



## An Overview: Nipah Virus Infection and Its Outbreak

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### ABSTRACT

Nipah virus illness is an emerging disease of public importance in South East region. The virus belongs to Henpa virus in the sub family paramyxovirinae. The first outbreaks were observed in Malaysia with the mortality rate of 40%, later the outbreak occurred in Bangladesh and India. Fruit bats and pigs were the reservoirs of the virus. The virus is transmitted through the ingestion of date palm sap and also by the half eaten fruits of animals. Encephalitis is the most common clinical presentation seen. The main diagnostic technique is Reverse Transcriptase Polymerase Chain Reaction. Symptomatic treatments are only available. Ribavirin can be used for the patients, since it can be used for DNA and RNA virus. Development of vaccine is at an infant stage; only animal studies have been done. Protective measures need to be taken.

**Keywords:** Nipah virus, Fruit bat, Encephalitis, Ribavirin.

### INTRODUCTION

Nipah virus (NiV) is an emerging infectious disease that gained public importance in the South East Asia region. The infection caused a considerable mortality in various regions like India, Malaysia and Bangladesh and Singapore.

#### The virus

The virus is named after the Malaysian village where it was first discovered. The virus along with *Hendra* virus comprises a new genus named as *Henpavirus* in the sub family *Paramexovirae*.

#### Reservoir of virus

Fruit bats of the genus *Pteropus* have been identified as the natural reservoirs of NIV. There are four bat species *Pteropus hypomelanus*, *Pteropus vampirus*, *Cynopterus brachyotes* and *Eonycteris spelaea*. Apart from this an insectivorous bat *Scotophilus kuhili* is also a reservoir. Nipah virus has been isolated from the brain and spinal fluid of victims in Malaysia. Infective virus has also been isolated from environmental samples of bat urine and partially eaten fruits in Malaysia. The bats are migratory. This has generated an intensive surveillance in the affected countries. Evidence of NiV has been demonstrated in *Pteropus giganteus* in Bangladesh. NIV have been isolated from *Lyle's* flying fox in Cambodia and viral RNA found in the urine and saliva in the *Pteropus Lylei* and *horse fields round leaf bat* in Thailand. Antibodies to a NIV have been found in sera from the fruit bats collected in India and Indonesia. The status of NIV infection in other countries is not known. Antibodies of *Henpia virus* have also been found fruit bats of Madagascar and Ghana indicating a wide geographic distribution of the virus.<sup>1</sup>



Figure 1: Reservoir bat and Nipah virus

### OUTBREAKS OF NiV

#### In Malaysia and Singapore

An outbreak of a previously unrecognized *Paramyxovirus* infection that caused and encephalitis syndrome mainly among pig handlers occurred in Malaysia and Singapore in late 1998 and early 1999. In Malaysia the outbreak was started in pig farm in Ipoh in the state of Parak and was spread by the movement of sick pigs to a second place about 160 miles south to the state of Niger Zebulon.<sup>2</sup> Later the infection spread to Singapore center from the pigs migrating from Niger Zebulon, 105 deaths among 205 cases of encephalitis with the mortality rate of 40%. Most patients are presented with severe acute encephalitis syndrome, but some also had severe pulmonary manifestation. A syncytium forming virus was isolated from the cerebrospinal fluid of several patients. Electron microscopic studies revealed an enveloped virus with filamentous nucleocapsids which when negatively stained showed a honing bone structure characteristic of the family *paramyxoviridae*. Reactivity of the infected culture cell and tissues from the fatal cases with anti *Hendra* antibodies by immuno-fluorescence and immuno-histochemical techniques as well as detection of anti

Hendra IgM in the serum and in the cerebro spinal fluid suggested the possibilities of Hendra or Hendra like viral infection. Preliminary autopsy showed that central nervous system was the major target. Viral genome sequence revealed sheet previously unknown virus was discovered, but it distinct from hendra virus. The virus was subsequently named as *Nipah virus* after kemburg Singa Niph where the first viral isolates were obtained.<sup>3</sup>

