Disease Outbreaks Caused by Emerging Paramyxoviruses of Bat Origin

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Introduction

Newly emerging and re-emerging infections are recognized as a global problem and 75% of these are potentially zoonotic (Woolhouse & Gowtage-Sequeria, 2005). Emergence of a new "killer" disease in any part of the world is likely to be a threat world wide in today's society with very rapid means of transportation of both human and animal/animal products. Recent examples include the global outbreaks of severe acute respiratory syndrome (SARS), H5N1 avian influenza, and the outbreaks of West Nile virus in United States. The rapid economic development in the Asian region during the last few decades was accompanied by massive urbanization and environmental changes, which are believed to be one of the triggers leading to the emergence of new zoonotic diseases. Wildlife animals play an ever-increasing role in the emergence of zoonotic diseases, and bats have been identified as natural reservoir host of several lethal zoonotic viruses that emerged in recent times. This review will focus on the disease outbreaks caused by emerging bat viruses in the family *Paramyxoviridae*.

Viruses and Natural Hosts

Viruses in the family *Paramyxoviridae* are well-known due to their ability to cause a variety of severe diseases affecting humans (measles, mumps, and respiratory and encephalitic illnesses) and livestock animals (Newcastle disease, distemper, and rinderpest). Paramyxoviruses contain a nonsegmented negative strand (NNS) RNA genome and share similar genomic features with three other NNS RNA virus families, *Rhabdoviridae* (which contains rabies and vesicular stomatitis viruses), *Filoviridae* (Ebola and Marburg viruses), and *Bornaviridae* (Borna virus). These four families are grouped taxonomically in the order *Mononegavirales* (Pringle, 1991). Members of the family *Paramyxoviridae* are further divided into two subfamilies, *Paramyxovirinae* and *Pneumovirinae*. The *Paramyxovirinae* include five genera: *Respirovirus*, *Morbillivirus, Rubulavirus, Avulavirus,* and *Henipavirus* (Mayo, 2002).

Since 1994, at least three novel paramyxoviruses of bat origin in the subfamily *Paramyxovirinae* have emerged in Australia and south Asia, some of them causing severe diseases in both human and animals. They are Hendra virus (HeV), Nipah virus (NiV), and Menangle virus (MenV), isolated from infected horses and humans in Australia in 1994, humans and pigs in Malaysia in 1999, and pigs in Australia in 1997, respectively (Chua et al., 2000; Murray et al., 1995b; Philbey et al., 1998).

HeV and NiV represent a new group of paramyxoviruses in this subfamily, and are classified in a separate genus named *Henipavirus* (Mayo, 2002; Wang et al., 2000). Several molecular features distinguish henipaviruses from other paramyxoviruses. While most paramyxoviruses have a genome of approximately 15,000–16,000 nt, the genome length of HeV and NiV is over 18,000 nt. The increase in genome size is mainly due to the expansion of noncoding regions located mainly at the 3' ends of the viral genes. The functional significance of these features is not known. Henipaviruses also have unique biological features. They are the only currently recognized zoonotic paramyxoviruses and are highly pathogenic with mortality rates reaching 75% or greater for NiV (Eaton et al., 2006). The wide host range of henipaviruses is also considered uncommon for paramyxoviruses. For example, NiV naturally infects five terrestrial species in four mammalian orders. Experimental infection extends the number of susceptible terrestrial orders to five by including Rodentia. The highly virulent nature of henipaviruses combined with the lack of therapeutic treatments has led to the classification of HeV and NiV as Biosafety Level 4 (BSL4) pathogens.

In contrast, MenV has a genome length of 15,516 nt, typical of most paramyxovirus genomes (Bowden & Boyle, 2005; Bowden et al., 2001). Comparative sequence analyses indicated that MenV is a new member of the genus *Rubulavirus* in the subfamily *Paramyxovirinae*, but is not closely related to any existing members of the genus, which include mumps virus, porcine rubulavirus, human parainfluenza viruses 2 and 4, and simian viruses 5 and 41. Instead, MenV is closely related to another bat paramyxovirus, Tioman virus (TiV), which was discovered during the search for NiV in bats on Tioman island, east of peninsular Malaysia (Chua et al., 2001b; Chua et al., 2002b). TiV is antigenically related to MenV, but its disease-causing potential in humans or animals is unknown.

