

Nipah Virus: Effects of Urbanization and Climate Change

Shweta Rana and Sanjana Singh

Abstract---The increased urbanization and changing climate has led to rise in epidemics with incidences of new diseases affecting human health every year. Most of these are zoonotic. Nipah Virus Encephalitis (NVE) is one such example which is caused by bats (flying foxes). Nipah virus (NiV) was first identified in Malaysia in 1998 and in Bangladesh and India in 2001. Since then there have been cases reported in Bangladesh on a regular basis with the last known case being in 2015. Till 2013 there have been 524 reported cases and 293 deaths due to NVE. In Malaysia NiV was first transmitted to pigs and from pigs to humans, however in Bangladesh and India NiV travelled directly from bats to humans. Even though humans and bats have co-existed for long, known cases of NiV are recent. This case study explores the effects of urbanization and climate change in spread of NiV.

Keywords---Climate Change, Flying Foxes, Nipah Virus, Urbanization

I. INTRODUCTION

It usually starts with headache and fever, and then gradually progresses into drowsiness, disorientation and maybe coughing. Soon the infection affects the Central Nervous System, reaching the brain and within 24-48 hours the patients may enter a coma. Three out of ten fortunate people wake up from this coma; only to be left with persistent convulsions [1], [2] and sometimes permanent, crippling neurological disorders [3]. Such is the fate of those unfortunate enough to contract Nipah Virus (NiV).

Nipah Virus Encephalitis (NVE) is an incipient zoonotic disease that caused havoc in Malaysia and Singapore from September 1998 to May 1999 [4]. It affected 276 people and led to 106 deaths [5]. It also led to an estimated loss of US \$3.5 million by Malaysia for discarding 1.1 million pigs and US \$100 million revenue was lost due to the temporary shutting down of the pig industry [6]. The word 'Nipah' comes from a village 'Sungai Nipah' in Malaysia where the first case of this virus occurred [7].

Flying foxes or fruit bats of the Pteropus species are found to be the carrier of Nipah virus [8].

Shweta Rana is Associate Professor with Department of Physical and Natural Sciences in FLAME University, Pune, Maharashtra- 412115, India.

Sanjana Singh Author was with FLAME University, Pune, Maharashtra-412115, India. She is now Research Associate with Indian Institute of Management, Ahmedabad, India. (e-mail: sanjana.asana@gmail.com)

In Malaysia the virus spread from bats to pigs, and from pigs to humans. Nipah Virus is also known as "barking pig syndrome" or "one mile cough" since the pigs that died of this virus showed symptoms of whooping and coughing in Malaysia.



Fig. 1(a) The extent of the flying foxes shown in grey. Image taken from "Transmission of Human Infection with Nipah Virus" by Luby, Stephen P., Emily S. Gurley and M. Jahangir Hossain, 2009. Copyright by Clinical Infectious Diseases. Reproduced with permission from PubMed.

<http://cid.oxfordjournals.org/content/49/11/1743.full>
(b) A flying fox in Malaysia. Courtesy Stephane Bidouze, Shutterstock, "The Climatic Origins of the Malaysian Nipah Virus Outbreak." Discover Blog by Rebecca Kreston.
http://blogs.discovermagazine.com/bodyhorrors/2013/04/30/climatic-ori-nipah-virus/#.VSE89_mUc9z

Nipah Virus is closely related to Hendra Virus which broke out in Australia in 1994 among the horses [8] and they both belong to the family Paramyxoviridae. On investigating the horses it was suspected that flying foxes were responsible for the outbreak through spillovers. And that once a horse started showing symptoms it could transfer the virus through bodily fluids to other horses. When the Nipah virus broke out in Malaysia among the piggeries it was confirmed, by Dr. Tan and his team, that flying foxes were the carriers of the virus. The neutralizing antibodies for NiV were also found in bat species in Australia, Malaysia, Singapore, Cambodia, India, Bangladesh and Madagascar [8].

Though bats are the primary reservoir of the virus, it can be transferred to pigs that can act as vectors and transmit the disease to humans and dogs in close contact [8]. It is demonstrated that the pigs may have been infected by a fomite such as half eaten banana which contained bat saliva [4]. The last reported cases were in January and February 2015 in Bangladesh where 9 cases and 6 deaths were reported [9]. Till 2013 the virus had affected 524 people and resulted in 293 deaths having an average fatality rate of 40-70% [5]. Currently, NiV cases have been reported in Bangladesh only.

