Emerging Trends in the Transmission Pathways of Nipah virus: A Comprehensive Review

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ABSTRACT

Nipah virus (NiV), a highly pathogenic zoonotic virus belonging to the Paramyxoviridae family and Henipavirus genus, was first identified during an outbreak in Malaysia in 1998-1999 and has since been reported in South and Southeast Asia, primarily in Bangladesh and India. The virus is transmitted through zoonotic spillover from animal reservoirs, particularly fruit bats (Pteropus species), as well as human-to-human transmission. Pigs can become infected by consuming fruits contaminated by infected bats, and humans can contract the virus through contact with infected pigs or bats. This review provides a comprehensive overview of the transmission dynamics of Nipah virus, emphasizing zoonotic spillover, direct contact with infected animals, and human-to-human transmission during outbreaks. Understanding these transmission pathways is essential for developing effective control and prevention strategies. NiV outbreaks have occurred in Malaysia, Singapore, Bangladesh, India, and the Philippines, often resulting in severe respiratory and neurological diseases with high mortality rates in both humans and pigs. Diagnosis of Nipah virus infection involves various techniques, including serological, molecular, virological, and immunohistochemistry methods. The potential for human-to-human transmission poses a significant public health concern, highlighting the need for improved diagnostic and surveillance measures..

INTRODUCTION

Nipah virus is a bat borne paramyxo-virus that is found throughout south asia and southeast asia(14).Nipah virus (NiV) poses a significant public health threat due to its high fatality rate and potential for human- to-human transmission. Nipah virus (NiV) is widely prevalent zoonotic virus with high mortality rate , genus Henipavirus of the Paramyxoviridae family(1). It is spherical enveloped, single-stranded, negative-sense RNA virus with a size of approxmately 150nm and full genome length of appromately 18.2 Kb. In Malaysia during 1998's NiV was first identified in pigs and infections by this virus have been discovered in recent years. In 2018, the World Health Organization placed Nipah virus disease (NVD) on restricted list of diseases that poses a serious threat to public health(2). The disease bio-geography of NiV is critical to comprehending the potential geographic distribution of this dangerous zoonosis.NiV infected pigs developed a unique clinical condition called "Barking pig syndrome.(7) . NiV is a serious disease that often kills people infected and because it can be transmitted from person to person there is some risk that, during human infection, the virus could evolve to become more easily transmissible from person-to-person, increasing the risk of a pandemic(10).

Most zoonotic viruses have shared characteristics, such as being single-stranded RNA (ssRNA) viruses, and causing mild or asymptomatic infections in its natural host animal, while provoking profound pathologist in humans (13). NiV can cause fever, headache, respiratory distress, and encephalitis, which kills in days(16). It is an emerging virus that can cause severe respiratory illness and deadly encephalitis in humans. This review aims to explore the transmission pathways, clinical manifestations, risk factors, and current preventive and diagnostic measures for Nipah virus infection.

METHODOLOGY

This review synthesizes information from various studies and reports on Nipah virus, focusing on epidemiological data, transmission pathways, clinical outcomes, and control strategies. Sources include peer-reviewed journal articles, outbreak reports, and data from the World Health Organization (WHO). The review also examines diagnostic techniques such as polymerase chain reaction (PCR), serological assays, and immunohistochemistry methods, along with current research into vaccines and therapeutics for NiV.

RESULT AND DISCUSSION

The results and discussion of this review focus on a deeper understanding of the transmission, clinical manifestations, risk factors, and preventive measures associated with Nipah virus (NiV) infection.