All these newly emerged viruses are believed to have flying foxes (fruit bats in the genus *Pteropus*) as natural hosts. Bats have been identified or implicated as the natural reservoir host for an increasing number of new and often deadly zoonotic viruses. In addition to the emergence of paramyxoviruses from frugivorous *Pteropus* bats, insectivorous *Rhinolophus* species have been identified as natural hosts of SARS-like viruses (Lau et al., 2005; Li et al., 2005), and Ebola virus has been shown to have fruit bat reservoir hosts (Leroy et al., 2005). Bats typically respond asymptomatically to virus infection and display a capacity to permit persistent virus infections (Sulkin & Allen, 1974). Their wide distribution and abundant status (one mammalian species in five is a bat) makes them prime candidates for reservoirs of viruses, which may cross the species barrier and infect man and other animals.

Hendra Virus Outbreaks in Australia (1994–2004)

In September 1994, a spectacular outbreak of an acute respiratory syndrome occurred in thoroughbred horses in Hendra, a suburb of Brisbane, Queensland, which resulted in the death of 13 horses and their trainer (Murray et al., 1995b). The causative agent was a novel paramyxovirus, later named Hendra virus after the location of the index case. During this outbreak, two human infections were identified. Both patients presented with myalgia, headaches, lethargy, and vertigo. One recovered after a two-week severe flu-like illness, but the other developed pneumonitis, respiratory failure, renal failure, and arterial thrombosis and died from a cardiac arrest. Findings at autopsy were consistent with a viral infection. Histology revealed focal necrotizing alveolitis with many giant cells, some syncytial formation, and viral inclusion bodies (Selvey et al., 1995). HeV was isolated from the lung, kidney, liver, and spleen of the lethal case (Murray et al., 1995b). Sequence analysis indicated that HeV isolates obtained from horses and humans had identical genetic sequences.

A second outbreak of HeV occurred in Mackay, 1,000 km north of Brisbane, which resulted in the death of two horses and one human (O'Sullivan et al., 1997). The horses died of unknown causes in August 1994, and the farmer who assisted with the necropsies developed a mild meningitic illness, but recovered. Thirteen months later, the farmer became ill and died of severe encephalitis, which was confirmed to be caused by HeV (O'Sullivan et al., 1997). Retrospective investigation revealed that the two horses had also died of HeV infection, and the farmer was infected at that time in August 1994 (Hooper et al., 1996; Rogers et al., 1996). Compared with the two human cases involved in the Hendra outbreak, the human case in the Mackay outbreak presented two interesting differences. First, the virus seemed to have remained latent for 13 months before reactivation to eventually kill the patient. Second, the patient died of encephalitis, whereas the other two human cases presented with respiratory symptoms (Selvey et al., 1995). In this regard, it is interesting to note that although paramyxoviruses are mainly known for their ability to cause respiratory diseases, some do have the capability to infect brain and cause encephalitic illness, such as measles viruses in subacute sclerosing panencephalitis (SSPE) patients (Griffin, 2001).

HeV re-emerged in Queensland in Cairns in January 1999 and in Townsville in December 2004. Both occasions resulted in the death of a single horse. The Cairns case involved a 9-year-old thoroughbred, and there was no horse-to-horse or horse-to-human transmission observed. In the Townsville case, a veterinarian involved in the autopsy developed a HeV-related respiratory illness soon after and recovered (ProMed, 2004).

Extensive seroepidemiologic surveillance of wild and domestic animals revealed the presence of HeV antibodies in four species of flying foxes found in Australia (Young et al., 1997; Young et al., 1996). They are the spectacled flying fox (*Pteropus conspicillatus*), the black flying fox (*P. alecto*), and the grey-headed flying fox (*P. poliocephalus)* in which species seroprevalence can be as high as 47% in some areas (Field et al., 2001a). For reasons that are not yet clear, the

seroprevalence rate in the fourth species(the most widely distributed of the four species, the little red flying fox (*P. scapulatus*)) is lower, approximately 15% (Field et al., 2001a). HeV was isolated from uterine fluid and a pool of fetal lung and liver from one grey-headed flying fox and from the fetal lung of a black flying fox (Halpin et al., 2000). The bat isolates had almost identical sequences to those of human and horse isolates.

