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Commentary

The pandemic potential of Nipah virus

Stephen P. Luby *

Woods Institute of the Environment, Stanford University, Yang and Yamazaki Environment and Energy Building, Room 231, 473 Via Ortega, Stanford, CA 94305, United States

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ABSTRACT

Nipah virus, a paramyxovirus whose wildlife reservoir is *Pteropus* bats, was first discovered in a large outbreak of acute encephalitis in Malaysia in 1998 among persons who had contact with sick pigs. Apparently, one or more pigs was infected from bats, and the virus then spread efficiently from pig to pig, then from pigs to people. Nipah virus outbreaks have been recognized nearly every year in Bangladesh since 2001 and occasionally in neighboring India. Outbreaks in Bangladesh and India have been characterized by frequent person-to-person transmission and the death of over 70% of infected people. Characteristics of Nipah virus that increase its risk of becoming a global pandemic include: humans are already susceptible; many strains are capable of limited person-to-person transmission; as an RNA virus, it has an exceptionally high rate of mutation: and that if a human-adapted strain were to infect communities in South Asia, high population densities and global interconnectedness would rapidly spread the infection. Appropriate steps to estimate and manage this risk include studies to explore the molecular and genetic basis of respiratory transmission of henipaviruses, improved surveillance for human infections, support from high-income countries to reduce the risk of person-to-person transmission of infectious agents in low-income health care settings, and consideration of vaccination in communities at ongoing risk of exposure to the secretions and excretions of *Pteropus* bats.

1. Introduction

Nipah virus was first discovered in an outbreak of acute encephalitis in Malaysia in 1998, in which 39% (109) of 283 people with recognized infection died. Using diagnostic tests developed as part of the first investigation, Nipah virus outbreaks have been recognized nearly every year in Bangladesh since 2001, and occasionally in neighboring India. Over 70% of people infected with Nipah virus in South Asia have died (Luby et al., 2009a). One-third of survivors have permanent neurological deficits (Sejvar et al., 2007). Several outbreaks have included short chains of person-to-person transmission among persons who contact secretions from Nipah patients. The ability of Nipah virus to spread to patient caregivers has raised concern that the virus might adapt to more efficient human-to-human transmission. This paper examines the potential of Nipah virus to cause an expanding epidemic, describes epidemiological patterns observed to date, summarizes relevant research and suggests measures that should be taken for surveillance, prevention and infection control.

2. Nipah virus: pathogen and clinical onset

Nipah virus is a paramyxovirus (genus Henipavirus) whose wildlife reservoir is bats of the genus *Pteropus* (Halpin et al., 2011). Nipah virus does not cause any apparent disease in infected bats (Middleton et al., 2007) and likely co-evolved with these bats. The ephrin-B2 and ephrin-B3 molecules which Nipah virus exploits to enter epithelial cells are widely conserved across mammals, and many mammals are therefore susceptible to Nipah virus infection (Bossart et al., 2008).

In humans, Nipah virus infection causes a widespread vasculitis (Wong et al., 2002). The brain and lung are the most commonly affected organs (Wong et al., 2002). Most patients present with fever and headache; a reduced level of consciousness, focal neurological signs and cough are commonly observed (Goh et al., 2000; Hossain et al., 2008; Paton et al., 1999). Most people infected with Nipah virus develop severe disease. A serological study of 612 contacts of Nipah cases in Bangladesh identified 15 people who developed Nipah infection. Eleven of the 15 (73%) developed severe illness, while four had only fever (Hossain, 2010).

3. Epidemiology of Nipah virus infection

The large outbreak in Malaysia began in 1998 when Nipah virus spilled over from bats to pigs. Within an industry in which large numbers of pigs were raised in close proximity, Nipah virus was widely transmitted from pig to pig (Chua, 2003). Many people who had close contact with sick pigs, especially those in contact with respiratory secretions and urine, became infected (Parashar et al., 2000). Among 283 recognized human infections, 109 people (39%) died (Chua, 2003).

