
Commentary

Controlling Nipah virus encephalitis in Bangladesh: Policy options

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Abstract Nipah virus (NiV) encephalitis is endemic in Bangladesh, with yearly seasonal outbreaks occurring since 2003. NiV has a notable case fatality rate, 75–100 per cent depending on the strain. In Bangladesh, primary transmission to humans is believed to be because of consumption of bat-contaminated date palm sap (DPS). Both the disease and the virus have been investigated extensively, however efforts to implement preventive strategies have met social and cultural challenges. Here we present a variety of community approaches to control the spread of Nipah encephalitis, along with advantages and disadvantages of each. This information may be useful to health workers and policymakers in potential NiV outbreak areas in Southeast Asia.

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Introduction

Nipah virus (NiV) is an emerging infectious disease (EID) and belongs to the genus *Henipavirus* (family *Paramyxoviridae*). First identified and isolated in the village of Sungai Nipah, Malaysia in 1999 during a severe disease outbreak in humans and pigs, NiV was initially diagnosed as a Hendra-like virus and named ‘Nipah’.¹ During this outbreak the virus was isolated from multiple species, including humans, horses, dogs, cats, cattle, and rats.^{2,3} Clinical symptoms in humans occurred in those with direct contact with pigs. Further investigation found that Malaysian outbreaks had begun in September 1998 and lasted until April 1999, resulting in 105 human deaths and culling of 1.1 million pigs.³



In Western Bangladesh, NiV was first identified in April/May 2001 in an encephalitic outbreak with high case fatality (9 out of 13).⁴ A second outbreak in Bangladesh occurred in January 2003, during which 8 people died (out of 12).⁴ Traceback information suggested two risk factors: climbing date palm trees and close association with patients.⁵ In 2004, 49 deaths (out of 65 cases) were reported in a third outbreak in two separate communities.⁴ It was found to be a result of direct or indirect contact with fruit bats, including date palm sap (DPS) consumption.⁶ During a subsequent outbreak in 2005, researchers established a significant relationship between the consumption of raw date farm syrup contaminated by fruit bat saliva and NiV infection (11 out of 12 cases died).⁴ Between 2001 and 2012, 280 cases of Nipah or Nipah-like virus encephalitis were identified, with 211 deaths (case fatality rate of 75 per cent).⁷

NiV appears to be increasingly virulent in Bangladesh, with greater case fatality rates each year, peaking at 100 per cent in 2011 and 2012. Recently, bats have been vectors in many EIDs, including speculation that the current Ebola virus disease outbreak in West Africa could be because of a spillover from bats.⁸

Blum *et al* (2009), Homaira *et al* (2010) and more recently Gurley and colleagues (2015), analyzed the social conditions associated with the spread of NiV. They studied key stakeholders, operating beliefs, and scientific message responses.^{9–11} For knowledge translation and transference to occur, all these authors suggest that appropriate communication and community engagement is needed. In their absence, potential interventions are unlikely to be considered acceptable and adhered to by at risk community members.

Transmission

For Bangladesh, Luby (2013) described the main routes of NiV transmission, all involving contact with materials containing the virus: (i) ingesting NiV contaminated raw DPS, (ii) person-to-person transmission (short chain transmission either from live or dead hosts), and (iii) contact with sick animals (less frequent).⁵ Person-to-person transmission is not as commonly observed as for Ebola, but it has been observed in hospital settings.¹² Person-to-person transmission was also observed during the Faridpur outbreak in 2004¹³ during which one physician died.⁵ This highlights the importance of appropriate training

for health-care workers and frontline caregivers when dealing with any EID outbreak. A separate study of nosocomial transmission of Nipah encephalitis found no risk to health-care workers.¹⁴

Epidemiology

Since the first Bangladeshi outbreak in 2001, more than 500 people have been infected with NiV, in more than 20 different outbreaks.¹⁵ Outbreaks occur between November and May (most commonly December–April), and infections appear to be limited to the northwestern and central parts of the country,¹ probably due to a greater number of people who eat DPS in this region.¹¹ Case mortality averages 75 per cent, with some strains reaching 100 per cent.⁴ Fortunately the period of DPS consumption (November–April) has not coincided with peak infection and transmission within bat colonies (June–July).¹⁶ Similarly, although the potential for a ‘super spreader’ event is apparent (with a more infectious virus developing or increased shedding by specific individuals), this has not yet occurred.