Nipah Virus Outbreaks in Malaysia (1998–1999)

Between September 1998 and April 1999, a major outbreak of disease in pigs and humans occurred in peninsular Malaysia, which resulted in 265 human cases, 105 of them fatal (Chua et al., 2000). In Singapore, 11 cases and one death were reported among abattoir workers who slaughtered pigs imported from affected areas of Malaysia (Paton et al., 1999). The outbreak was controlled by culling of over 1 million pigs and strict quarantine measures on pig movement.

While the disease in pigs was highly contagious and characterized by acute fever mainly with respiratory involvement, mostly without neurological signs, the predominant clinical syndrome in humans was encephalitic rather than respiratory. The major clinical signs included drowsiness, areflexia, segmental myoclonus, tachycardia, hypertension, pin-point pupils, and an abnormal doll's eye reflex (Chua et al., 1999; Goh et al., 2000). The incubation period ranged from 2 to 45 days, but for most patients it was 2 weeks or less (Chua, 2003; Goh et al., 2000). A majority of patients who survived acute encephalitis made a full recovery, but about 20% had residual neurological sequelae, including cognitive difficulties, tetraparesis, cerebellar signs, nerve palsies, and clinical depression (Goh et al., 2000).

A Hendra-like virus, named Nipah virus (NiV) after the village of the index case, was isolated from the CSF of several patients (Chua et al., 2000). Retrospective investigations suggested that the virus was also responsible for previous disease outbreaks in pigs in peninsular Malaysia since late 1996. Knowledge of the similarities between HeV and NiV facilitated the rapid identification of fruit bats as the reservoir host of NiV. Serological sampling of various bats in Malaysia found five species with neutralizing antibodies to NiV (Field et al., 2001a; Yob et al., 2001). They included four fruit bat species, *P. hypomelanus*, *P. vampyrus*, *Cynopterus brachyotis*, *Eonycteris spelaea*, and an insectivorous bat, *Scotophilus kuhlii*. NiV was subsequently identified and isolated from bat urine samples of *P. hypomelanus* and from a partially eaten fruit swab (Chua et al., 2002a). The genome sequences of bat isolates were largely indistinguishable from human NiV isolates (Chua et al., 2002a).

There is very little knowledge available on the treatment of NiV infection. Ribavirin was used during the NiV outbreak in Malaysia in an open-label study in which 140 patients with encephalitis were given the drug, and 54 patients who presented before the drug became available or who refused treatment acted as controls (Chong et al., 2001). Mortality in the treated and control groups was 32%

and 54%, respectively, indicating a significant reduction in the treatment group. *In vitro*, ribavirin has been shown to inhibit replication of HeV (Wright et al., 2004). In the absence of other therapies, ribavirin is an option for treatment of henipavirus infection. Other potential treatment approaches currently being developed include the use of neutralizing monoclonal antibodies (Zhu et al., 2006; Guillaume et al., 2006), soluble receptor or attachment protein molecules, and fusion-inhibiting peptides (Bossart et al., 2005a,b; Bossart & Broder, 2006).

Nipah Virus Outbreaks in Bangladesh (2001–2005)

Five outbreaks of NiV have been recognized in Bangladesh between 2001 and 2005, and each occurred between January and May. The first recorded outbreak occurred between April and May of 2001 in the western Meherpur District and involved 13 cases with nine fatalities (69% mortality). The second outbreak was in January 2003 in the western Naogaon District. Among the 12 patients who met the case definition, eight died (67% mortality). Patients from both outbreaks displayed similar clinical courses, starting with onset of fever, followed by headache and varying degrees of diminishing consciousness. Coughing and difficulty in breathing were also common and half of the patients had vomiting, but seizures and diarrhea were uncommon (Hsu et al., 2004).

The second and third outbreaks occurred in 2004 in two locations with no apparent link between the two outbreaks. Between January and February 2004, a total of 29 laboratory-confirmed or probable cases were identified with 22 fatalities (75% mortality) (ICDDRB, 2004a). Most cases were located in the central Rajbari District. Among the first group of 12 patients, all but two were between the ages of 7 and 15 years old. From February to April, a separate outbreak occurred in the Faridpur District with 36 patients and 27 deaths (75% mortality) (ICDDRB, 2004b). At least six patients from this outbreak developed acute respiratory distress syndrome, which has not been seen in previously documented Nipah patients. Another unique feature of this outbreak was the epidemiologic evidence supporting human-to-human transmission, the first for NiV infection in the human population.