* Tel.: +1 650 723 4129; fax: +1 650 725 3402.
E-mail address: sluby@stanford.edu

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Since the virus was discovered and diagnostic assays became available, outbreaks have been identified nearly every year in Bangladesh and occasionally in neighboring India (Fig. 1). Outbreak investigations in Bangladesh have identified consumption of raw date palm sap as the primary route of transmission of Nipah virus from *Pteropus* bats to people. Date palm sap is harvested in the winter in Bangladesh by shaving the bark from the sugar date palm tree (*Phoenix sylvestris*) and collecting the sap into open clay pots (Nahar et al., 2010). *Pteropus* bats that occasionally shed Nipah virus in their saliva (Middleton et al., 2007; Reynes et al., 2005; Wacharapluesadee et al., 2005), frequently visit the trees during sap collection and lick the sap as it is running into the pot (Khan et al., 2010; Rahman et al., 2012). Although most date palm sap in Bangladesh is cooked into molasses (Halim et al., 2008), raw sap is a local seasonal delicacy (Luby et al., 2006), and it is consumption of this raw sap that has been repeatedly implicated in human outbreaks (Luby et al., 2006; Rahman et al., 2012; Sazzad et al., 2013).

Some human Nipah virus infections in Bangladesh have followed contact with sick animals (Luby et al., 2009b), but this is a much less important source of human infection in Bangladesh than date palm sap. In contrast to Malaysia, where large commercial farms raised thousands of pigs in close quarters that facilitated amplification of the epidemic (Pulliam et al., 2011), pigs, cattle and goats in Bangladesh are raised by scattered small producers at much lower densities. In both Bangladesh and India, Nipah patients occasionally transmit the infection to other people, though sustained person-to-person transmission beyond 5 generations has not been recognized (Chadha et al., 2006; Gurley et al., 2007a; Homaira et al., 2010; Sazzad et al., 2013). People providing direct care for fatally infected patients with prominent respiratory symptoms are at greatest risk of becoming infected (Gurley et al., 2007a; Luby et al., 2009a).

4. The threat of zoonotic diseases

Wolfe and colleagues conducted a systematic assessment and concluded that 80% of the most devastating infectious diseases in human history were zoonoses (Wolfe et al., 2007). They proposed a classification of zoonotic disease whereby stage I infectious agents are those only transmitted among non-human animal hosts; stage II agents can spill over from animals to humans, but humans cannot further transmit the infection; stage III agents can spill over to humans and cause limited outbreaks of person-to-person transmission; stage IV agents are capable of sustained human to human transmission; and stage V are exclusively human agents (Wolfe et al., 2007). Reflecting on this taxonomy, Lloyd-Smith and colleagues suggested that the zoonotic stages are best understood as progressive increases in the basic reproductive number (R_0) of the agent for humans (Lloyd-Smith et al., 2009). R_0 is the average number of people to whom one patient transmits the infection. The transition from a stage III to a stage IV zoonosis results when a pathogen's R_0 changes from <1 to >1. Stage III zoonotic pathogens display stuttering chains of transmission where occasional individuals transmit to a few people, but the chains of transmission are not sustained.

Most Nipah patients do not transmit infection to anyone. Among patients in Bangladesh only 7% transmit the infection (Luby et al., 2009a). Most commonly, person-to-person Nipah transmission occurs as a single case followed 1–2 weeks later by a cluster of infections among the index patient's family care providers.