Structure of Nipah Virus

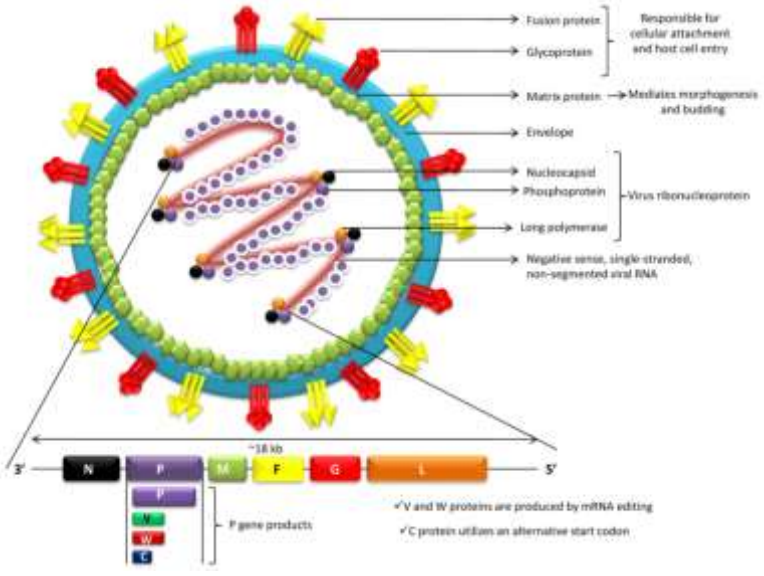

Figure 1. Structure of Nipah virus (3).

It is a negative sense , single -stranded non segmented, enveloped RNA virus possessing helical symmetry. The RNA genome, from the 3' -5' contains consecutive arrangement of six genes, nucleocapsid (N), phosphoprotein (P), matrix (M) , fusion glycoprotein (F), attached glycoprotein (G) and long polymerase (L).The N,P and L attached to the viral RNA forming the virus ribonucleoprotein (vRNP). F and G protein are responsible for cellular attachment of the virion and subsequent host cell entry. The M protein mediates morphogenesis and budding. Antibody to the G protein is essential for neutralization of the NiV infectivity. The fusion (F)(class I) and attachment (G) glycoprotein the target cell i .e host cell is entered upon after binding by the Henipaviruses including NiV.

NiV infects its host cell in two glycoprotein - G and F protein. The G glycoprotein mediates attachment to host cell surface receptors and the fusion (F) protein makes fusion of virus- cell membranes for cellular entry(3).

The clinical signs and symptoms of the NiV disease include fever along with laboured breathing, cough and headache.(3). NiV infection is an emerging zoonosis that causes severe disease in both animals and humans(9). Pig-to-Pig and Pig- to- human transmission thought to form direct contact with pigs excretion including Urine, saliva, pharyngeal and tracheal secretion, except for two cases of transmission from infection dogs(11). NiV has a wide host range, multiple routes of transmission , strong transmissibility and high mortality.

Zoonotic Transmission

In pigs infected with NiV, shortness of breath progresses to respiratory distress accompanied by involuntary coughing(2). Zoonotic transmission of Hendra virus in Australia and Nipah Virus in Malaysia and the Philippines occurred through an amplifying host, pigs and horses, where zoonotic transmission in Bangladesh is through out to occur directly from bats to humans mainly through the consumption of raw date contaminated with Nipah virus by fruit bats(5).