The fifth and the latest outbreak occurred in January 2005 in the central Tangail District, and it involved 12 patients with 11 deaths (92% mortality) (ICDDRB, 2005). The most common clinical symptom was unconsciousness. Death occurred between 2–9 days after the first reported symptom of illness with a median of 4 days. The onset of illness for all patients occurred within two weeks of each other.

NiV was isolated from four patients during the 2004 outbreaks. Complete genome sequence was obtained from one isolate (from the Rajbari outbreak), and partial sequences were obtained from the other three (Harcourt et al., 2005). The overall genome organization of the Bangladesh NiV isolate is very similar to that of the Malaysian isolate. At a genome size of 18,252 nt, the NiV-Bangladesh genome is 6 nt longer than that of the NiV-Malaysian isolates. The overall nucleotide

sequence identity between the two isolates is approximately 92%. Phylogenetically, all of the Bangladesh isolates clustered together and can be distinguished from the cluster of Malaysian isolates.

Although no virus isolation has been made from bats in Bangladesh, there is substantial evidence suggesting that the fruit bat (*P. giganteus*) is the likely reservoir of NiV in Bangladesh. During the investigation of the Naogaon outbreak in 2003, two out of 19 *P. giganteus* bats had antibodies to NiV (Hsu et al., 2004). A larger animal study conducted during the investigation of the 2004 Rajbari outbreak also found that *P. giganteus* was the only species with anti-NiV antibodies (ICDDRB, 2005).

Nipah Virus Outbreak in India (2001)

During January to February of 2001, an outbreak of febrile illness with altered sensorium occurred in Siliguri, West Bengal, India, among hospitalized patients, their family contacts, and the medical staff of four different hospitals (Chadha et al. 2006; Kumar, 2003). While epidemiologic features and serological testing excluded the possibility of Japanese encephalitis, initial laboratory investigations failed to identify an etiological agent for the outbreak (Kumar, 2003).

Among the 66 patients who fit the working case definition, the case-fatality ratio was approximately 74%. All patients were greater than 15 years of age, and 75% of the patients had a history of hospital exposure. The outbreak started at a single hospital, and subsequently spread to three other hospitals. There was no definitive information about the possible index case. Clinical symptoms included fever (exhibited by all patients), headache and myalgia (57% of patients), vomiting (19%), altered sensorium (97%), respiratory symptoms (51%), and involuntary movements or convulsions (43%). Death occurred within 1 week of disease onset for 10 patients, within 2 weeks for 5 patients, and on day 30 for 2 patients (Chadha et al., 2006).

Because of the close geographic proximity of Siliguri to the Nipah outbreak regions in neighboring Bangladesh, a retrospective study was conducted to investigate the possibility of NiV as the causative agent. A total of 17 serum samples from 18 patients were analyzed for NiV-specific antibodies by ELISA. Nine out of the 17 sera were positive for IgM and IgG, and one sample was positive for IgG, but negative for IgM. In addition, six urine samples collected from the 18 patients were also tested by PCR and virus isolation. While there was no virus isolated using Vero E6 cells, five of the six urine samples were PCR-positive, four from sero-positive patients and one from a sero-negative patient. Analysis of a partial sequence from the M gene indicated that the etiologic agent was a strain of NiV, which has a close sequence homology with both the Malaysian and Bangladesh NiV isolates (94% and 99% sequence identity, respectively) (Chadha et al., 2006). The reservoir host for NiV in India has not been identified yet, but it is most likely to be the bat species *P. giganteus*, as suspected to be the case for the Bangladesh NiV outbreaks (Hsu et al., 2004; ICCDRB, 2005) or another closely-related flying fox species.

Presence of Henipaviruses in Other Countries in the Region

The identification of fruit bats in the genus *Pteropus* as the reservoir hosts of HeV and NiV in Australia and Malaysia, respectively, prompted searches for related viruses in other nations in the region. Fruit bats are widely dispersed geographically in a range that extends from the east coast of Africa, through the Indian subcontinent and Southeast Asia, north to Okinawa, and south to Australia (Koopman, 1992).