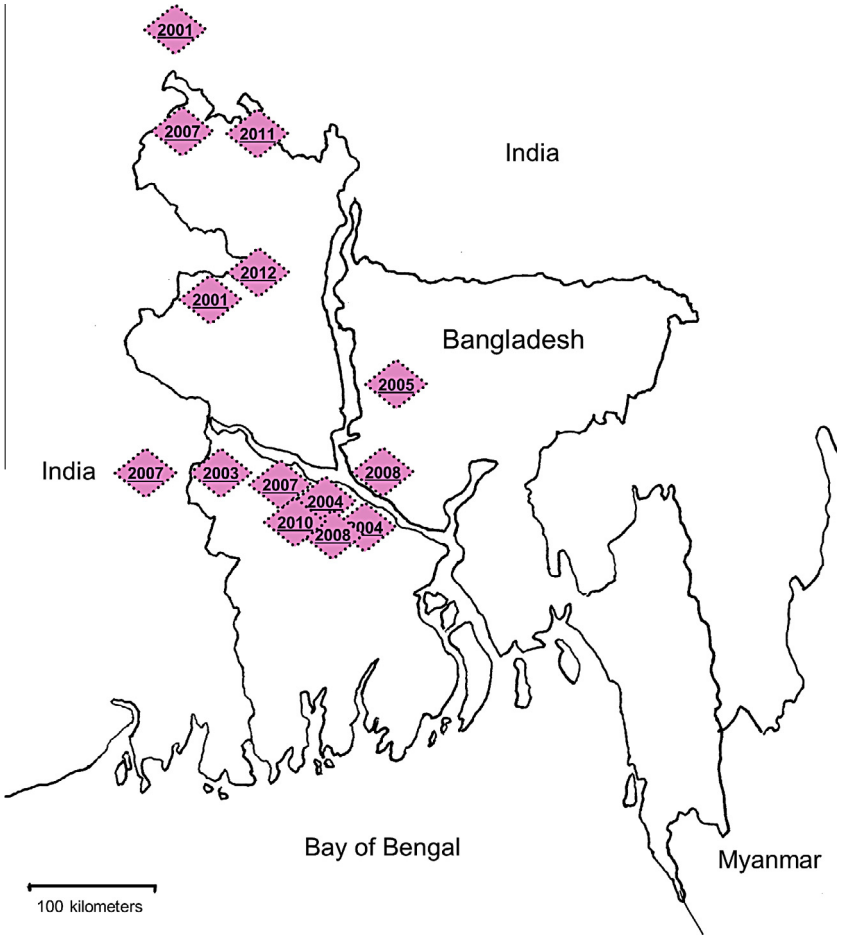

Fig. 1. Nipah virus outbreaks in Bangladesh and India from 2001 to 12.

An outbreak in Thakurgaon District, Bangladesh in 2007 illustrates a typical short chain of person-to-person transmission (Homaira et al., 2010). The index case first developed fever, then fatigue, headache and cough. His wife cared for him at home during the first four days of illness. She fed, cleaned and massaged him; wiped froth and saliva from his mouth and slept in the same bed. On the fourth day of illness his cough became more severe and he developed difficulty breathing. A friend and cousin seated the patient between them on a motorcycle and brought him to a doctor. On the fifth day of illness, the patient lost consciousness and was transported to the hospital in a microbus, accompanied by the same friend and his cousin, wife and sister-in-law. The driver of the microbus helped carry the patient into the hospital. The patient died on the day of admission, and these five people who had physical contact with him during his last two days of life subsequently developed Nipah. The wife and cousin died.

Occasionally there are subsequent generations of transmission, but the longest confirmed transmission chain terminated after 5 generations (Gurley et al., 2007a; Luby et al., 2009b). Among the countless agents infecting animals, stage III zoonoses are a particular concern as a source of human pandemics, because these agents have already demonstrated that they can cross the species barrier into humans and that they can be transmitted from person to person. If they acquire the ability to transmit efficiently from person to person, they can become established in the human population.

5. Possible mechanisms of respiratory transmission of Nipah virus

Electron microscopic evaluations that show high concentrations of Nipah virus inclusions in human respiratory epithelium suggest that the virus replicates within this epithelium (Goldsmith et al., 2003; Wong et al., 2002). The most likely mechanism of person-to-person transmission is the passage of respiratory secretions contaminated with Nipah virus from a patient to the respiratory tract of an uninfected person following physical contact. Evidence supporting this pathway includes the isolation of Nipah virus from respiratory secretions (Chua et al., 2001), the reduced risk of infection observed among people who had physical contact with patients and then washed their hands with soap and water, compared with persons who had similar contact, but did not wash their hands (Gurley et al., 2007a), and the transmission of Nipah virus to a person whose only contact with the index patient was preparing the corpse for burial, including wiping away respiratory secretions with a cloth (Sazzad et al., 2013). Person-to-person transmission typically occurs in the final day or two of life of an index patient, when symptoms of respiratory involvement are most prominent (Homaira et al., 2010; Hossain et al., 2008; Luby et al., 2009a; Sazzad et al., 2013). There is no evidence of person-to-person transmission before the onset of severe illness (Luby et al., 2009a).