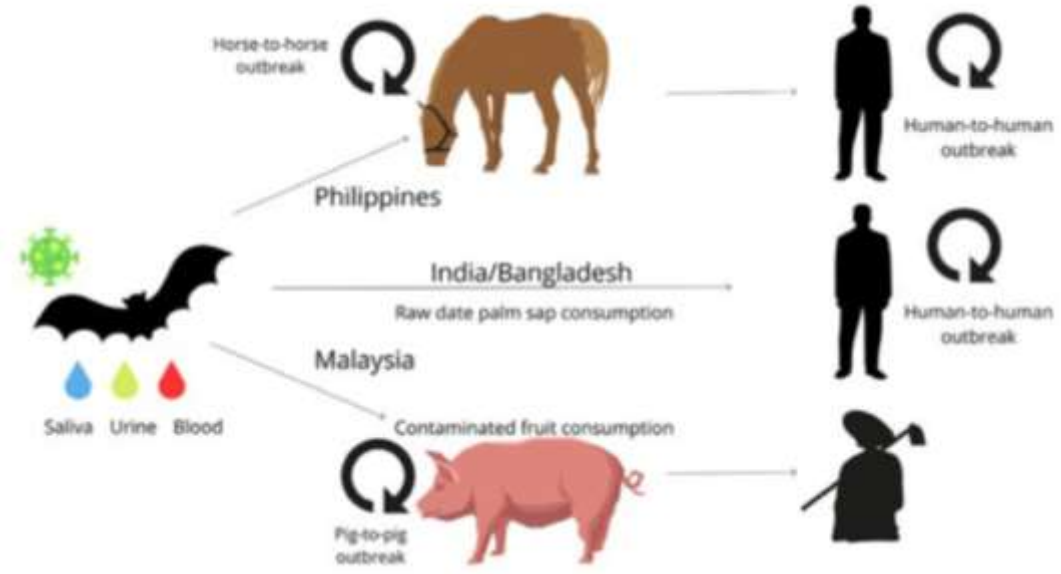

Figure 2. Representation of the Zoonotic NiV cycle (28)

Fruit Bat Reservoirs

Fruit bats of the Pteropus genus (family Pteropodidae) are the natural hosts of NiV(6).Fruits bats are the major reserviors of the virus and it is the contact with such bats infected or intermediate hosts like pigs which are responsible for infection in man. Fruits bats acts as natural reservior of Nipah viruses and among various outbreaks documented from the different geographical parts of the globe these bats have been associated in one or other way for transmission of the virus and associated infected(3).The natural reservoir for NiV is Old World fruit bats of the genus Pteropus, which are found in eastern Africa and throughout Asia, Australia, and the Pacific islands(8).Pteropus fruit bat saliva, urine, and feces disseminate NiV to local plants and fruit trees. Direct contact with diseased bats or their excreta or eating contaminated fruits or date palm sap causes most human diseases, Hospital personnel and the community are at risk from transmission.[16]

Figure 3 Geographic distribution of Henipavirus outbreaks and fruit bats of the Pteropodidae family. Megabats represent NiV reserviors in endemic geographical areas of southeast asia and Sub-Saharan Africa. Fig 3 (23).