### In Bangladesh

Nipah virus was isolated from Malaysia (NiV-MY) and Bangladesh (NiV-BD) each cause human disease characterized by febrile encephalitis and high fatality ratio, but they present different epidemiological features. Person to person transmission is an important pathway for NiV-BD infection of the people, while NiV-MY infected through domestic pigs. It has been found that a greater prevalence of and severity of respiratory disease signs were found in people infected with NiV-BD may facilitate person to person transmission by this strain and exposure to respiratory secretion from patients is reported to be a major risk factor for the transmission of NiV-BD. NiV-MY has also been isolated from respiratory secretion and so the factors responsible for different strain rates have been poorly understood.

In particular viral transmission occurs within a social and environmental framework which includes co-morbidities like malnutrition and pre existing respiratory disease or exposure to factors like patient care and interaction between patients and at risk individuals, each of these may play an important role in differentiating NiV transmission rate.<sup>4</sup> Outbreaks of encephalitis in Merherpur, Bangladesh occurred in 2001 was not investigated until 2003, when another cluster of febrile diseases with neurological features 8 reported deaths have occurred on the adjoining village of Naogaon district about 150 km

from the village in Merherpur district .similarities in the clinical manifestation were observed in patients in Naogaon and Merherpur raised question whether the outbreaks were caused by the same agent.

### In India

During January and February 2001 and outbreaks of febrile illness associated with altered sensorium was observed in Siliguri and West Bengal. Laboratory investigation at the urine of outbreaks did not identify any known infectious agent. A detailed retrospective investigation in the first two villages in Bangladesh was conducted in March 2003 to characterize their clinical feature and determine the etiological agent, presence of any asymptomatic infection, risk factors for infection and disease health care workers and possible animal reservoir. Samples were sent to Centers for Disease Control and prevention (CDC), tested with an immunoglobulin-M (IgM), immunoassay (EIA) for the detection of IgM antibody and interact EIA for Nipah /Hendra IgM antibodies along Nipah (Malaysian proto type) virus antigen.

Antibodies reactive with Nipah virus antigen were found in seriously ill patients with encephalitis, but absent in asymptomatic or those with serious illness. Because Siliguri is in close proximity Bangladesh where outbreaks of Nipah virus infection had been described, clinical samples obtained during Nipah virus outbreaks were subsequently, retrospectively analyzed and was found positive for NiV infection in half of them. Many of them epidemiological outbreaks in Siliguri were similar to the NiV outbreaks in Bangladesh.<sup>5</sup> Unlike in Malaysia and Singapore pigs were not involved as an intermediary host. Bangladesh is a predominant Muslim country with no pig farming available, while in West Bengal, India there are pig farms, it is not the same scale as in Malaysia.