Ferrets have been used as models of Nipah virus infection and pathogenesis (Bossart et al., 2009; Pallister et al., 2009). Like humans, ferrets develop both severe neurological and respiratory disease. Respiratory symptoms in ferrets infected with Nipah virus include cough, serous nasal discharge and dyspnea (Bossart et al., 2009). Ferrets have been used successfully to model both contact and respiratory droplet transmission of human influenza viruses (Maines et al., 2006; Sorrell et al., 2009), and could be used to model person to person transmission of Nipah virus.

6. Is Nipah a new disease?

The wide distribution of henipaviruses among *Pteropus* bats (Chua et al., 1999; Field et al., 2011; Hsu et al., 2004; Wacharapluesadee et al., 2010) and related species (Drexler et al., 2009) and the lack of symptoms in infected bats (Halpin et al., 2011; Middleton et al., 2007) suggest that Nipah virus likely co-evolved with *Pteropus* bats and has been shed by these bats for millennia. People have been harvesting date palm sap in South Asia for centuries (Blattner, 1978), so it is likely that sporadic human infections have also been occurring for centuries. The recognition of Nipah outbreaks in Bangladesh apparently awaited improvements in public health surveillance in rural areas and the development of specific diagnostic tests. This likely long history of occasional human infection without sustained person-to-person transmission provides some reassurance that there is not a new immediate high risk for a Nipah pandemic. However, human population densities in the date palm sap harvesting regions of South Asia were much lower throughout history than they are today, which may have limited ongoing transmission if a dangerous strain emerged.

7. Could Nipah virus cause a pandemic?

Nipah virus infection is a stage III zoonotic disease. Stuttering chains of person-to-person transmission have been repeatedly recognized (Chadha et al., 2006; Gurley et al., 2007a; Homaira et al., 2010; Sazzad et al., 2013). So far, the R_0 of the strains of Nipah virus that have spilled over in Bangladesh have averaged 0.48 (Luby et al., 2009a). As long as all of the virus strains that spill over have an $R_0 < 1$ and do not change within their human host, then each spill-over will produce only stuttering chains of person-to-person transmission. However, if a strain with an $R_0 > 1$ spills over, or if a strain infecting a person develops an $R_0 > 1$, then in our globally connected world, humanity could face its most devastating pandemic.

RNA viruses have the highest rate of mutation of any virus or living organism (Drake and Holland, 1999). These high rates of mutation contribute to viral adaptation to new environments (Makeyev and Bamford, 2004), a force that has driven evolution of life on earth for billions of years. Measles virus, a paramyxovirus and major cause of human mortality for centuries (Cliff et al., 1994), apparently evolved between the 11th and 12th century from mutation of the progenitor of rinderpest, a paramyxovirus whose hosts are ruminants (Furuse et al., 2010). As humans domesticated livestock, variant strains of this ruminant-associated paramyxovirus developed an $R_0 > 1$ within humans and proceeded to kill tens of millions of people in subsequent centuries.

There is substantial genetic heterogeneity among strains of Nipah virus observed in human isolates from Bangladesh (Lo et al., 2012). By contrast, in Malaysia essentially a single strain of the virus was identified throughout the outbreak (AbuBakar et al., 2004; Chua et al., 2000). *Pteropus* bats have a wide geographical range stretching from Pakistan across South and Southeast Asia, up the coast of southern China and down into Australia (Fig. 2) (Nowak, 1994). Wherever *Pteropus* bats have been studied, evidence of Nipah or closely related Hendra virus infection have been confirmed (Hsu et al., 2004; Wacharapluesadee et al., 2010; Yob et al., 2001; Young et al., 1996).