Serological studies carried out on two species of bats from Madang (*Dobsonia moluccense*, and *P. neohibernicus*) on the north coast of Papua New Guinea (Halpin, Field, Mackenzie, Bockarie, Young & Selleck, unpublished data) and four species of bats (*P. capistratus*, *P. hypomelanus*, *P admiralitatum*, and *D. andersoni*) from Port Moresby and New Britain (Field, Hamilton, Hall, Bornacosso, Halpin, & Young, unpublished data) were found to have antibodies to a HeV-like virus (cited in Mackenzie et al., 2003). Similarly, serological studies from fruit bats (*P. vampyrus*) trapped on the Indonesian islands of Sumatra and Java were found to have neutralizing antibodies for a virus more closely related to NiV than to HeV. In these studies, 11 bat sera neutralized NiV only, one serum neutralized HeV only, and 17 sera neutralized both viruses (Sendow et al., 2006).

A study by Olson et al. (2002) sampled 96 Lyle's flying foxes (*P. lylei*) from restaurants in Cambodia and conducted serological tests using ELISA and the neutralization test for henipavirus antibodies. Of the 96 serum specimens examined, 11 sera (11.5%) were positive in ELISA for NiV antibodies and the results were confirmed by serum neutralization. Some of these sera were also tested for their ability to neutralize HeV and were shown to have equivalent titers to both NiV and HeV. The authors concluded that a closely related virus, which might be neither NiV nor HeV, was circulating in the Cambodian bat population (Olson et al., 2002).

A second study in Cambodia was conducted during 2000–2001, in which a total of 1,303 bats were sampled either from restaurants or at their roosts in the wild, covering 35 locations in nine provinces (Reynes et al., 2005). These animals represented 16 species from six of the seven bat families known to be present in Cambodia. Serum samples from 1,072 bats were taken for NiV antibody ELISA testing and positive signals were obtained only in the species *P. lylei* with a seroprevalence of 10.9% (50 out of 458), corroborating the results conducted in the first study (Olson et al., 2002). Sera from other bat species were all negative and so were the limited number of human sera ($n = 8$) tested from individuals who had contact with sero-positive Lyle bats in restaurants. Attempts to isolate live virus from 769 urine samples yielded two virus isolates from urine samples collected at the same time from a roost of *P. lylei* bats in a village. Sequencing of the N and G genes indicated that the two isolates had identical sequences and that they shared a nucleotide sequence identity of 98% and 98.2%, respectively, with their Malaysian counterpart. Phylogenetic analysis based on current available henipavirus sequences suggest that the NiV isolate from Cambodian bats is more closely related to Malaysian isolates of NiV than isolates from Bangladesh.

A similar study was conducted in Thailand and recently reported (Wacharapluesadee et al., 2005). During March 2002 and February 2004, 1,304 bats were sampled from 15 sites covering nine provinces in central, eastern, and southern Thailand. Among the 12 bat species sampled, six were frugivorous and six were insectivorous. In addition to serum samples taken for NiV antibody tests, saliva (1,286 samples) and urine (1,282) swabs were also taken and analyzed by PCR for the presence of NiV-related sequences. From 1,054 sera tested, 82 positive samples (i.e., positive in NiV IgG ELISA) were obtained from four different species: 76 from *P. lylei*, four from *P. hypomelanus*, and one each from *P. vampyrus* and the insectivorous *Hipposideros larvatus*. PCR analysis using NiV N-gene specific primers demonstrated the presence of NiV-related viruses in both saliva and urine samples collected from different sites. While most of the positive samples were collected from *P. lylei* as expected, there was one positive saliva pool sample from *H. larvatus* (Wacharapluesadee et al., 2005). It is interesting to note that sequence analysis based on a 181-nt N gene PCR fragment indicated that the *H. larvatus* isolate was more closely related to the Malaysian NiV isolates, whereas the *P. lylei* isolates were more closely related to the Bangladesh isolates. It remains to be seen whether this pattern of homology will hold when the full-length genome sequences are compared.