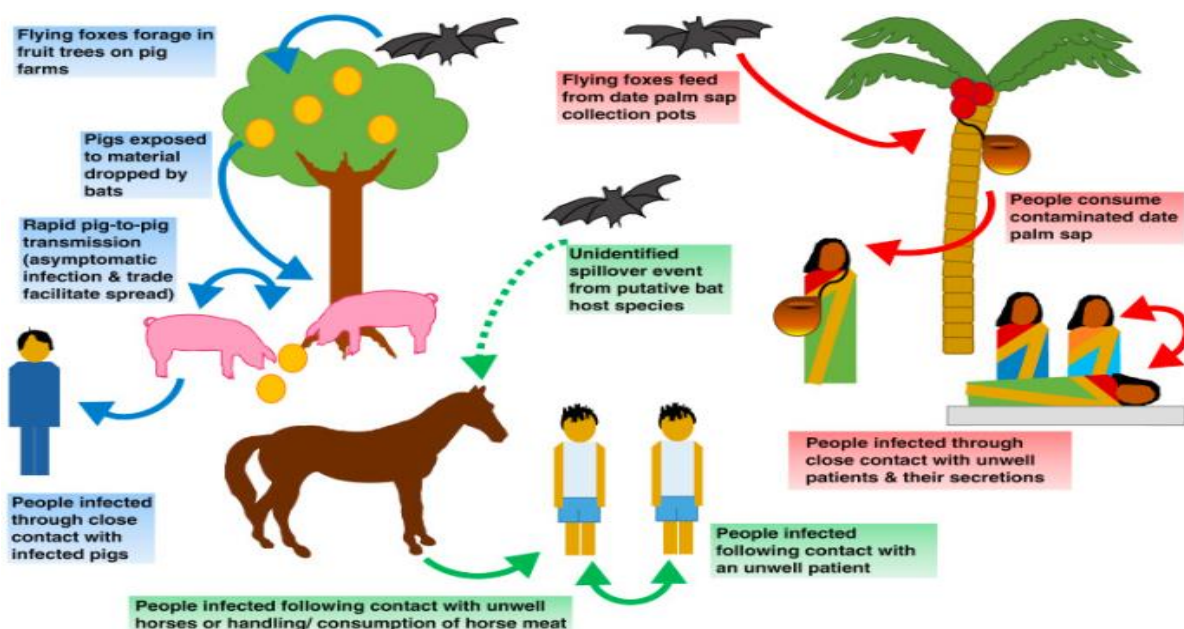


Figure 2: Transmission of Nipah virus

Transmission of NiV acquisition has been by different routes. In Bengali culture sap harvested from date palm is used for fresh consumption or fermented into alcoholic drinks. A tap section of the date palm tree bark is shaved allowing the sap to ooze overnight into collection pots attached to the tree. A previous NiV study reported that *Pteropus* bats frequently feed on the shaved barks and often contaminate a sap with saliva, urine and excreta and investigations of NiV outbreaks in Bangladesh have identified consumption of fresh date palm sap as the primary route of bat to human transmission. Other risk factor included climbing trees (probably infected with palm sap) and contact with sick animals. Fruit bats drop partially eaten saliva laden fruits which are then eaten by domestic animal as their feed. NiV outbreaks have continued occur in Bangladesh and India on annual basis.

In Kerala, the first outbreak of NiV was detected when three members of the family, two brothers aged 26 to 28 and aunt aged 50 died at Kozhikode dist. they died with the signs of viral encephalitis. Laboratory testing using blood and fluid samples of the patient revealed that their death as due to NiV encephalitis. After that the father of the two siblings has also died and thus four members of the family died. This begins the index case. Since the incubation period of NiV varies from 4 to 14 days. It is difficult to determine the index case.<sup>6</sup>The early genetic analysis seemed to indicate the outbreak was caused by a virus which is closely related to NiV-BD strain. Up to now there are seventeen confirmed cases with fourteen deaths with a mortality rate of about 80% about thirty-one species of bats have been documented in Kerala, including five species of fruit bats. The recent reports stats that twenty one samples of bats and pigs from the affected area where tested for NiV should be interpreted with caution and regards to exposed virus. The bats tested were insectivore's bats.

### Microbiology and strains of NiV

Nipah virus is a member of the genus *Henipa virus* and in the family of *Paramyxoviridae*. The genus includes *Sendra virus* and *Sedar virus* but apparently non pathogenic virus was found in Australian bats and additional uncharacteristic was found in various locations. There seems to be multiple strains of Nipah virus. At least two major strains have been isolated from the pigs in Malaysia and the strains that cause human cases in Bangladesh and India which differ from the outbreaks strains in Malaysia.<sup>7</sup>A Henpa virus that recently caused an outbreak in Philippines is also thought to be Nipah virus based on Reverse Transcriptase-Polymerase Chain Reaction results. It appears to be similar to the viruses isolated from Malaysia.

