Nipah virus outbreak: A comparative study from Southeast Asia
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Background

Nipah Virus is a recently emerging zoonotic virus with disease causing potential in both animals and humans. Nipah virus belongs to the family of paramyxovirida, genus Henipavirus along with Hendra virus. (1) The knowledge of human infection with Henipavirus was limited to a very small number of cases infected with Hendra virus in Australia during 1994-1999 which was responsible for deaths of two humans and seventeen horses. (2) Nipah virus was first identified and isolated in 1999 in Malaysia during an outbreak of febrile illness among pig farmers and people who were in close contacts with pigs. (3) In 2001, Nipah virus was identified as the causative agent of outbreak in Bangladesh. Since then number of outbreaks has been reported in various districts of Bangladesh. (4) In India, a total of three outbreaks of Nipah have been reported, latest being on 19th May 2018, from Kozhikode district of Kerala. (5) With a fatality rate of 58%, Nipah virus is primarily seen to cause encephalitis and severe respiratory distress. Despite of the severe pathogenicity and high pandemic potential there is no specific treatment for Nipah virus encephalitis except for supportive and symptomatic treatment.

Keyword

Nipah Virus, Henipavirus, Zoonotic virus

Aims & Objectives

This review was done to describe outbreaks of Nipah virus with respect to place of origin, transmission, pathogenesis and types of diagnostic test.

Material & Methods

We systematically searched three electronic databases (PubMed, Cochrane and EMBASE) for relevant studies on Nipah virus. Information on the recent outbreak was collected through news reports till July 2018.

Chronology of outbreaks: The outbreak was first noticed in 1998 when more than 265 encephalitis cases were reported in Malaysia, including 105 deaths and 11 cases of encephalitis with one death had been reported in Singapore. (6) The first epicenter of the outbreak was the pig farms in the suburbs of Ipoh, Malaysia. Around 27 cases with 15
fatalities were reported. (7) From Ipoh, the virus spread through infected pigs to the neighboring areas which became the second and severe epicenter of the outbreak with 180 cases and 89 deaths. (8) Due to unrerained selling of pigs, cases also emerged from Sepang and Sungai Buloh in Selangor. (8) Further, 11 cases of Nipah encephalitis emerged in Singapore with one fatality amongst slaughterhouse workers who handled pigs imported from Malaysia. (8)

The second outbreak of Nipah virus encephalitis was reported in 2001 from Meherpur district of Bangladesh with 13 cases and 9 deaths. Since then multiple outbreaks have been reported in various districts of Bangladesh- Naogoan, Rajbari, Faridpur, Tangail, Thakurgaon, Kushtia, Naogaon, Manikgonj, Rangpur, Madaripur, Lalmohirhat, Dinajpur, Comilla, Joypurhat, Rajshahi and Natore. Up to March 31, 2012 a total of 209 human cases of Nipah virus encephalitis were identified in Bangladesh with 161 reported deaths. (4)

India reported two outbreaks in the eastern regions of West Bengal which is bordered by Bangladesh. In 2001, outbreak of febrile illness with neurological symptoms was reported from Siliguri, West Bengal. A total of 66 cases were confirmed for Nipah viral encephalitis out of which 45 succumbed to death. (4) Similarly, in 2007, five cases of Nipah viral encephalitis were reported from Nadia in West Bengal and none of them survived.

The third outbreak was confirmed on 20th May 2018 in Kozhikode, (5) Kerala when four members of a family Mohammad Sahid, his brother Mohammad Saliah, father Moosa and aunt Mariumma residents of Changaroth presented with features of viral encephalitis that were being treated at Perambra Taluk Hospital, succumbed to death. (11) The four deaths occurred in a family cluster and fifth death was subsequently reported in a health care worker who was involved in treatment of the family in the local hospital. This is the first Nipah virus outbreak reported in Kerala State and third outbreak known to have occurred in India.

**Transmission:** The flying foxes of the genus Pteropus are considered as the reservoir of Nipah virus. The virus can be transmitted from bats to pigs which act as the amplification host. The humans can get infected either through direct contact with infected pigs, bats or indirectly through contaminated fruits. It can also spread through close contact with infected person.

During the outbreak in Malaysia, most of the humans were infected either through direct contact with sick pigs or their contaminated tissues.