In summary, direct isolation or genetic sequence amplification of henipaviruses from flying foxes has been demonstrated in Australia, Malaysia, Cambodia, and Thailand and the sero-prevalence has been observed in these countries and in Bangladesh, Indonesia, and Papua New Guinea. These studies indicate that further henipavirus-related infection can be expected within the area of distribution of flying foxes and highlight the potential of future henipavirus emergence in this wide region.

Menangle Virus Outbreak in Australia (1997)

Menangle virus (MenV) emerged in 1997 as the etiological agent of a severe reproductive disease in a large intensive piggery in Menangle, near Sydney, in Australia (Philbey et al., 1998). The outbreak caused a reduced farrowing rate and stillbirths with deformities and mummified fetuses (Philbey et al., 1998; Love et al., 2001). No disease was observed in postnatal animals of any age. Affected stillborn piglets frequently had severe degeneration of the brain and spinal cord, arthrogryposis, brachygnathia, and occasionally fibrinous body cavity effusions and pulmonary hypoplasia (Philbey et al., 1998). A high proportion (>90%) of serum collected from pigs of all age groups at the affected piggery from May to September 1997 contained high titers of neutralizing antibodies. MenV antibodies were also detected in pigs from two piggeries that received only weaned pigs from the affected piggery. Other than these three piggeries, an extensive serological survey failed to find any sero-positive pigs from other piggeries throughout Australia.

Two human cases associated with the pig disease outbreak were reported (Chant et al., 1998). In early June 1997, Patient 1 from the piggery where the disease outbreak started had a sudden onset of malaise and chills followed by drenching sweats and fever. He was confined to bed for the next 10 days with severe headaches and myalgia, but had no cough, vomiting, or diarrhea. A few days after the onset of illness, he noted a spotty red rash. He returned to work after two weeks' absence and reported a 10 kg weight loss during his illness. Patient 1 had frequent and prolonged contact with birthing pigs, and exposure to splashes of amniotic fluid and blood was common in his job. He often received minor wounds to his hands and forearms.

Patient 2 worked at one of the two other associated piggeries. He also had an onset of illness in early June 1997 characterized by fever, chills, rigors, drenching sweats, marked malaise, back pain, severe frontal headache, and photophobia (Chant et al., 1998). Similar to Patient 1, Patient 2 had no cough, vomiting, or diarrhea. Four days after onset of illness, he noted on the torso a spotty, red, non-pruritic rash, which lasted for 7 days. He recovered after 10 days, noting a 3 kg weight loss.

Serological investigation indicated that both patients had significant levels of convalescent neutralizing antibodies to MenV and showed no alternative cause. Seroepidemiologic testing of more than 250 persons with potential exposure to infected pigs revealed no additional infection other than the two patients described above. This included the partner of Patient 1, who also tested negative. Although the exact mode of transmission from pigs to humans remains unknown, it was almost certain that the two patients became ill following MenV infection (Chant et al., 1998).

A large breeding colony of grey-headed fruit bats as well as little red fruit bats roosted within 200 m of the affected piggery. A serological study indicated the presence of MenV-neutralizing antibodies in at least three fruit bat species collected in New South Wales and Queensland, and positive samples covered the period from 1996 (prior to the outbreak) to November 1997 (post outbreak). These results strongly suggest that MenV originated from fruit bats. This notion was further supported by the isolation of a closely-related paramyxovirus, Tioman virus (TiV), from fruit bats in Malaysia. MenV and TiV have a high level of sequence homology, almost identical genome organization, and strong antigenic cross reactivity (Bowden et al., 2001; Chua et al., 2001b).

Epidemiology

The mechanisms of henipavirus transmission within flying fox populations remain obscure. Horizontal transmission is suggested by the presence of NiV in urine and the observed licking of the ano-genital area, a behavior that occurs during the breeding season, and urination on the fur followed by licking, which occurs in males as part of their grooming behavior (Hall & Richards, 2000). In contrast,

vertical transmission is suggested by the transplacental transmission of HeV in experimentally infected flying foxes without apparent harm to the fetus (Williamson et al., 2000).