The Bangladeshi epidemics differ from the outbreaks in Malaysia where 90 per cent of infected individuals had contact with pigs.¹ In Bangladesh most cases can be traced to bat excretion contamination, with few linked to livestock (depending on outbreak year).² Person-to-person transmission has been common in the Bangladeshi outbreaks, compared with Malaysia.⁵ Evidence suggests a relationship between NiV infection and consumption of fresh, raw DPS (*Phoenix sylvestris*), although consumption of contaminated fruits cannot be excluded.²

In addition, the NiV strains observed in the Malaysian and Bangladeshi outbreaks show genotypic differences. These are also observed between outbreak years in Bangladesh.¹⁷ Though strains appear to be fairly stable within specific localities, they do differ geographically.¹⁶ This divergence could, in the future, impact infectivity in different areas. NiV antibodies have also been isolated from pteropid bats through most of southeast Asia – India, West Bengal, Thailand, and Cambodia, among others. Full strain lineages are still being investigated.^{18,19}

Unfortunately, no vaccine exists at this time, although trials in African Green monkeys using the vaccine for Hendra virus, are currently showing promise.²⁰



Current Policy

Currently, the government of Bangladesh strongly recommends against consuming raw DPS during outbreak seasons unless the sap was protected by using bamboo skirts during collection or by boiling it for ten minutes. Bamboo skirting effectively reduces sap contamination by fruit bats. Sap harvesters consider it cost-effective and acceptable.^{21,22} Boiling the sap is less attractive to harvesters, as they believe it changes the taste and consistency of the drink, although it disables the virus. A report by the *New York Times* mentioned a government ban on the sale of raw DPS during the 2011 outbreak, suggesting a movement toward stricter prevention protocols, although they are difficult to enforce.²³ In addition, a surveillance system has been implemented in five hospitals in the NiV belt to detect outbreaks early.²⁴

As there are no treatment options other than supportive care, nor a vaccine for people or animals, the government currently focuses on prevention by increasing public awareness. They use newspaper advertisements, talk shows, and discussions on local TV and radio. Educational programming airs before and during each Nipah virus season (November–May).²⁵ The International Centre for Diarrheal Disease Research, Bangladesh in collaboration with Stanford University, is conducting trials in the districts of Rajbari and Natore. They want to compare the effectiveness of advising people not to drink raw DPS versus drinking sap only from trees protected by skirts to prevent DPS from contamination by bats. The results from the first phase of the study are due December 2015.²⁶

Disease Intervention Alternatives

In February 2014, a diverse group of graduate students (of which we were part) chose the NiV problem as a case study for the Integrated Training Program in Infectious Disease, Food Safety and Public Policy (ITraP) at the University of Saskatchewan, Canada. They framed and suggested policy options using Laswell's problem orientation.^{27,28} Please note that for optimal prevention of NiV infection, the policies suggested here would be used in combination. Specifically, the most effective intervention would include an integrated education and multi-species surveillance program that maximized public outreach and training (especially in high-risk areas), as well as early identification of disease and early outbreak response.



Option 1: Education

Preliminary studies show the local population, including health professionals, in Bangladesh are generally misinformed about the transmission and spread of the Nipah virus;⁹ they remain unaware of the signs of infection and methods of protecting themselves and family members.⁹ Lack of communication, combined with reduced trust in the medical system and hospital care, has created a stream of misinformation, contributing to continued spread of the disease.⁹

An education strategy would inform the local population, providing key facts about the disease and how it is spread, both from bat-to-human and from human-to-human. One facet of the education program could pertain to what the local population, specifically the date palm harvesters, could do to limit their contact with bats. It could also illustrate the signs and symptoms of the disease and offer advice on how to care for loved ones in the event of an outbreak.

At the same time, educating hospital staff and traditional healers about Nipah virus, and how to provide information to patients and their families, would allow these well-respected groups to disseminate their knowledge to the local population in a culturally acceptable manner. Adding education on NiV into school curricula could provide information about risk factors to the younger generation. Knowledge of an increased likelihood of NiV (and EID) transmission in ecological environments with degraded and fragmented geographical landscapes, where wildlife share food resources with people and livestock, can empower individuals to make proactive choices about prevention strategies.

Advantages

Education is a relatively inexpensive way to spread awareness about Nipah and its mode of spread. Involving the local population in the planning and decision process would help generate public acceptance of the education policy. Educating people about Nipah could help limit transmission, as people can be made aware of both bat-to-human and human-to-human transmission chains. Educating the present generation will go a long way in disseminating the information to future generations, limiting future outbreaks.