During the outbreaks in Bangladesh and India, consumption of fruits including raw date palm juice contaminated with urine or saliva from infected fruit bats was the most likely source of infection. Human-to-human transmission of Nipah virus was also documented during the outbreak in Faridpur, Bangladesh. (12)

Regarding the outbreak in Kerala, the bats living in Moosa family’s well were identified as the source of the outbreak by National Institute of Virology. (13) Samples of fruit bats and a rabbit were collected from Perambra, where the first case of Nipah infection was reported. The initial tests conducted at the National Institute of High Security Animal Diseases Laboratory in Bhopal and they came out to be negative. (9) Though bats were suspected to be the main culprits behind Nipah’s spread, experts were divided over this. Epidemiologists were also considering human-to-human transmission as the source of spread of Nipah. (13)

**Pathogenesis of Nipah virus:** The outbreak in Malaysia was primarily associated with severe viral encephalitis while that in Bangladesh and India were associated with respiratory disease. Though the exact route of entry of virus is still debatable, experimental studies have shown that viral infection is efficiently initiated after inhalation of the virus as shown in (Figure 1). Following the entry of the Nipah virus, it starts replicating in the respiratory epithelium. Infection of the respiratory epithelium may progress to acute respiratory distress syndrome. (14)

During the early phase of illness, virus can be detected in bronchiolar epithelial cells that are shed off in nasopharyngeal and tracheal secretions and can act as potential source of infection for human to human transmission. During late phases, the virus may spread from the epithelium to endothelium in the lungs causing vasculitis of small vessels. Nipah virus may enter the blood stream either in free form or by binding to the leucocytes. Apart from the lungs, other majorly affected organs are brain, spleen and kidney.

Entry to the CNS occurs via two pathways either antegradely through the olfactory nerve or...
hematogenous route through choroid plexus and cerebral blood vessels. Infection of the CNS in humans is characterized by vasculitis, thrombosis, parenchymal necrosis and presence of viral inclusion bodies. (14)

Clinical manifestations: Human infection with Nipah virus may range from asymptomatic infection to acute respiratory infection and fatal encephalitis. The incubation period may vary from 4 days to 45 days. (15) The symptomatic cases from Malaysia predominantly presented with neurological symptoms. Like any other viral encephalitis, prodromal symptoms of fever, headache, sore throat, vomiting, myalgia and altered mental state was present. Half of the patients presented with decreased level of consciousness along with signs of brainstem dysfunction i.e. abnormal vestibulo-ocular reflex, pinpoint pupils, hypertension and tachycardia. Seizures occurred in patients with reduced level of consciousness with almost all having generalized tonic-clonic attacks. (15) A few patients from Singapore developed atypical pneumonia. Majority of the clinical features in cases from Bangladesh were similar to that of Malaysia. People presented with fever, headache, altered level of consciousness. (12) In the Kerala outbreak, people presented with moderate to high grade fever, headache, and vomiting, general weakness along with myalgia. Cough and breathlessness often progressed to respiratory failure rapidly. Neurological symptoms included headache altered, sensorium and seizures which progressed to coma in few cases. Few patients also developed myocarditis, pulmonary edema, heart failure often associated with cardiogenic shock.