The genetic heterogeneity among strains of Nipah virus is associated with phenotypic heterogeneity. In Malaysia, person-to-person transmission was observed only rarely (Abdullah et al., 2012; Mounts et al., 2001; Tan et al., 2000), but in Bangladesh person-to-person transmission has accounted for over one-third of recognized cases (Luby et al., 2009a). Nipah patients in Malaysia received treatment in facilities with better supplies and infrastructure than those in Bangladesh (Gurley et al., 2007b; Mounts et al., 2001). Moreover, the close physical contact with severely ill patients characteristic of Bangladeshi culture exposes family members of patients to substantial quantities of patient secretions, which undoubtedly contributes to person-to-person

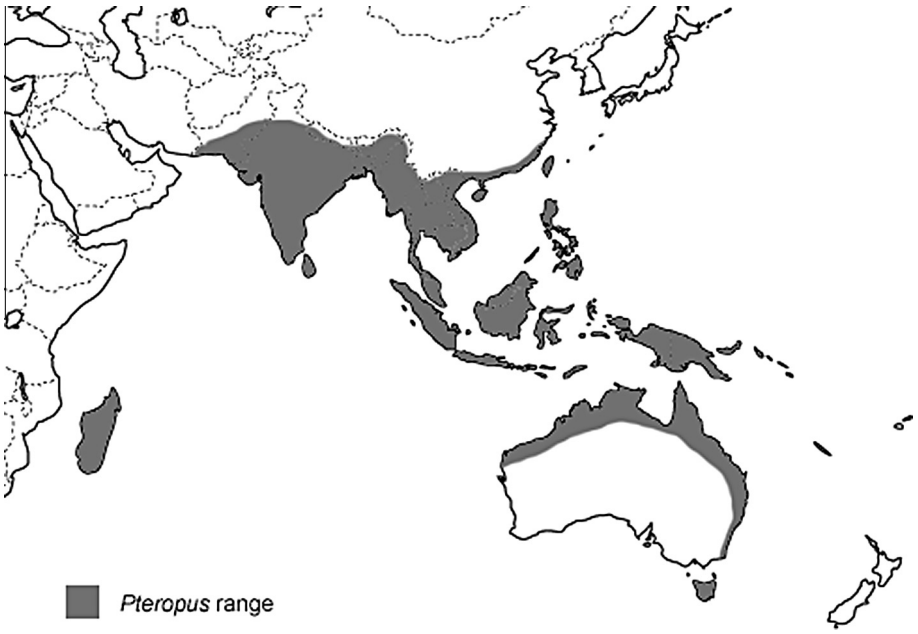

Fig. 2. Geographic range of *Pteropus* bats, based on (Nowak, 1994). Reprinted with permission (Luby et al., 2009a).

spread (Blum et al., 2009; Gurley et al., 2007a). However, strain differences, including the proclivity for severe respiratory disease, are likely responsible for some of the difference in the frequency of transmission between Bangladesh and Malaysia. Only 14% of patients infected with the Malaysian strain presented with cough, and only 6% had abnormal chest radiographs (Goh et al., 2000). By contrast, 62% of confirmed patients in Bangladesh had cough, 69% developed difficulty breathing and chest radiographs frequently showed substantial pulmonary involvement (Hossain et al., 2008). The recent confirmation of transmission of Nipah virus from a corpse (Sazzad et al., 2013) suggests a strain that was particularly infectious to humans. In addition, ferrets inoculated with a strain of virus from Bangladesh had 10 times as much virus shed in saliva than those inoculated with the Malaysian strain (Clayton et al., 2012).

The combined evidence of genetic heterogeneity of virus strains in Bangladesh, the different transmission pattern seen in outbreaks with different strains and the ferret studies suggests that different strains of Nipah virus possess different capacities for person-to-person transmission. It is conceivable that one of the numerous strains circulating in bats throughout Asia may have an R_0 value >1.0 for humans or acquire mutations during human infection that lead to more efficient and sustained human-to-human transmission. While human infection is not part of the normal viral life cycle and is not necessary for its continued survival and propagation within bats, when changes in the environment provide an infectious agent with new opportunities for an expanded range, natural selection favors agents that produce more variants, such as RNA viruses. The historical devastation of zoonotic diseases, the high case fatality rate of human Nipah infection and its recognition as a stage III zoonotic disease suggest that scientists, the public health community and policy makers should respect the pandemic risk of Nipah virus.