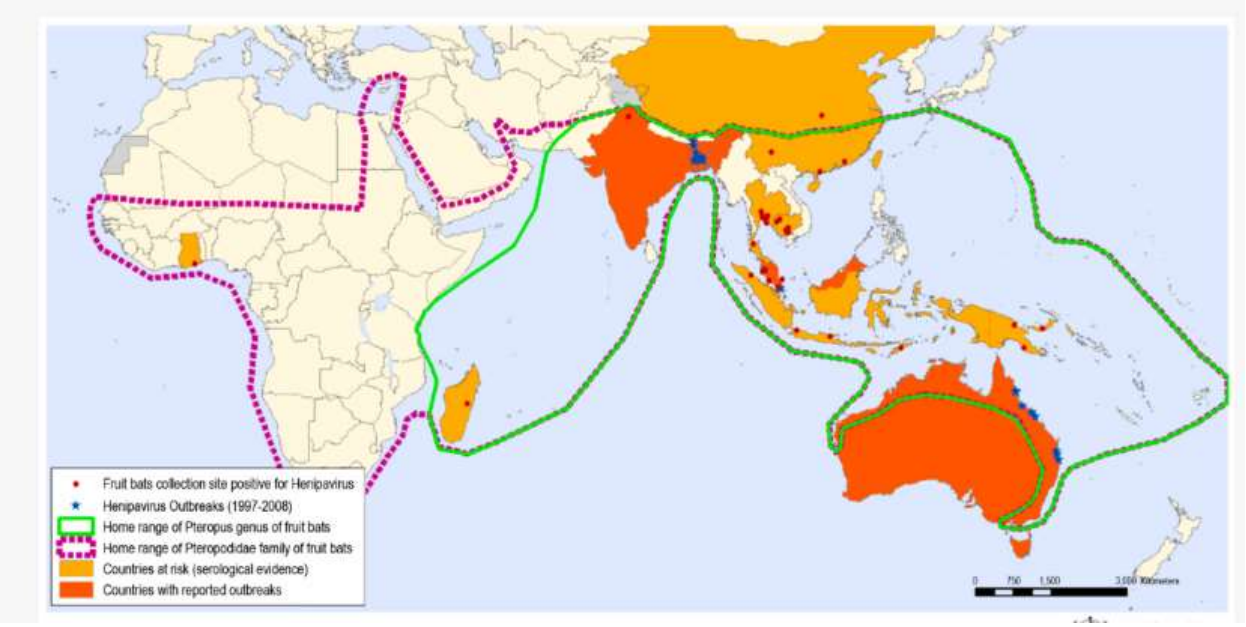

Figure 3. Geographic distribution of Henipavirus outbreaks and fruit bats of the Pteropodidae family.

Fig 2 shows countries at risk of outbreaks based on collection of positive serological specimens from fruit bats (Orange) and countries with reported outbreaks (Red). violet spot indicate collection sites of fruit bats that resulted positive for Henipavirus while blue stars indicate site where Henipavirus outbreaks occurred between 1997 and 2008. Area indicating the home range of Pteropus genus of fruit bats (Green solid contour) and Pteropodidae family of fruit bats (Violet dotted contour)(23).

Transmission of the Nipah virus. 1. Fruit bats act as natural reservoirs of Nipah viruses. Fruit bats with NiV feed on date palm sap. Virus can survive in solutions which are rich in sugar, viz., fruit pulp. 2. Virus transmitted to human through the consumption of date palm sap. 3. Fruit bats of Pteropus spp. which are NiV reservoirs visited such fruit trees and got an opportunity to naturally spill the drop containing virus in the farm to contaminate the farm soil and fruits. 4. Contaminated fruits are consumed by pigs and other animals. Pigs act as intermediate as well as amplifying host. Combining close surroundings of fruiting trees, fruits-like date palm, fruit bats, pigs, and human altogether form the basis of emergence and spread of new deadly zoonotic virus infection like Nipah. 5. Pork meat infected with NiV are exported to other parts. 6. Consumption of infected pork can act as a source of infection to human. 7. A person affected by the NiV disease is likely to spread the virus from a close contact he makes with an affected human being.