Diagnosis: The initial signs and symptoms of Nipah virus infection are not very specific; hence it cannot be diagnosed at the time of presentation. The main tests used are real time polymerase chain reaction (RT-PCR) from body fluids and antibody detection by enzyme-linked immunosorbent assays (ELISA). Other tests used include polymerase chain reaction (PCR) assay and virus isolation by cell culture. During the outbreak in Malaysia, the signs and symptoms were confused with Japanese encephalitis as few patients tested positive for JE-specific IgM and JE nucleic acid through RT-PCR. It was the isolation of Nipah virus from CSF of victim by medical virologist at University of Malaya that led to the discovery of a highly fatal viral agent. (16) Later autopsies were performed on outbreak victims which tested positive for Nipah virus and indicating endothelial damage which resulted in systemic vasculitis of small blood vessels, extensive thrombosis, and necrosis. Autopsies also revealed involvement of brain, lungs, heart, kidneys. During the outbreak in Bangladesh, after excluding the diagnosis of Japanese encephalitis, dengue fever, malaria, Bangladesh ministry of health and the World health organization sent 42 serum samples to U.S. Centers for Disease Control and Prevention (CDC). The blood samples were centrifuged on site, transported on wet ice and stored at –20°C. Serum samples were shipped frozen at -70°C to CDC and tested with an immunoglobulin IgM capture enzyme immunoassay (EIA) for detection of Nipah IgM antibodies and an indirect EIA for detecting IgG antibodies. (12) In Siliguri, laboratory tests were done to rule out malaria and other bacterial infections. Serological tests were done at National Institute of Virology to rule Japanese encephalitis, West Nile virus, dengue virus, measles virus, Leptospira species and Hantavirus. Later, serum samples were tested for IgG and IgM antibodies to Nipah virus by enzyme linked immunosorbent assay by Center for Disease Control and Prevention. (17) Laboratory testing of various bodily fluids like urine, blood, throat swabs collected in Kerala from four initially suspected patients was conducted by National Institute of Virology, Pune. Out of four, three reported deaths were confirmed positive for Nipah virus by real-time polymerase chain reaction (RT-PCR) and IgM Elisa for Nipah virus (5) To detect the source of the outbreak, two set of samples of fruit bats were sent from Kozhikode to Bhopal's National Institute of High-Security Animal Diseases (NIHSAD). Tests done on first set of 21 bats came out to be negative, but the tests done on second set of 55 bats was found to be positive for Nipah virus. (9) Fruit bats were the source of Nipah virus according to the Indian Council of Medical Research (ICMR).

Prevention, control and treatment: The outbreak in Malaysia was suspected to be due to Japanese Encephalitis; hence the initial preventive measures taken were health education of pig farmers,
Nipah virus is a rare but dreaded zoonotic virus which has severely infected both animals and humans. It causes mild disease in animals but it severely affects human beings. It was first identified and isolated in 1999 during the outbreak in Malaysia. Since then, it has infected around 574 people out of which 334 have succumbed to death. The main reservoir of Nipah virus is fruit bats of Pteropus species which were the primary source of infection in the outbreaks of Bangladesh and India, while infected pigs were the source of infection in the outbreak which occurred in Malaysia. The cases infected with Nipah virus either present with neurological symptoms like fever, headache, vomiting and altered mental state or respiratory symptoms like cough and breathlessness. The disease quickly progresses to either coma or respiratory failure. Laboratory diagnosis can be made of a patient suffering from infection with Nipah virus by virus isolation or real time polymerase chain reaction (RT-PCR) from throat swabs, nasal swabs, cerebrospinal fluid, urine and blood. Management of virus encephalitis is mainly symptomatic and supportive. Various preventive and control measures were implemented so as to control the spread of Nipah virus which were quite effective. 

Apart from the symptomatic treatment, Ribavirin administration was associated with 36% reduction in mortality and more survivors without neurological deficits. Various strategies were made for prevention of Nipah virus transmission like awareness program, early case detection through different surveillance systems, early case management, infection control measures at the level of household, community, hospital. Prevention and control of Nipah virus transmission depends on controlling the risk factors i.e. ingestion of raw date palm sap and person to person transmission. 

Precautionary methods were taken in India along with symptomatic and supportive management. All meetings scheduled in the Kozhikode and Malappuram were cancelled, Kerala Public Service postponed all exams, locals of the Kozhikode district were asked to stay away from crowds, schools were closed. Health education was provided to be careful while consuming fruits and vegetables which come from that area, avoid drinking palm sap in these places, physical barrier was kept around while rearing animals like piglets, create a physical barrier so that bats cannot enter the place where other animals are kept. 