Disadvantages

The engagement of a community and changing age-old beliefs and traditions takes time and can be challenging. Yet it has worked for Kuru in Africa, and is also beginning to work in West Africa, where people are beginning to change traditional burial practices to help curb the spread of Ebola. Education alone may not stop the spread of NiV, as communities live in close proximity to bats, resulting in some unavoidable interspecies contact. Preventing bats and other wildlife from coming into contact with DPS can prevent disease spillover. Changing beliefs and traditions through community engagement will need some time and resources to spread awareness.

Option 2: Surveillance

Several options exist for choice of surveillance techniques

1. *Establishment of a health information network based on Geographic Information Systems (GIS)*: It should be possible to identify hotspots at risk of viral infection by looking at reported human infections from 2001 to 2014. Mapping the distribution of fruit bat habitats and date palm harvesting locations would add more information for locating potentially high-risk areas.
2. *Annual Community Surveillance*: It should be possible to undertake surveillance of people, livestock, and wildlife (pteropid bats in Bangladesh, but potentially other species elsewhere). Human sero-surveillance using ELISA of IgG antibodies (stratified or cluster sampling) from exposed population will help outline yearly hotspots at the end of every seasonal outbreak of Nipah. Surveillance of hospital staff biweekly or monthly during the outbreak season (November–May) will help monitor the potential nosocomial spread of the disease and will also assess the human-to-human transmission potential of the evolving Nipah virus. Although nosocomial spread was found to be minimal by Gurley *et al* (2007), this cannot be ruled out as a possible route of transmission. Molecular epidemiology of the viruses isolated from patients will provide further information.

Routine ELISA sero-surveillance of livestock in the Nipah-belt will help monitor the viral strain circulating in livestock. This is important, as bats have been found to shed NiV year round,¹⁶ and may be capable of



transmitting NiV to livestock via various means other than date palms, increasing the potential for transmission to communities through contact with their livestock.

Bat surveillance using serum antibody and virus isolation from feces, urine, and post mortem or trapping samples would again help track changes in the virus. Ecological and GIS surveillance of bat habitats will help define potential outbreak regions. Surveillance of bats will help focus education and awareness programs on communities where NiV infected bats cluster.

Advantages

Routine surveillance will allow for early disease detection, avoiding economic and social disruption. Early detection will also help reduce cases and case fatalities. The social and psychological benefits are immediate because of reduced apprehension and greater understanding. Furthermore, reporting data from disease surveillance on a global level helps attract funding from international donors and the WHO. These can be used to strengthen the surveillance infrastructure.

Disadvantages

Disease surveillance systems take a long time to reach laboratory-based conclusions. Our ability to detect novel, emerging, or reemerging infections in a low-technology environment is poor. Therefore the surveillance infrastructure needs upgrading. Surveillance may be biased, accounting only for reported cases.

Option 3: Development of a human vaccine

For infectious diseases, vaccination may achieve herd immunity levels where the disease cannot persist. Two recent advances against NiV-like diseases (*Henipavirus*) are worthy of note:

1. *Hendra-sG subunit vaccine and a human monoclonal neutralizing antibody, m102.4*. The Hendra-sG vaccine was developed in Australia for equine use (known as Equivac HeV) and is the first BSL-4 (biosafety level 4) agent vaccine for public use.
2. *Hendra-sG vaccines for humans and pigs*. Development of human and pig Hendra-sG vaccines are underway, but meeting ethical



standards for clinical trials is challenging.²⁹ The m102.4 has been used in people on a ‘compassionate use’ basis in Australia and remains in pre-clinical development. Although highly effective, the costs of vaccine per animal and for the human population (sap drinkers) remain high due to low demand in the absence of repeated outbreaks.

Advantages

A vaccine would save lives in the Nipah belt, and potentially in other at risk Southeast Asian countries. A preventative vaccine would help alleviate the economic burden placed on the health-care system because of the long-term supportive care required of infected patients. A single dose vaccine, if developed, would also overcome the issue of compliance for boosters. The vaccine might also protect international travelers, thus reducing the disease’s impact on tourism in the future.

Disadvantages

The absence of repeated outbreaks increases the cost of vaccine development, thus raising the cost per dose. Adequate external funding might address this issue, as with the two Ebola vaccines undergoing trials in Liberia currently. It takes a long time to develop a vaccine, but it might be a long-term objective, as NiV still has the potential to become a pandemic.¹⁶ A vaccination strategy (mass vaccination or ring vaccination) would need to be evaluated and decided upon by all stakeholders. Is there a sufficient incentive for the pharmaceutical industry to produce a vaccine that does not yet have a global demand? Surely repeated introduction of the same virus is a precursor to widespread disease, as with other viral EIDs such as SARS, avian influenza, and HIV.