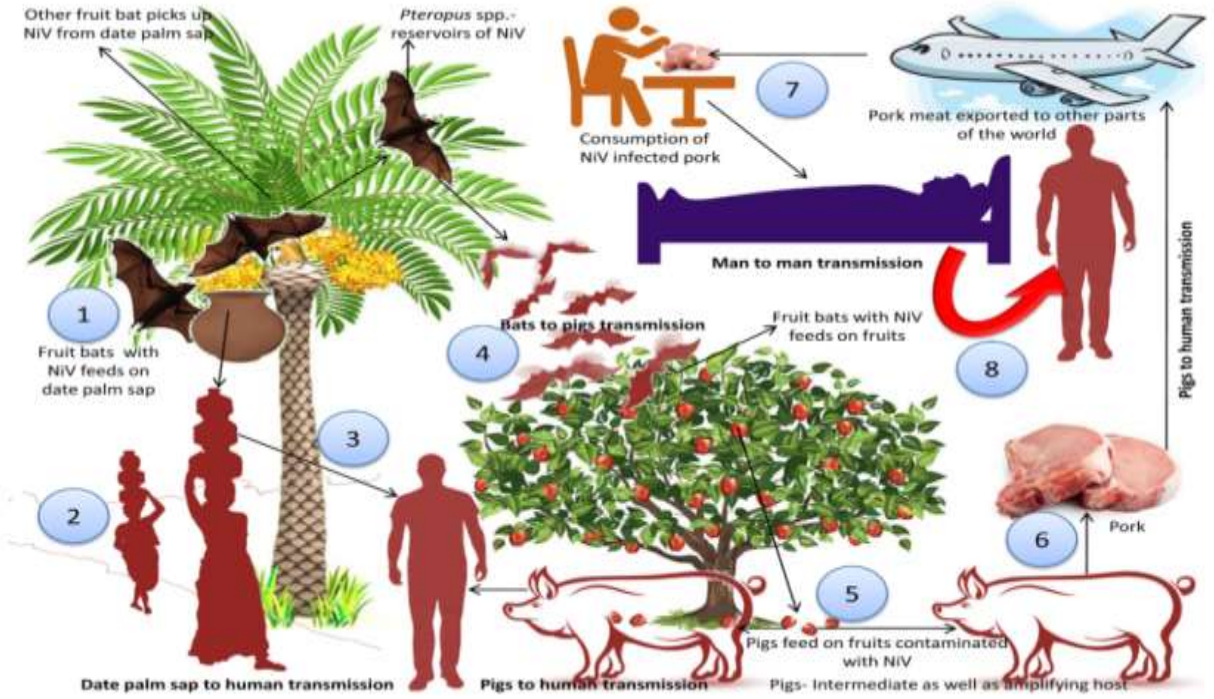

Figure 4. The mode of transmission of the Nipah Virus (3)

Fruits bats of the genus Pteropus have been idnetified as natural reservoir of NiV-MY and NiV-BD, and in Thailand, Pteropus lylei serves as the primary natural NiV host(4).

Spillover Events

Flying foxes are considered natural hosts of NiV with spillover crossing the species barriers to susceptible hosts, including humans, pigs acts as amplying intermidiate hosts (2). from bats, the virus has crossed its species-barrier frequently to several other species including through spilled over transmission but with limited transmission from person to person(3). Initial spillovers during these outbreaks have been amplified by person-to-person transmission; the largest of these outbreaks involved 66 persons, primarily patients and healthcare workers, in Siliguri, India, in 2001 .

In addition, an outbreak in Faridpur, Bangladesh, in 2004 involved 5 generations of transmission. Although the case-fatality rate for patients in Malaysia and Singapore was ≈40%, it exceeds 70% in Bangladesh and India(8) .Infected bats shed NiV in their saliva and urine, and spillover might occur between humans and bats throughout this region.Date palm trees (Phoenix sylvestris) are tapped overnight to collect the sap in clay pots, and the sweet sap is retrieved from the tree first thing in the morning and drunk raw. Wildlife studies have shown that date palm sap is commonly consumed by Pteropus bats, particularly during winter months when other fruits are not available (8).

Respiratory and neurological disease was also produced in cats with recovery of virus from urine as well as from the oropharynx.(24)

The initial outbreak has devastating consequences with over 300 cases and 100 fatalities among pig farm workers in Malaysia and Singapore. Nearly yearly outbreaks have been documented in Southeast Asia, with particular focus on Bangladesh and eastern India. As a February 2023, this year has already witnessed 10 reported cases, resulting 7 tragic deaths in Bangladesh and this marks the sixth

outbreak of NiV in India.(26).

Tabel 1. The morbidity and mortality data of human NiV in Malaysia, India, and Bangladesh from 1999 to May 23 2018.(27)

Year/Month	Country	No. of cases	No. of deaths	Case fatality rate, %	Predominant mode of transmission
1998-1999	Malaysia, Singapore	276	106	38	Direct contact with sick pigs
Jan-Feb 2001	India	66	45	68	Human-to-human transmission and nosocomial
Apr-May 2001	Bangladesh	13	9	69	Consumption of fruits or fruit products (e.g., raw date palm juice) contaminated with urine or saliva from infected fruit bats From 2001 to 2008, around half of reported cases in Bangladesh were due to human-to-human transmission through providing care to infected patients
Jan 2003	Bangladesh	12	8	67	
Jan 2004	Bangladesh	31	23	74	
Apr 2004	Bangladesh	36	27	75	
Jan-Mar 2005	Bangladesh	12	11	92	
Jan-Feb 2007	Bangladesh	7	3	43	
Mar 2007	Bangladesh	8	5	63	
Apr 2007	Bangladesh	3	1	33	
Apr 2007	India	5	5	100	
Feb 2008	Bangladesh	4	4	100	Around half of reported cases in Bangladesh were due to human-to-human transmission *Possible NiV outbreak
Apr 2008	Bangladesh	7	5	71	
Jan 2009	Bangladesh	4	1	75	
Feb-Mar 2010	Bangladesh	16	14	88	
Jan-Feb 2011	Bangladesh	44	40	91	
Feb 2012	Bangladesh	12	10	83	
Jan-Apr 2013	Bangladesh	24	21	88	
2014	*Philippines	17	9	53	
2014	Bangladesh	18	9	50	
2015	Bangladesh	9	6	67	
May 2018	India (Kerala state)	13	11	85	Initial cases suspected of consumption of fruits or fruit products Human-to-human transmission and nosocomial during later phase
Total		637	373	59	