A. Nipah Virus outbreak in India

In 2001, from January 31st to February 23rd, 66 people were infected with Nipah Virus and 45 of them died [10] in Siliguri, West Bengal, India. Siliguri is a commercial center that shares borders with China, Bangladesh and Nepal. This

outbreak occurred among hospitalized patients, family of these patients and medical staff of 4 different hospitals [11]. A few years later, another outbreak of Nipah Virus took place in 2007 from April 9th to 28th in the village Belechuapara in Nadia, West Bengal [12]. This time 5 cases were reported and all those who were diseased died. The one question that arises here is how did Nipah Virus originate and travel to India?

It is known that this virus can spread through fomites but in 2001 outbreak in Bangladesh and India no intermediating vector was found between the bats and humans. It was later found that the virus was transmitted directly to humans due to the consumption of date palm sap in Bangladesh [5].

It is not known how the virus first entered Siliguri or who the index case was, but most of the reported cases in 2001 were clustered around one hospital called Medinova Hospital [11]. When a team of epidemiologists and physicians from the National Institute of Virology, Pune, India, along with local public authorities visited Siliguri and reconstructed the scenario they found a clear lineage in 43 reported cases [11]. A patient, case 1, was admitted in the Male Medical Ward of one hospital where he is suspected of transmitting NiV to 4 other patients in that ward [10]. These patients transmitted the virus to their family members and the medical staff who worked in that ward. One of the patients who was admitted in that ward was later shifted to a Nursing Home where he infected 32 people including 24 staff and 8 attendants [10]. Of the 66 cases identified as an encephalitis, 5 were discharged against medical advice and 45 died making the case-fatality ratio ~74% [11]. The epidemic curve in Fig 2 shows that the initial deaths recorded were on January 31st and after that there is a slight rise on February 1st and then the number of cases and deaths decrease to zero for a few days which is then followed by a sudden rise in NiV cases around the 14th and 15th of February. This is caused by the patient who was shifted from the hospital to a nursing home.

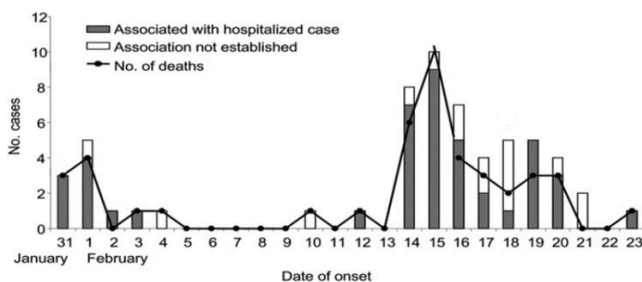


Fig. 2. Epidemic Bar graph showing the outbreak of Nipah Virus in Siliguri, West Bengal, India, from January through February 2001. Graph courtesy by Dr. Chadha and team, 2006, PubMed Central (PMC site). "Nipah Virus-associated Encephalitis Outbreak, Siliguri, India"

A few years later, in 2007, another outbreak of Nipah virus occurred in India in Balachuapara village of Nadia district in West Bengal. This time a clear index case is known and the reason for the outbreak is also known.

The index case was a 35 year old male farmer who was addicted to country liquor that is made from date palm juice [12]. A horde of bats were observed hanging from the trees around his residence which suggests direct contact of the liquor with bat fluids. The index case then affected 3 of his relatives who showed symptoms within 12-14 days of contact

and a man who collected his blood samples showed symptoms 12 days after contact [12].

From the two cases it can be concluded that the incubation period can range from 4 to 20 days [13]-[15]. However, the incubation can be as short as two days or as long as a month. Sometimes NiV infection can be mild but most cases suffer from acute neurological signs which start with flu-like symptoms such as fever and headache. Most patients develop encephalitis that leads to altered sensorium – confusion and coma – in almost 97% of the cases. Some suffer from nausea and vomiting (19%) and some from respiratory disorders (51%) [11]. In severely ill patients complications like septicemia, renal impairment and bleeding from GI (gastrointestinal) tract may occur. Those who survive are left with mild to severe neurological damage. In few cases it is also observed that the initial infection is asymptomatic but it can develop into a severe neurological disease up to four years later [13]-[15]. Also it was observed in the Siliguri and Nadia cases that all patients were above 15 years of age, this helped in distinguishing NiV symptoms from that of Japanese Encephalitis. However there is no age limitation for NiV victims since Bangladesh has reported cases of 2 year old children and 60 year old adults suffering from this disease.