### Animal models for NiV

Thung Wong et al, proposed animal models for Nipah virus, NiV was isolated from the cerebrospinal fluid of a patient after two passages in viro cells. Virus stock was obtained after third passage on viro cells. After one to two days, viro cells show fusion and syncyte formation. The

supernatant was harvested for virus. Virus stocks was titrated in six well plates by incubating 200µl of serial ten times dilution of supernatant in each well (containing 10<sup>6</sup> viro cells per well) for one hour 37°C. Three sets of animal studies were done using five mice, two guinea pig and hamsters. The virus was inoculated using intra Nasal Route (IN), Intra Peritoneal (IP) route. The animals were host in ventilated containment equipped with HEPA filters and observed for the signs of NiV infection. A second study was done using IV and IP route to determine the lethal dose to kill 50% of hamsters. Tissues specimens of blood, brain, lungs, heart, liver, spinal cord, spleen and kidney were collected from the hamsters which died recently. Tissues were frozen for -60°C for viral culture and analyzed using Reverse Transcriptase-Polymerase Chain Reaction. Then histopathological, electron microscopy and other studies like virus isolation, Nipah antibody testing, light microscopic and immunochemistry were carried out. They found that, no mice were infected by virus using IN and IP routes and there were wide variations of LD<sub>50</sub> between IN and IP routes. Histopathological studies in the tissues in central nervous system showed the development of vasculites characterized by necrosis and intra neural inflammation. There were indications of viral infections of endothelial vessel wall and stomach muscle which is evidence by the presence of endothelial multi nucleate syncyta and detection of viral nucleate antigen and genome of vascular wall. The neurons in the brain were also infected by the presence of neuronal viral inclusions, antigens and genomes. Evidence of extra vascular tissue infections was found in non CNS organ to a lesser extent. In the lungs inflamed areas adjacent to the vasculitic occasional inflammatory cells showed the presence of viral antigen and genomes.<sup>8</sup> In kidney vasculitis and glomerular lesions were found. Viral antigen is present in the renal papilla epithelium.

### Clinicopathological Profile of Nipah Virus Encephalitis.

- Closed contact with the infected pigs was the main mode of transmission to humans. This followed the basis for pig culling that eventually stopped the outbreaks.
- There is a possibility of human to human transmission which resulted in substantial mortality among health care workers.
- The presenting features are fever, head ache, dizziness, and vomiting.
- About 50% of patients had reduced consciousness and brain stem dysfunctions.
- Other clinical features are segmental myoclonus, hypotonic, hypotension, Tachy cardia, suggesting of brain stem, upper cervical cord involvement and atypical pneumonia.
- Autopsies of the Malaysian outbreaks victims showed the presence of NiV. The NiV targets medium and





small sized blood vessels resulting in endothelial multi nucleated syncytia and fibroid necrosis.

- The presence of cerebro spinal fluid virus specific IgM showed the presence of increased inflammatory activity. But it does not have a protective effect on illness.
- The symptoms appear from 4days to 2months.<sup>9</sup>
- The mortality rates were about 40%. The main duration of illness from onset of symptoms to death is 16days.

### Pathogenesis of NiV

NiV targets the vascular neurons and lympho reticular systems. It enters through the oro nasal cavity and infects that epithelial cells, immune cells and peripheral nerve endings of the cranial nerves. After then it directly enters into the brain through nerves causing neurological symptoms. The virus also targets the endothelial cells of the small vessels as well as immune cells leading to white spread dissemination. Viremia results out of increased viral load in tissue parenchyma including the central nervous systems and lower respiratory tract.<sup>10</sup>NiV infects monocytes and T- lymphocytes and NiV antigens were found in macrophages and dendrite cells.