Source: Updated from WHO-SEARO

Animal-to-Human Transmission

Nipah virus can transmit directly from bats when humans consume date palm sap that is contaminated with bat saliva, urine, or feces or can transmit indirectly through spillover to domesticated animals(12) The bat- to - pig - to - human pathway model can guide strategies to reduce the spillover of the virus from its natural reservoir (bats) to humans which is key to reducing the overall Nipah Virus.(26)

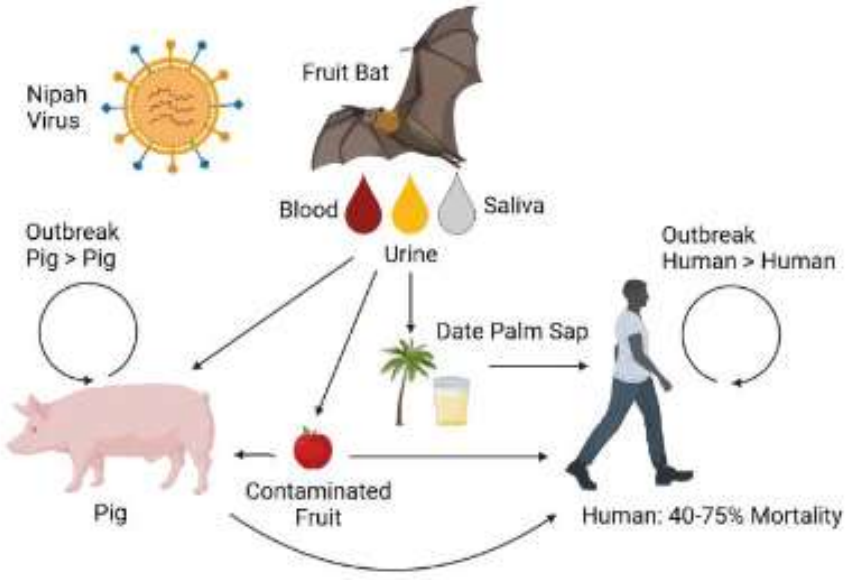

Figure 5. Nipah Virus Transmission and Mortality (26)

Human-to-Human Transmission

During the outbreaks in Bangladesh and west Bengal and India a Human - to - Human transmission occurred among the close contacts and including healthcare workers (HCWs)(6). NiV infection produces severe respiratory symptoms in pigs compared to humans. A rapid spread of NiV seen in human airway epithelial which express high levels of the NiV entry receptors ephrin-B2, and the expression levels vary between cells of different donors(3).

Human- to - human transmission of Nipah virus has significantly contributed to the Nipah viruses cases in India, Bangladesh and Philippines(5).Human infection occurs either through transmission from Pteropus bats, the natural reservoirs or from subsequent human-to-human transmission.Human consumption of date palm sap contaminated by infected bat urine or saliva has been identified in Bangladesh as the primary route of transmission from bats to people(15).

Nipah virus-infected patients do not appear to present high risk of transmitting the virus to health care workers (HCWs) and some are risk for human-to-human transmission, since viral antigens have been detected in human kidney and respiratory tract tissues, and virus has been isolated from human urine and respiratory secretion specimens(17).