Nipah virus is a rare but dreaded zoonotic virus which has severely infected both animals and humans. It causes mild disease in animals but it severely affects human beings. It was first identified and isolated in 1999 during the outbreak in Malaysia. Since then, it has infected around 574 people out of which 334 have succumbed to death. The main reservoir of Nipah virus is fruit bats of Pteropus species which were the primary source of infection in the outbreaks of Bangladesh and India, while infected pigs were the source of infection in the outbreak which occurred in Malaysia. The cases infected with Nipah virus either present with neurological symptoms like fever, headache, vomiting and altered mental state or respiratory symptoms like cough and breathlessness. The disease quickly progresses to either coma or respiratory failure. Laboratory diagnosis can be made of a patient suffering from infection with Nipah virus by virus isolation or real time polymerase chain reaction (RT-PCR) from throat swabs, nasal swabs, cerebrospinal fluid, urine and blood. Management of virus encephalitis is mainly symptomatic and supportive. Various preventive and control measures were implemented so as to control the spread of Nipah virus which were quite effective. Drug Ribavirin was shown to be effective against the virus during the outbreak in Malaysia but its clinical usefulness remains in doubt. Currently, research works are being done for preparation of Vaccine against Nipah virus. A neutralizing human monoclonal antibody (m102.4) was found to be protective for African green monkeys from Hendra virus infection. Human clinical trials have begun against Hendra virus using this monoclonal antibody in Australia. 

**Conclusion**

In spite, of being in the top of the list of 10 priority disease that WHO has recognized as potential threats for major outbreaks, there is no curative treatment for Nipah viral infection yet. With a high fatality rate of Nipah virus infection, there is an urgent need for post exposure therapy along with immunization of the susceptible population. Though the researches are being carried, but it needs to be done at a faster pace before another group of population gets infected.

**Recommendation**

At personal level, people in the community should stay away from infected pigs and bats in endemic areas and avoid using raw date palm. Health care providers should be well educated with the signs and symptom of Nipah virus infection for early detection of outbreaks. Proper precautions should be taken while handling a case infected with Nipah virus so as to prevent human to human transmission. Research workers should develop reliable laboratory assays for early detection of the viral infection. Focused surveillance strategies needs to be set up in endemic areas and avoid using raw date palm.
areas to prevent any further outbreaks. In cases of any outbreak, a standard protocol needs to be setup for the treatment and prevention of human to human transmission of the infection in hospital settings. The local governing bodies in the areas of outbreak have an important role to play in preventing the spread of virus to adjacent areas they hence should also have the knowledge about the Nipah virus spread.

**Limitation of the study**

The source of information regarding recent outbreak was news reports which is not an authentic source, but that was the only source of information at the time of outbreak.

**Relevance of the study**

Now we have information about the modes of transmission, pathogenesis of the virus and methods to diagnose Nipah virus infection, this information should be advocated to the community, health care providers and researchers in order to have a better understanding and preparedness for any future outbreaks.

**Authors Contribution**

DS: Substantial contributions to concept, design, acquisition of data; MKV: Drafting the article; PKJ, SK; PK: revising and finalize the manuscript.

**References**


Tables

**TABLE 1 TABLE SHOWING NUMBER OF CASES, DEATHS AND FATALITY RATE OF NIPAH VIRUS INFECTION IN BANGLADESH (4)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>No. Of Cases</th>
<th>No. Of Deaths</th>
<th>Case Fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Meherpur</td>
<td>13</td>
<td>9</td>
<td>69%</td>
</tr>
<tr>
<td>2003</td>
<td>Naogaon</td>
<td>12</td>
<td>8</td>
<td>67%</td>
</tr>
<tr>
<td>2004</td>
<td>Rajbari</td>
<td>31</td>
<td>23</td>
<td>74%</td>
</tr>
<tr>
<td>2004</td>
<td>Faridpur</td>
<td>36</td>
<td>27</td>
<td>75%</td>
</tr>
<tr>
<td>2005</td>
<td>Tangail</td>
<td>12</td>
<td>11</td>
<td>92%</td>
</tr>
<tr>
<td>2007</td>
<td>Thakurgaon</td>
<td>7</td>
<td>3</td>
<td>43%</td>
</tr>
<tr>
<td>2007</td>
<td>Kushtia, Pabna, Natore</td>
<td>8</td>
<td>5</td>
<td>63%</td>
</tr>
<tr>
<td>2007</td>
<td>Naogaon</td>
<td>3</td>
<td>1</td>
<td>33%</td>
</tr>
<tr>
<td>2008</td>
<td>Manikgonj</td>
<td>4</td>
<td>4</td>
<td>100%</td>
</tr>
<tr>
<td>2008</td>
<td>Rajbari And Faridpur</td>
<td>7</td>
<td>5</td>
<td>71%</td>
</tr>
<tr>
<td>2009</td>
<td>Gaibandha, Rangpur And Nilphamari</td>
<td>3</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>2010</td>
<td>Rajbari</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>2010</td>
<td>Faridpur, Rajbari, Gopalganj, Madaripur</td>
<td>16</td>
<td>14</td>
<td>87%</td>
</tr>
<tr>
<td>2011</td>
<td>Lalmohirhat, Dinajpur, Comilla,</td>
<td>44</td>
<td>40</td>
<td>91%</td>
</tr>
<tr>
<td>2012</td>
<td>Joypurhat, Rajshahi, Natore, Rajbari</td>
<td>12</td>
<td>10</td>
<td>83%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>209</td>
<td>161</td>
<td>77%</td>
</tr>
</tbody>
</table>