B. Virology

Nipah Virus is a spherical virus that is single stranded negative sense RNA. It consists of F – fusion protein, G – attachment protein, nucleocapsid, phosphoprotein, Viral RNA, M – matrix protein and a bilayer lipid envelop [16]. After host cell samples were collected from infected pigs and humans it was found that in humans the virus is mostly found in neuronal cells, lung fibroblasts cells and monocytes. It can replicate very well and almost anywhere at the site of entry [17]. It infects other cells either through release of infectious virus particles or by cell-to-cell spread mechanisms. Two different strains of NiV have been isolated. The Malaysian strain varies slightly from the Bangladesh/India strain since NiV in Malaysia was caused by *P. vampyrus* and by *P. giganteus* in Bangladesh [18]. This variation leads to the difference in clinical symptoms seen in both cases. Also the Bangladesh strain has a higher mortality rate and is capable of transferring from human-to-human [19].

C. Detection of NiV in host cells

In order to detect the viral cells in the Siliguri cases enzyme-linked immunosorbent assay (ELISA) test was performed to check for antibodies containing immunoglobulins G and M (IgG and IgM). In order to study the RNA structure of NiV reverse transcription – polymerase chain reaction (RT-PCR) was performed. Immunohistochemistry and virus isolation are other diagnosis for humans with NiV symptoms. This virus is considered biosafety level 4 in US and Australia and strict laboratory containment at limited labs while testing is followed [20].

D. Treatment for NVE

NiV has no cure and the treatment is limited to supportive care [7]. Some suggest that ribavirin can be administered to the patients to reduce the mortality rate in case of acute Nipah encephalitis but most research has proven ribavirin to be

ineffective in reducing mortality rate [7], [20]. In recent experiments done on hamsters it has been found that an interferon inducer, Poly (I) – poly [C (12) U] has been found to be effective where it prevented mortality in 5 out of 6 infected hamsters [7]. However, no treatment is universally accepted and the focus of epidemiologist is on prevention of spread of NiV in flying fox populated regions.

E. Containment and Prevention methods

In Malaysia in order to curb the virus the Malaysian government ordered the slaughtering of all the pigs from the infected piggeries [20]. The Singapore government temporarily stopped import of pigs from Malaysia in order to control NiV. Ever since 1998 and 1999 there have been no further outbreak in Malaysia or Singapore, hence active disease surveillance and biosecurity practices prove to be most effective in containing Nipah virus [20]. In India and Bangladesh it has been found that the virus spreads through the consumption of date palm sap that is contaminated by bat urine or saliva. One way to prevent this is by heating the palm juice to 40°C or higher to kill the virus or by covering the palm juice collection pot by jute skirt [21].

II. URBANIZATION, CLIMATE CHANGE AND NIPAH VIRUS

Nipah Virus has existed in the bats for centuries and this virus has not undergone an evolutionary change [7], so why did this infection spread only now?

There are many ecological factors that contribute to the emergence of Nipah virus, however the most prominent is human intervention into the bat infested areas due to rapid urbanization. In Malaysia the virus spread due to unplanned deforestation of pulp wood, which is the natural habitat for NiV carrying bats, and mismanagement of large piggeries. [7]. Malaysia has lost 14.4% of its forest cover from 2000-2012, it has lost 4.5 mil ha of its dense forest at the rate of a football pitch every 1.5 minutes [22].

Fig. 3 was generated as a part of the Central Forest Spine Master Plan in 2009 to explain the importance of ecological linkages in Peninsular Malaysia. Through the study it was observed that the deforestation has taken place predominantly in the lowlands and coastal regions. This was mostly done for plantation and agricultural purposes. The piggeries were surrounded by durian and rambutan fruit plantation which are eaten by fruit bats increasing the chances of NiV outbreak.

Fragmentation of Natural Forest Cover in Peninsular Malaysia

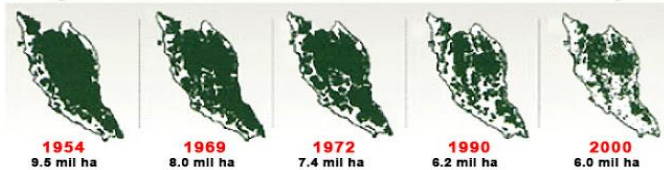


Fig. 3. Fragmentations of natural forest cover in Peninsular Malaysia from 1954 to 2000. Image courtesy Greenwood International Blog

<http://greenwoodinternational.blogspot.in/search/label/Malaysia>

In 1997 and 1998 in Malaysia large tracts of the tropical rainforest, around 12 million acres, were slashed and burned resulting in an impenetrable haze over the Malaysian peninsula [6]. This haze not only cloaked Malaysian peninsula

but also surrounding Southeast Asian countries obstructing sunlight and disabling the flowering and fruiting trees from photosynthesizing [6]. At the same time there was a drought due to the El Nino Southern Oscillation (ENSO), which was responsible for the bats migration from the coastal forest into the villages with piggeries [7]. Southern oscillation refers to the variation in the surface pressure of the oceans between the Southeastern tropical Pacific and Australian-Indonesian regions [7]. The El Nino occurs when the Pacific waters become abnormally warm.