Human - to - human transmission is a potential public health problem and a significant route of infection.overcrowded bedrooms due to the lack of space and poverty or the willingness of families and friends to be close contact with infected person can expose the other family and community members leading to the transmission. An additional way of human - to - human transmission needed further investigations is the sexual route. Virus is found in the semen of infected individuals using PCR at 2 weeks after clearance from blood and urine in a survivor of an outbreak in kerala.(23)

Nosocomial Transmission

The risk of Nosocomial transmission of Nipah virus is very low.Lack of Nosocomial transmission is persist with the most of the Nipah virus-infected patients who had direct contact with pigs and few are infected with household members(17). Disease often progresses to acute respiratory distress syndrome and severe neurological disease with long- term consequences and relapses. Nosocomial transmission of Nipah virus was rare in Malaysia and Bangladesh. Despite the risk for transmission through aerosols or respiratory or respiratory droplets with the virus that causes infection of the respiratory tract(5).

From the respiratory epithelium the virus disseminated to the endothelial cells of the lungs in the later stage of the disease. The virus can gain entry into the blood stream followed by disseminated freely in host leukocyte bound form. From lungs, spleen and kidneys along with brain may acts as target organs leading to multiple organ failure(3). Respiratory secretions and saliva carry the greatest risk. It was demonstrated that infectivity is higher with individuals that have respiratory symptoms.(23)

Household Transmission

Human-to-human transmission is also common within households where family members are in close contact with infected individuals. This has been seen especially during caregiving activities involving exposure to respiratory secretions or body fluids.Risk Factors for Transmission:- Understanding the key risk factors for NiV transmission is critical for prevention. Some of the identified factors include:

Cultural Practices

In Bangladesh, cultural practices like collecting and consuming raw date palm sap have been linked to outbreaks. Public awareness and educational programs to reduce exposure to bat-contaminated sap are essential.

Direct human - to-human spread contact with the bodily secretions of infected individuals show a transmission route which is aided by the cultures practices of family members caring for sick relatives. Figure of transmission(19).