**Figure 3:** Pathogenesis of Nipah virus

### Human to Human Transmission

In the Malaysian outbreaks reports of person to person transmission in the affected index cases have come. In a study with three hospitals that had linked 80% of encephalitis patients, there were no reports of serious illness, encephalitis or hospital admission among the patients. However three nurses who had cared for the outbreaks related patients when their second blood samples were tested, positive for Nipah virus IgG antibodies. It was concluded as false positive because they had no symptoms of encephalitis and blood samples showed no IgM response and were negative for anti Nipah virus neutralizing antibodies. One staff nurse who had MRI changes similar to those was seen in acute MRI. Since she had cared for infective patients and but had no contact with pigs, it is likely she had an asymptomatic or mild NiV infection.

This situation was very different in Bangladesh and India where several outbreaks have come from person to person

transmission. About half of the cases identify in Bangladesh between 2001 and 2007 involved human to human transmission. The clearest illustration of person to person transmission occurred being the Faradpur in 2004 where the chain of transmission eventually involved five generation and affected 14 people.<sup>11</sup>

### Clinical Presentation

Encephalitis is the most important competition of Nipah virus which is associated with high mortality rate. Even though the incubation period is 4-14 days there are reports of incubation period as long as 45 days. The patients present with sudden onset non specific flu like or febrile illness sometimes with gastro intestinal symptoms. Pneumonia and other respiratory manifestation were described but their onset is variable. Many patients have been reported meningitis apart from encephalitis which developed 3-14 days after initial illness. Cerebro spinal fluid abnormalities are similar as those seen in other acute viral central nervous system infections. Magnetic resonance imaging of the brain may reveal multiple small sub cortical and deep white matter lesions without surrounding edema, these abnormalities may be seen in other CNS infections. Rapid progression to critical illness occurred in 60% of the patients.<sup>12</sup> Mortality has also varied between the outbreaks, which is high overall (40-70%). Neurological sequelae may occur in survivors including relaxing encephalitis with delayed reactivation of latent virus infections.

### Patient Assessment

Nipah virus is classified as an air born High Consequence Infectious Disease (HCID) in England and clinical assessment should be performed by specialist hospital staff with adherence to strict infection prevention and clinical precaution to prevent secondary transmission. There are currently no agreed case criteria for Nipah virus infections.<sup>13</sup> The Nipah virus patients should be consider with an exposure history with presence if compatible illness with its onset in 14 days after exposure. Nipah virus is a rare disease and other travel associated common infection should also be considered.

### Laboratory Diagnosis

The main diagnostic technique is reverse transcriptase polymerase chain reaction. Serology for Nipah virus is not available. Any suspected case should be discussed with local infection specialist. The specialist will decide the laboratory test in need and will decide about the type of sample required and will advisable the sample collection precaution and transport requirements.

### Neuro Radiology Findings

The MRI scans of the Malaysian out breaks resulted in the invasive involvement of the cortex, temporal lobe, pones. Patients who had relapaced are had late onset encephalitis were found with multiple areas of patchy and confluent cortical involvement. In patients of Singapore outbreaks MRI scan was different with multiple, small (<1cm)

bilateral abnormalities within the sub cortical and deep white matter and some lesions were found out after contrast media injection. Other areas involved are cerebral cortex; brain stem and corpus callosum. Most of the lesions were detected by Diffusion Weighted (DW) MRI, a pulse sequence that is used to detect ischemic stroke and cerebral infraction. This pattern of tiny DW abnormalities followed by T<sub>1</sub> hyper intensities was distinctly different from the characteristic feature of Herpes virus and Japanese encephalitis and may contribute with the virus associated micro angiopathy and subsequent ischemic micro infraction.

In a follow up study involving Singaporean patients it was found the disappearance of lesions overtime and no MRI

evidence of relapse but multiple transient T<sub>1</sub> weighed hyper intensities in the cerebral cortex, similar in appearance to laminar cortical necrosis among group of zero positive abattoir workers who were exposed to infection but symptomatic, delayed MRI produced discrete small lesions in the brain, similar to those detected in patients with symptomatic encephalitis.<sup>14</sup> The difference between Malaysian and Singaporean cases may be due to the active surveillance of at risk patients. In Singapore cases have come much sooner its exposure and at a much earlier stage of the disease. Fewer patients had MRI in the Bangladesh and India outbreaks. But MRI also shows multi focal and confluent lesions in both white matter and cortex.