Option 4: Habitat modification

Changing the interface between humans and bats could have a dramatic impact on lowering infection rates. One option to inhibit virus spillover is to improve DPS biosecurity by preventing bats from coming into contact with sap. This can be done with physical barriers. Three types of physical barriers have been shown to prevent bats from coming into contact with DPS: bamboo, ‘dhoincha’, and polythene skirts (For photographs of each of these barrier types, see Khan SU *et al* (2012).

A Randomized Controlled Trial of Interventions to Impede Date Palm Sap Contamination by Bats to Prevent Nipah Virus Transmission in Bangladesh).²¹

Advantages

It is an inexpensive and economically feasible alternative, and would effectively keep bats off DPS pots. Using physical barriers (skirts) does not impact the quality or quantity of sap collected. It is also socially acceptable for the sap harvesters.²² Using skirts can reduce cases almost immediately in outbreak affected areas. This option has the added benefit of demonstrating cultural respect for the value placed on the custom and history of drinking DPS.

Disadvantages

This option may not completely eliminate the disease as it targets only one form of virus transmission (bats-to-humans), but may help prevent the index cases in future sporadic outbreaks. There must also be community engagement and ‘buy in’ for this option to be successful.

Option 5: Infection control and quarantine

Infection control interrupts disease transmission chains, especially person-to-person spread. Five or more rural hospitals (including Rangpur, Rajshahi, Bogura, Faridpur, and Rajbari) with the highest numbers of clinically reported cases, based on data analysis from 2001 to 2014, have been identified. They now require an infectious disease control infrastructure to be itemized, documented, and procured.

Advantages

Appropriate protocols, procedures, and equipment reduce the risk of health care-associated transmission and limit person-to-person transmission, once the virus is no longer spread within or from the hospital. Good quarantine practices reduce the risk of developing pandemic strains of other diseases such as influenza as well, thus providing multiple benefits for increasing the biosafety and biosecurity of these institutions. Nosocomial transmission of all infectious diseases will be prevented, because case management will be improved. With early recognition, patients will have better chances of survival.



Disadvantage

The initial development of protocols and procurement of paraphernalia is expensive in the short run, but economically justified on the basis of long-term control and prevention of future cases of Nipah encephalitis, plus other infectious diseases. This option requires extensive training campaigns that may be possible with the help of the government and external funding agencies.

Future goals: Wildlife vaccination

Although vaccination of wildlife reservoirs would immediately reduce the levels of NiV (elimination of disease in bats), this is not a currently available option, as there is no vaccine for wildlife. Vaccinating bats may be difficult because of their large geographic spread and their ability to fly. A bait system similar to the raccoon rabies vaccine used in Quebec, Canada would be needed.

Little is understood about bat immunology, thus developing a vaccine is a challenge. Bats seem to be persistently infected with viruses that they harbor without developing disease. Antibodies against some viruses have been isolated, but bats fail to completely eliminate the viruses they carry.³⁰ Understanding the physiology behind this would help develop a wildlife vaccine for bats.³¹ To curb sporadic outbreaks, we believe current goals should be focused on reducing exposure to bat contaminated sap.

Most Feasible Option

There are a myriad of options; a combination will surely work best. During the Canadian students' 2014 ITraP session, individuals from different training and philosophical backgrounds scored the feasibility, practicality, social acceptability, and ethical considerations of the options to identify the best possible strategy to control NiV. The single option most likely to succeed, if only one were put in place, was 'education'. Once the results from the clinical trial being conducted by the International Centre for Diarrheal Disease Research become available, an evidence-based policy should be possible. However, as previously noted, a combination of all of the alternatives is most likely to prevent a future pandemic, as human behavior drives spillover risk. In the mean time, the

surveillance infrastructure should be improved to allow better reporting of cases.

Conclusion

Controlling Nipah is a complex challenge. Controlling the consumption of contaminated DPS by targeting the communities where consumption is high appears to be the simplest way to control NiV outbreaks. However challenging centuries old traditional beliefs and behaviors may pose problems. Any solution must therefore consider the values of all stakeholders.

Prevention of human cases would inhibit the virus from adapting further to the human host. The adaptation is a step whereby it could gain full potential against human-to-human transmission. Thus acting early on this virus is important. With no vaccines or antivirals available yet, education is crucial to spread awareness among community members, making it possible to control disease spread in every season. It will require communities to promote consumption of skirt-protected sap rather than the unprotected sap. Although behavioral change is challenging, with consistent community engagement and support, it can be done. It could be a painfully long process to convince communities to modifying their age-old practices, but it has worked in Africa for Kuru and is beginning to work in West Africa for Ebola. Gaining the trust of the affected community goes a long way in winning the battle against an infectious disease.

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