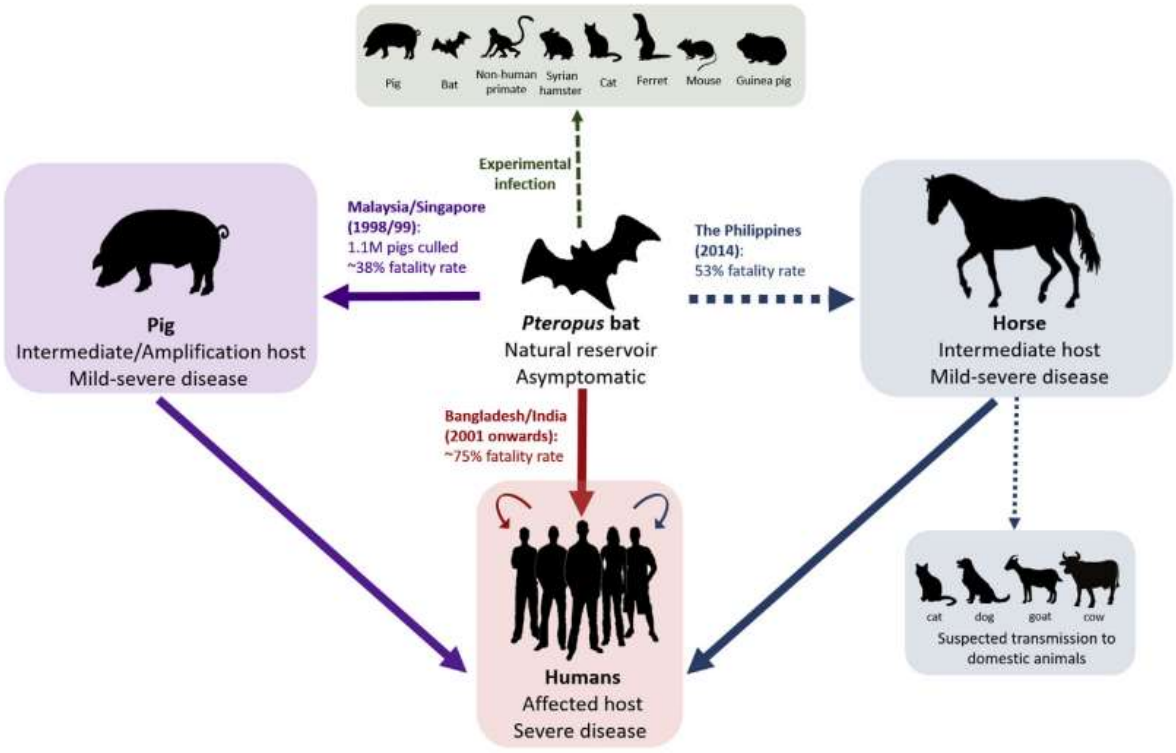

Figure 6. Figure of transmission (19).

Healthcare Settings

Insufficient infection control measures, lack of proper PPE, and inadequate surveillance in healthcare settings increase the risk of Nosocomial transmission. Monitor the patients for pulmonary and neurological signs at early stage of NiV infection. Early implementation of infection control precautions which will minimize spread of infection. Paracetamol can use for fever, myalgia, headache. Aspirin is strictly contraindicated in patients with Nipah virus cases due to its potential complication. Even the relatives of patient are also not allowed to see while isolation ward. Standard infection control precautions for all those entering the room must use hand washing practices, high efficiency masks, goggles, gloves, cap and shoe cover. Wash hands with soap and water after coming in contact with patient(18). Ribavirin administrated through intravenously or orally to patients(22).

Close Animal Contact

People involved in the livestock industry, such as pig farmers and abattoir workers, are at high risk due to their close contact with animals.

Prevention and Control Measures

Preventing NiV transmission requires a multi-faceted approach, including public health education, wildlife surveillance, and strengthening healthcare systems for early detection and management of cases(21). For health worker or caregiver infection can controlled by regular hand washing and avoiding shared foods and bedding with infected patients. Preventive measures such as bamboo skirt method, can be used to reduce date palm sap contamination.Fruits should properly washed and after each preparation individual should washed tp prevent the spread of the disease.(22).

Public Health Interventions

Nipah virus infection is highly contagious and an emerging infectious disease of public health caused by Nipah virus.In regions where NiV is endemic, efforts to raise awareness about the risks of consuming raw date palm sap and handling contaminated fruits are vital. Additionally, protective coverings on date palm trees during harvest season can prevent bat access and reduce human exposure(18).

Healthcare Precautions

Implementing strict infection control practices in healthcare facilities is essential to prevent Nosocomial transmission. Nursing must be use of PPE, isolation of infected patients, and proper disinfection protocols should be enforced during outbreaks. Patients advice to drink plenty of fluids(19).

Diagnosis

Diagnosis can be done in both live and deceased carriers.Samples like cerebrospinal fluid, throat swab, nasal swab, blood, and urine can be used for diagnosis. Samples such as spleen, kidney and lung biopsy can used for diagnosis in death patients. A wide assays test can be done in detection of NiV including virus isolation and neutralization, immunohistochemistry, molecular and serological assays, and enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR). NiV culture can be performed using Vero cells and within three days, cytopathic effects can be observed. PCR is more sensitive and widely used of diagnosis(22).

Vaccination and Therapeutics

While no licensed vaccines or antiviral treatments exist for NiV, ongoing research into vaccines and therapeutics offers hope for future prevention strategies(20). recently there have been ongoing investigations on the vaccine administration and the efficacy of antiviral therapies in the treatment(22).

CONCLUSION

Nipah virus spreads through a combination of zoonotic and human transmission pathways, with food contamination and close human contact being the most significant routes. Prevention focuses on minimizing contact with bats and infected individuals, and ensuring rigorous infection control in healthcare settings.

Nipah virus is a zoonotic pathogen with a complex transmission cycle involving bats, animals, and humans. Zoonotic spillover remains the primary transmission route, but human-to-human transmission, especially in healthcare settings, has been increasingly observed. Understanding the different pathways of transmission and the risk factors associated with each is essential for effective prevention and control measures. Public health strategies should focus on reducing human contact with

bat reservoirs, improving healthcare infection control, and promoting research into vaccines and antiviral treatments.

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