Deforestation of rainforests in the equatorial region like Amazon, Central Africa and Southeast Asia are accountable for 15% of carbon-emission caused by human activities [23]. With the increase in greenhouse gas (GHG) emissions the global temperatures have been changing at an unprecedented rate. While some areas are cooling most of the globe is becoming warmer, this is most prominent in surface temperatures of the oceans. Since oceans are natural carbon sinks, they regulate the atmospheric GHGs by absorbing the excess. However, the oceans take a longer time to absorb GHGs and get heated up in the process. As the sea surface temperatures rise, the sea level pressure drops. This creates a pressure gradient which is accompanied by weakening of the low-latitude easterly trade winds [7]. This combination of events results in floods and droughts. In Malaysia in 1997-98, a severe drought played an important role in fruit bat migration into the villages. Another reason for the migration was loss of habitat and shortage of food due to deforestation and forest fires [7]. However, the ENSO case has been debated as the human index case of NiV in Malaysia was in January 1997 and ENSO occurred in mid-1997 [24]. However, there is still a possibility that the drought could be responsible for bat migration since flying foxes are very sensitive to temperature variation and live only within a certain temperature range, even slight changes in the weather can disturb all the bat colonies of a particular region. This migration could have then led to the large scale spread of NiV among the piggeries in 1998 and subsequently among humans in 1999.

All these factors together contributed to the spread of Nipah Virus in Malaysia and Singapore. The regions that were most adversely affected in Malaysia were those that suffered from maximum deforestation like Perak, Negeri Sembilan, and Selangor. In Malaysia, most cases occurred between January and March 1999 with more than 40 cases being reported in March in Negeri Sembilan, Malaysia and around 20 cases in Singapore [25].

The increase in the human-bat interaction could be one reason why the NiV outbreak occurred in Bangladesh and India where humans got this virus from drinking date palm juice contaminated by bat urine or saliva. Date palm sap is a popular delicacy in Bangladesh which is harvested by making a cut in the palm trunk and collecting sap which streams down into a clay pot held below the cut. This drink is usually sold raw and is a favorite among the children. However, the Bangladesh government enforced a law after the 2011 outbreak which killed 21 children, banning the distribution of raw sap. The law isn't implemented in the rural areas where the raw sap is still sold. But despite this practice NiV has been reported only in the villages of certain areas. Most outbreaks

were clustered around a strip of central, western and northwestern Bangladesh that is now known as the “Nipah Belt” [26]-[27].

One thing to notice here is that Siliguri is located near the northwestern boundary of Bangladesh and Nadia near the western boundary. The main reason for cases to be centered around the Nipah belt was deforestation for urban expansion and agricultural purposes. In Bangladesh the forest cover has gone from 14% to 7% from 1989 to 2006 [25] with most deforestation taking place in the Nipah belt region. These areas are high in terms of population density and low in terms of forest density, whereas the bat population is more or less the same as the areas outside of the Nipah belt. What this means is that the bats have lesser stress to nest on as people move into the once-forested areas coming in closer contact with the bats. According to the United Nation’s Food and Agriculture Organization, in the last 30 years Bangladesh has lost three-fourths of its forested land. In fact the forest cover ratio per person is 0.022 hectares per person, this is one of the lowest in the world. In a study conducted by Dr. Hahn and team on “Roosting behavior and habitat selection of *Pteropus giganteus* reveals potential links to Nipah virus epidemiology,” it was found that 87% of all fruit bat roosting sites were located around 50 meters from residences and households water pumps in Bangladesh [26]-[28]. With bat habitat being fragmented and reduced, more bats come in contact with humans and domestic animals leading to the emergence of newer zoonotic diseases. Nipah, Ebola and Hendra are just few of the many epidemics to come if the future continues to grow at an exponential rate.