### Clinical Presentation and Outcome of NIV Infection

**Table 1:** Clinical presentation and outcome of NIV infection<sup>15</sup>

S.no	Feature or outcome	Malaysia and Singapore	Bangladesh and India
1	Age and exposure	Mainly adult pig farm workers.	Adult, children and health care workers.
2	Spread	Bat to pig, pig to human.	Direct bat to human beings by the consumption of date palm juice and fruits contaminated by bats.
3	Transmission	Human to human occasional.	Human to human spread.
4	Respiratory involvement	Malaysian cases 14-29%, two out of eleven patients in Singapore.	Cough 62%, respiratory difficulties 69%, chest x-ray with acute respiratory difficulty in some patients.
5	Encephalitis	Segmental myoclonus seen in 32-54% cases.	Segmental myoclonus not reported.
6	MRI	Disseminated, small, high signal intensity lesions.	Confluent high signal brain lesions in limited MRI.
7	Relapsed and late onset encephalitis.	About 5-10%	Delayed and neurological abnormalities in four out of twenty two patients in a follow up study.
8	Persistent morphological defects.	About 20%	About 32%
9	Mortality	32-41%	70%

### Morbidity and Mortality of NIV in Different Region

**Table 2:** Morbidity and mortality of NiV in different region, 1998-2014<sup>16</sup>

Year/Month	Region / Country	No.Cases	No. Deaths	Case Fatality
Sep 1998 - Apr 1999	Malaysia	265	105	40%
Mar 1999	Singapore	11	1	9%
Jan -Feb 2001	Siliquri (India)	66	45	68%
Apr-May 2001	Megerpur (Bangladesh)	13	9	69%
Jan-2003	Nagogaon (Bangladesh)	12	8	67%
Jan- 2004	Faridpur (Bangladesh)	36	27	75%
Jan-Mar 2005	Tangail (Bangladesh)	12	11	92%
Jan - Feb 2007	Thakurgan (Bangladesh)	7	3	43%
Mar 2007	Kustia,Pabna,Natore(Bangladesh)	8	5	63%
Apr-2007	Nagogaon (Bangladesh)	3	1	33%
Apr-2007	Nadia (India)	5	5	100%
Feb-2008	Manikonj (Bangladesh)	4	4	100%
Apr -2008	Rajbariand Faridpur (Bangladesh)	7	5	71%
Jan -2009	Rajbari (Bangladesh)	1	1	100%
Feb- Mar 2010	Faridpur, Rajbari, Madripurand Gopalganj (Bangladesh)	16	14	87.50%
Jan-Feb 2011	Lalmohirhat, Dinajpur, Comila, Nilphamai And Rangpur (Bangladesh)	44	40	91%
Feb - 2012	Joypurhat, Rajbari and Gopalganj (Bangladesh)	12	10	83%
Mar-May 2014	Philippines	17	9	53%
<b>Total</b>		<b>280</b>	<b>211</b>	<b>75%</b>



## DIAGNOSIS

### Tests to detect nucleic acids, virus or antigens

For a definitive diagnosis virus isolation need to be perform in an area of newly suspected outbreaks. NiV detected in oropharyngeal and nasal swaps within two days post infection from experimentally infected animals continue to shed virus until three weeks post infection. Monkey kidney or rabbit kidney cell lines are used for virus isolation. Quarantine Real Time PCR primers and probes have been developed for nucleocapsid proteins of NiV. Primers for conventional PCR and sequencing of the matrix gene have been described. Specific Quarantine Real Time PCR primers and probes for the N- gene of b-NiV, m-NiV has been described.

