernatural forces and continued to drink raw date palm juice despite requests from local health officials to stop. Participants in community meetings told that the initial messages did not explain that bats were the source of this virus. After our intervention, participants responded that they now understood how NiV could be transmitted and would refrain from consuming raw juice and maintain safer behaviors while caring for patients.
16.	Mazrura sahani et al.	2000	Malaysia	Seven (1.6%) of 435 slaughterhouse workers who slaughtered pigs versus zero (0%) of 233 workers who slaughtered ruminants had Nipah virus antibodies (P=0.05). All of the antibody-positive workers came from slaughterhouses in the three states that had reported cases of outbreaks among pig farmers. Workers in these three states were more likely to have Nipah antibodies (7/144 [4th86%] vs. 0/291 [0%], P and < 0.001) and report symptoms indicative of Nipah disease in pigs admitted to the slaughterhouses (P=0.001).

17.	Sudeep, A.B.Yadav et al.	2021	India	A rectal swab specimen and three visceral organs from bats tested positive for NiV. Interestingly, 20.68% (12/58) of the Pteropus were positive for anti-NiV IgG antibodies. NiV sequences of 18,172; 17,200 and 15,100 bps nucleotides could be obtained from three Pteropus bats.
18.	Jan felix Drexler et al	2009	South Africa	Feces from <i>E. helvum</i> housed in an urban setting in Kumasi, Ghana were tested for henipavirus RNA. The sequences of three new viruses that are phylogenetically related to known henipaviruses have been identified. Fecal virus RNA levels were low.
19.	Brain H.Harcourt et al.	2005	Bangladesh	Until 2004, identification of Nipah virus outbreaks in Bangladesh was based solely on serological testing. the isolation and genetic characterization of NV-B confirms that NV was the etiological agent responsible for these outbreaks.
20.	Paola Katrina G .Ching	Philippines	2015	Epidemiological data suggest that the most common route of transmission of the virus to humans was direct contact with infected horses, exposure to contaminated body fluids during slaughter of diseasedhorses, as well as the consumption of raw meat from infected horses. However, in at least 5 cases, clinical and epidemiological evidence points to direct human-to-human transmission of the virus. People caring for case patients at home did not wear protective gear and health workers wore gloves and a face mask but no eye protection. Evidence of human-to-human

				transmission in this outbreak confirms the need for preventive public health and home care interventions.
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DISCUSSION-

India's rapid population growth and consequent increase in human-animal interactions, combined with changing environmental conditions and inadequate sanitation and regulation, have made India one of the world's most important hotspots for infectious diseases, including zoonoses that are transmitted from animals to humans 75% of all human diseases.

Over the past two decades, the pathogenesis of Nipah virus, along with transmission, has become much better understood through extensive research. This understanding will continue to advance over the next decade. The Nipah virus encephalitis outbreak in Malaysia, a developing country, has taught us many important lessons. The initial assumption that JE virus was the cause of the disease was wrong, and much time and effort was wasted on controlling associated vectors and vaccination against JE-virus.

The study showed that infection with Nipah virus in case contacts resulted in overt disease with no evidence of asymptomatic infection, and that the risk of infection was higher in those who had prolonged contact with case patients and were exposed to bodily fluids. The number of secondary infections was related to the age of the Nipah virus-infected patients, but not to the total number of contacts.

Exposure histories of infected patients and the epidemiological curve showing multiple peaks of disease outbreak during this outbreak. Some case-control studies showed a 6-fold increased risk of infection for those reporting contact with patient F, a negative association with illnesses after hand washing, and specific exposures to sick people associated with transmission confirm that exposure-ill people increase the spread outbreak. Number of increased infections in the village from travelers entering and leaving the affected areas to visit family members. This movement caused new infections among caretakers in other villages and increased the number of affected villages. Detection of Nipah virus RNA on

hospital surfaces indicates that infected patients shed the virus into the environment, which could present an opportunity for Nipah virus transmission to others. It is not known how long the virus remains contagious in the environment. This outbreak proves that 1 person (patient GG) became infected during a hospital visit while sharing a bed with a confirmed case patient.

Somewhere around the outbreak of the Nipah virus, several community cases have been attributed to bat-to-human transmission linked to consumption of NiV-contaminated date palm sap. Absence of NiV RNA in bat-bitten fruit collected from the home of the index case and the village does not rule out zoonotic transmission from a bat to the index case. Several additional factors likely contributed to human-to-human transmission. Some cases involve inadequate infection control barrier measures. Although, healthcare workers were trained in infection control, only a minority used barrier measures such as face masks and gloves. Healthcare workers or caregivers with appropriate infection control barrier measures did not acquire NiV despite close contact with the index case.

The rapid response of the State and the Government of India's Department of Health and Family Welfare, the Indian Council of Medical Research and its public health institutes prevented the outbreak from spreading. Given the high prevalence of respiratory symptoms and clear transmission by droplet spread, any delay in containment would have resulted in a higher number of human-to-human transmissions, resulting in greater loss of life and significant economic and social impact.

Although there is strong evidence that *Pteropus* spp. While fruit bats are the natural reservoir hosts for NiV, there is also growing evidence of rapid adaptation of the virus to other hosts with different transmission routes. In just a few years after its initial discovery, NiV was being transmitted to humans through infected pigs, horses, bats, and other humans. While

infections from single indirect events may be limited to small, isolated outbreaks, repeated indirect events of a pathogen with the potential for human-to-human transmission can lead to a much higher burden of disease. Although physical barriers to prevent the spread of NiV between bats and humans can provide some protection, outbreaks continue to occur and human-to-human transmission remains a threat. More research on antiviral drug therapies and vaccines is needed, as well as broader public health responses that include a combination of education, hygiene and animal husbandry practices to prevent potentially larger future outbreaks.

Conclusion-

A different pattern of NiV disease was observed in the Malaysia-Singapore and Indo-Bangladesh outbreaks. In Malaysia and Singapore, NiV has been transmitted from pigs to humans, while in Bangladesh, cultural practices of consuming date palm sap contaminated by infected bats have led to repeated outbreaks. In India, due to the spread of the virus from Bangladesh, an outbreak has been observed in the West Bengal region, which borders Bangladesh. The outbreak in Kerala, India, began when people came into direct contact with bats and subsequently became hospital-acquired. The authors conclude that environmental factors play a crucial role in the occurrence of zoonotic diseases in humans. Climate changes due to factors such as drought or floods, deforestation, urbanization, large-scale industrialization lead to the destruction of animal habitats, leading to starvation and low immunity, increasing the viral load in their bodies, excreted in the bats' secretions and thus infecting the fruits, animals or people who come into contact with it. Therefore, it is necessary to adopt the “One Health” approach by considering human, animal and environmental health in the same context to combat this particular disease. Outbreaks of NiV in Malaysia and Singapore in 1999 ended in mass culling of pigs and have not recurred, while India and Bangladesh have had multiple outbreaks since 2001.

The reasons for the multiple outbreaks may vary, but the low capacity of the healthcare system and the lack of a solid surveillance strategy are major contributors. The interdisciplinary and multisectoral approach is crucial to prevent the occurrence of NiV. Besides these aspects, there is a need to conduct rigorous research for development of vaccines and drugs for the prevention and treatment of nipah virus.

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