**TABLE 2 MORTALITY DUE TO NIPAH VIRUS ENCEPHALITIS IN INDIA (10)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>No. Cases</th>
<th>No. Deaths</th>
<th>Case Fatality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Siliguri (West Bengal)</td>
<td>66</td>
<td>45</td>
<td>68%</td>
</tr>
<tr>
<td>2007</td>
<td>Nadia (West Bengal)</td>
<td>5</td>
<td>5</td>
<td>100%</td>
</tr>
<tr>
<td>2018</td>
<td>Kerala</td>
<td>14</td>
<td>12</td>
<td>86%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>85</td>
<td>62</td>
<td>72%</td>
</tr>
</tbody>
</table>

**TABLE 3 SUMMARY OF NO. OF CASES AND DEATHS DUE TO NIPAH VIRUS OUTBREAKS**

<table>
<thead>
<tr>
<th>Outbreak</th>
<th>Location</th>
<th>No. Of Cases</th>
<th>No. Of Deaths</th>
<th>Fatality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Malaysia</td>
<td>265</td>
<td>105</td>
<td>38.4%</td>
</tr>
<tr>
<td></td>
<td>Singapore</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bangladesh</td>
<td>209</td>
<td>161</td>
<td>75.3%</td>
</tr>
<tr>
<td>2nd</td>
<td>India</td>
<td>71</td>
<td>50</td>
<td>85.7%</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>570</td>
<td>329</td>
<td>57.7%</td>
</tr>
</tbody>
</table>

**TABLE 4 SAMPLES AND TECHNIQUES USED TO DETECT NIPAH VIRAL INFECTION**

<table>
<thead>
<tr>
<th></th>
<th>Malaysia</th>
<th>Bangladesh</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples Used</td>
<td>CSF</td>
<td>Blood Samples</td>
<td>Throat Swab, Urine Samples, Blood Samples</td>
</tr>
<tr>
<td>Technique Used</td>
<td>Virus Isolation</td>
<td>Igm EIA &amp; Indirect EIA</td>
<td>RT-PCR &amp; Igm ELISA</td>
</tr>
</tbody>
</table>
**Figures**

**FIGURE 1 TRANSMISSION OF NIPAH VIRUS**

- FRUIT BATS (Reservoir) ➔ Indirect transmission from date palm sap ➔ HUMAN ➔ HEALTH CARE WORKERS (Secondary transmission) ➔ PIGS (Amplification host)

**FIGURE 2 PATHOGENESIS OF NIPAH VIRUS INFECTION**

- Entry of nipa virus via inhalational route ➔ Major organs affected: spleen, kidney ➔ Hematogenous spread of the virus in free or bound form ➔ Multiorgan failure

- Replication of nipa virus in the respiratory epithelium ➔ Virus shed off in nasopharyngeal and tracheal secretions ➔ Transmission of virus via droplet infection

- Recruitment of immune cells leading to acute respiratory distress syndrome ➔ Nipah virus transmission to brain antegradely through olfactory nerve and hematogenous route ➔ Vasculitis, thrombosis, parenchymal necrosis

**FIGURE 3 CLINICAL FEATURES OF NIPAH VIRUS INFECTION**

- Seizures, coma
- Abnormal vestibulo-ocular reflex
- Pronounced papilloedema
- Pulmonary oedema
- Tachycardia, hypertension, heart failure
- Fever
- Headache
- Sore throat
- Breathlessness
- Vomiting
- Myalgia