Immuno Histo Chemistry can perform to detect NIV. The N-protein antigen is commonly targeted. Detection of phospho- protein (P) antigen can also be used with Immuno Histo Chemistry, although N-protein antigen is expressed in greater quantities than P-protein antigen and is therefore a better diagnostic value. Immune fluorescence and rapidly detect NiV but cannot differentiate between Henpa virus, since mono specific anti sera to detect individual proteins of NiV will cross react Henpa virus.<sup>17</sup> Negative contrast electron microscopy can be used to identify viral particles. Two monoclonal antibodies with affinity for N-protein or P, Vi and W- protein of Henpa virus have been developed.

### Tests to detect antibody

- An indirect Enzyme Linked Immuno Sorbent Assay (ELISA) using recombinant NiV N-protein has been described for use as a diagnostic test.
- Virus neutralization test have been described for high through screening.
- Multiplex microsphere have been developed to detect either antibody binding to recombinant soluble NiV or HeV G-protein or antibody inhibition of Ephrin B2 receptor binding.

## TREATMENT

Treatment is largely supporting consisting of the use of anticonvulsant, treatment of secondary infections, mechanical ventilation and rehabilitation. The empiric treatment may be started with Ribavirin, which is having a broad spectrum of activity against DNA and RNA virus.<sup>18</sup>

### Development of Vaccine

By nature paramyxovirus can infect both human and animals. The virus generally can infect one species severely and grow poorly in the second. Thus a virus which grows poorly in humans can be used to create vaccines.<sup>19</sup> By the use of modern biotechnology the antigen of the virus that is a human pathogen can be expressed from an equivalent animal virus in order to induce protective response. Vaccines for paramyxovirus, including NIV is under trial using Hamster model.<sup>20</sup>

### Advise for Travelers to Endemic Areas

- Those travelling in the areas of active outbreak should avoid contact with bats and environment and sick animals.
- Consumption of raw or fermented date palm sap should be avoided.
- Wash the fruits with clean water.
- Avoid fruits eaten by animals.

### Prevention of NIV Infection



Figure 5: Prevention of NIV infection

At present there is no vaccine available for NiV infection. Prevention is the key step to stop the spread of infection and be safe from the virus source. Some of the preventive measures are,

- Since fruit bats are the primary causes of NiV infection people who have domestic animals or have farm animals should prevent the animals from eating fruits contaminated by the bat.
- Consumption of contaminated date palm sap including toddy should be avoided.
- Physical barriers can be erected in order to prevent fruit bats from accessing and contaminating palm sap.
- People raising pigs can consider putting wire screens to prevent contact between fruit bats and pigs, if the pigs are raised in open sheds.
- Care takers are needed to quickly recognize the symptoms of infection in animals so that the infected animal can be isolated and the outbreaks of infection can be prevented.
- Avoiding any form of direct contact with infected fruit bats and humans are essential. Health professionals like nurses, doctors who are treating infected person should take preventive measures.
- Hospitals must take necessary sanitation procedure while treating NiV patients to avoid transmission of virus to other human being.
- Don't climb to the trees that is suspected to have fruit bat secretion.
- The primary carrier of NiV to the human being is respiratory secretion. There are changes of getting contaminated if you inbreath and outbreath the risk is

higher to the person showing respiratory symptoms like coughing and sneezing.<sup>21</sup> Avoid sharing cloths, foods, beds, wash room from the patients. Avoid staying close together.

- Fruit bates are to be avoided to prevent nesting near to our house.

## CONCLUSION

Nipah virus is a life threatening air born disease causing considerable morbidity and mortality. Until now only symptomatic treatment is available. Some broad spectrum anti-viral drugs may be useful. Hence strict preventive measures are needed. Animals like bat and pigs should be avoided to settle near human residences. There need to be taken measures to create awareness about these types of viral infections. Public health departments should take appropriate measures to prevent the spread of these infections.

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