8. What should be done?

An estimate of the probability of emergence of a Nipah virus strain with an $R_0 > 1$ for humans would guide an optimal response to the risk. Studies to explore the molecular and genetic basis of respiratory transmission of henipaviruses, the variability of the genome within nature and its stability with serial passages in mammals would help to estimate this risk. Since *Pteropus* bats commonly drop partially eaten saliva-contaminated fruit on ground accessible to herbivores, searching for evidence of henipavirus infection and adaptation in these other mammals naturally exposed to bat secretions and excretions would also help model risk of adaptation to humans. Extending high-quality active epidemiological surveillance in humans beyond Bangladesh would provide better estimates of the frequency of infection, which also contributes to pandemic risk. *Pteropus giganteus* bats fly between Bangladesh and India. Like residents of Bangladesh, people in the state of West Bengal, India, that immediately borders the area of Bangladesh where outbreaks have been repeatedly identified, collect and drink raw date palm sap and provide close care to dying relatives. While West Bengal is likely the area where the largest number of human cases are being overlooked, it would be prudent to establish human surveillance for clusters of infectious diseases (not just Nipah) across the geographic range of *Pteropus* bats.

In our interconnected world, once an infectious agent has developed an $R_0 > 1$ for humans and has been transmitted beyond its initial area of spillover, it becomes nearly impossible to contain. Early efforts to interrupt chains of transmission, especially reducing person-to-person spread, should therefore be a high global priority. This means that reducing the risk of health care-associated transmission in low-income countries is not only a prudent investment to reduce health burden within the country, but is in the interest of all people, including taxpayers in high-income countries. One could imagine a strain of Nipah virus with an R_0 of 1.2 infecting a hospitalized patient in Bangladesh, but if effective infection-control procedures were in place, this strain need never leave the hospital. Limiting person-to-person transmission in densely crowded settings in South Asia would not only reduce the risk of the emergence of a pandemic strain of Nipah virus, it would also reduce the risk of emergence of pandemic strains of influenza or other agents.

Animal studies have demonstrated that vaccines can protect against henipavirus infection (Bossart et al., 2011; Pallister et al., 2011). Although a human vaccine to protect against Nipah virus in Bangladesh would not meet the standard criteria for cost-effective prevention, because of the small numbers of people who are affected each year, the knowledge of how to make a safe vaccine and the development of contingency plans to scale up production

in the event of a global emergency could mitigate risk. Moreover, especially if future virological studies suggest that only few mutations are required to increase the transmission efficiency of Nipah virus between humans, it may be a prudent global investment to vaccinate residents and health care workers in rural areas of Bangladesh where Nipah virus outbreaks have repeatedly been identified. Such a program would not be a cost-effective strategy to prevent 10 or 20 deaths per year, but it may be a sound investment to reduce the risk of a pandemic strain of Nipah virus gaining a foothold in South Asia and spreading globally.

A human monoclonal antibody (m102.4) directed against the G glycoprotein of Nipah virus reliably prevents disease in ferrets when administered either pre-exposure or up to 10 h after exposure (Bossart et al., 2009). The primary barriers to using an antibody or antiviral drugs to prevent Nipah disease in Bangladesh are the poverty, isolation and low level of development of the health care system in affected communities. Nipah is an uncommon cause of encephalitis; even in hospitals in the Northwest region of the country, where most cases are seen, and during the winter, when most cases occur, Nipah accounts for <5% of patients presenting with encephalitis (Md. Abu Naser, personal communication). Most infections are diagnosed retrospectively. Family members are at greatest risk of contracting Nipah from patients (Luby et al., 2009a), while health care personnel have much less direct patient contact (Hadley et al., 2007). The health care system in Bangladesh does not identify people who are at risk of exposure quickly enough to identify contacts who are likely to benefit from post-exposure prophylaxis. The resources required to establish a system to reliably identify exposed individuals and deliver antibody or antiviral therapy are unavailable, especially considering that hospitals that treat Nipah patients do not even provide gloves or masks to health care providers (Sazzad et al., 2013) or soap and water for handwashing to patient attendants (Sultana et al., 2008). However, if the economy of Bangladesh continues to grow and point-of-care diagnostics are developed to reliably identify Nipah patients on presentation, then prophylaxis may become a viable strategy in the future.

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