However, extreme climatic changes have also been held responsible for triggering the NiV epidemic in Bangladesh and India. The Northwestern regions of Bangladesh have reported extreme temperatures and increased droughts. Droughts and heat waves are known to reduce bat populations; an example comes from Australia where 30,000 flying foxes were reported dead during 19 episodes of extreme temperatures. From 1981 to 2006, Bangladesh has experienced 4 major drought episodes and the area affected is expected to increase [29].

Apart from droughts, floods and sea level rise has also lead to the migration of the bats further into villages. The frequency of flooding has been on a rise with the “once-in-a-generation” floods occurring more often. There have been 8 major floods between 1974 and 2004, these include those that are expected to occur only once in every 20 years [28].

The availability of data on the Siliguri and Nadia are less and hence the effects of Urbanization and Climate Change on these regions are unknown. However due to their proximity to the ‘Nipah Belt’ of Bangladesh there is high possibility of NiV traveling to India due to spill-over effect in Bangladesh. This doesn’t only raise questions towards wildlife surveillance but also displays the potent interconnectedness of events in neighboring countries.

However, the most pressing issue is why do bats carry so many diseases? One reason could be that since most bats of different species roost together, it gives virus the opportunity to be transmitted interspecies. But when bats get infected with a virus they usually survive it due to their strong immunity. In a study done by Dr. Zhang and team on the comparative analysis of bat genome it was found that bats immunity is

closely linked to their ability to fly [30]. Mammals cannot develop the ability to fly without severely damaging their DNA. However when bats evolved to adapt to flight they modified their DNA and acquired specialized cells that improved their immunity to viruses. Most viruses need an optimum temperature of 37°C to survive in a mammal, but the internal temperature of bats is about 40°C due to their ability to fly [30]. This kills most viruses, while evolving other viruses in order to survive these temperatures. Hence a normal human fever of 39°C is unable to kill the virus. Thus those viruses that are able to survive in a bat’s body tend to thrive in a human or other land mammal bodies. Also different species of bats enable a single type of virus to evolve differently in each species, thus the Malaysian NiV strain spread from pigs to humans while the Bangladesh/Indian NiV strain spread from human to human [30].

III. CONCLUSION

By studying the Siliguri and Nadia outbreak, definitive linkages of bat-to-human and human-to-human disease transmission have been found. It is also known that most cases have occurred due to the human-to-human transmission. This emphasizes the importance of improved surveillance and instalments of laboratories that are equipped to diagnose and handle new pathogens [10]. Due to the high number of human-to-human transmission cases it is imperative to observe caution while dealing with patients by wearing protective covering and isolating the patient from other patients [10]. Also it cannot be ignored that the occurrences are more common in regions which have suffered from large scale deforestation due to human interference. Hence a forest and wildlife surveillance unit is important for keeping a check on deforestation and monitoring bat infested areas.

With the increase in population there has been an increase in the rate of urban expansion. This has led to fragmentation of forests due of construction of roads and large scale forest clearing for agricultural purposes. This has been the main cause that led to the spread of NiV. The only way to curb emerging zoonotic disease and to avoid emergence of any new disease would be to control the demographic and economic growth rate. Or come up with sustainable ways to utilize limited resources, such as land and forests, so that the animals are left alone in their habitats and are not given more opportunities to interact with human beings and their domesticated animals.

IV. FOR FURTHER DISCUSSION

This virus has left most of the scientists and epidemiologists with a lot of unanswered questions. It is not known if any cases of NiV have occurred before 2001 in India or Bangladesh, but there have been a lot of unexplained deaths in these regions especially in Bangladesh [4]. One of the questions is why is respiratory disease and human-to human transmission of NiV more common in Bangladesh and India than in Malaysia? One reason could be that the Bangladesh strain is slightly different from the Malaysian strain suggesting that the two strains of NiV that have originated from two different populations of migrating bats affect mammals differently [17]. But there is no sign of mutation in the virus

from the bat samples and human samples within the same of one region. Another question is how stable the Nipah Virus genome is. Could there be a mutation that could improve the efficiency of human –to-human transmission and one that may result in Nipah becoming a pandemic? [4] The overall homology between the Malaysian strain of NiV and the Bangladesh strain of NiV is 91.8% but due to lack of any discovery of mutated genome this question still remains unanswered [4]. Another question could be about how common the asymptomatic infection of NiV is [4].

Also there is a possibility that Nipah Virus is used as a bioweapon in the future, so what are the chances of this event occurring? And is it possible that NiV becomes deadlier than HIV? But a more common question is how can we effectively reduce human-bat interactions? One way can be to leave the bat habitats alone and not cause wide scale deforestation.

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