Human infections in Australia and Malaysia have occurred through transmission from horses and pigs, respectively, and there has been no evidence of direct transfer from bats despite many opportunities for bat carers to be exposed to HeV in Australia (Chua et al., 1999; Parashar et al., 2000; Selvey et al., 1996). Three hypotheses have been proposed for the transmission of henipaviruses from flying foxes to amplifying hosts:

1. Horses and pigs may have been infected in pastures or pigsties through contact with urine of infected bats (Chua et al., 2002a).
2. Viruses may have been transmitted in partially eaten fruit or fruit pulp, spat out by flying foxes (Chua et al., 2002a).
3. The amplifying hosts may have acquired the virus as a result of licking or eating infected placenta or aborted fetal material. HeV outbreaks occurred at the time of year when some species of flying fox are giving birth (Halpin et al., 2000; Field, et al., 2001b.

In Bangladesh, the role of amplifying hosts is equivocal. Each of the five outbreaks seems to have been associated with a different potential mode of transmission. In the Meherpur outbreak in 2001, Nipah cases were significantly more likely to have contact with sick cow and patient's secretions compared to controls (Hsu et al., 2004). In the 2003 outbreak in Naogaon, cases were more likely to have had contact with a herd of pigs that had passed through the area prior to the outbreak (ICDDRB, 2003). In Rajbari in 2004, Nipah cases were more likely to have climbed trees where bats had been and to have contact with patients. In the 2004 Faridpur outbreak, contact with ill persons was the primary risk factor. In the 2005 outbreak in Tangail, drinking fresh date palm juice potentially contaminated with bat secretions was considered the main route of transmission for most of the Nipah infections (ICDDRB, 2005).

Transmission of henipaviruses from bats to amplifying hosts depends on the susceptibility of the latter to oral infection and the titer of virus in urine, partially eaten fruit, or fetal tissues. The minimum infectious dose for horses or pigs is not known, but it is of interest that the minimum oronasal lethal dose of NiV for hamsters is 47,000 plaque forming units (pfu), compared with 270 pfu administered parenterally (Wong et al., 2003). It may also be pertinent that henipaviruses are isolated only rarely and in low titers from the urine of naturally or experimentally infected animals, but are more readily detected in tissues including those of the fetus (Williamson et al., 1998, 2000).

In contrast to the uncertainty concerning the mode of transmission of henipaviruses from bats to horses and pigs, the high titers of virus in the tissues and secretions of these amplifying hosts offer a range of sources for transmission to man during birthing, handling sick and dying animals, slaughtering, necropsy, and carcass handling (Chua et al., 1999; Murray et al., 1995a,b; Parashar et al., 2000). Although HeV generates predominantly respiratory infections, the virus was detected

infrequently in the upper respiratory tract of infected horses, suggesting that aerosol transmission to either man or horses is highly unlikely (Hooper et al., 1997). The failure to transmit HeV from experimentally infected to uninfected, in-contact horses is consistent with this suggestion (Williamson et al., 1998). The presence of HeV in equine saliva suggested that manual feeding of the animals may have facilitated horse to human transmission (Selvey et al., 1995). In contrast to the paucity of HeV virions in the upper respiratory tract of horses, NiV was readily observed in the respiratory epithelium of naturally and experimentally infected pigs. Thus the virus probably spread to humans and within the pig population by aerosol or by direct contact with oropharyngeal or nasal secretions (Middleton et al., 2002; Mohd. Nor et al., 2000).

Risk Factors and Disease Control Strategies

An understanding of the epidemiology of henipaviruses is essential for determining the risk factors associated with the transmission of virus from the reservoir host to either a domestic spillover or intermediate host or directly to humans. The destruction of native forest habitats by humans either to clear land for agriculture or to harvest timber has greatly increased the risk of fruit bats encountering spillover hosts as they seek new roosts and alternative food sources, and thus also increased the risk of emergence of epizootic disease.

For HeV, the risk factors are associated with the interaction between infected fruit bats and horses as the spillover hosts, and then from horses to humans. The risk of transmission between bats and horses appears to be a rare event, as is subsequent transmission between horses (Field et al., 2001b), whereas direct transmission from fruit bats to humans probably does not occur despite a high risk of occupational or recreational exposure among some groups (Selvey et al., 1996). Current strategies for controlling or preventing HeV epizootics are built around the three hypotheses for virus transmission from fruit bats to amplifying hosts listed above. They have centered around management strategies for horses rather than fruit bats and include minimizing exposure by stabling horses at night, excluding from horse paddocks, trees that bear fruit favored by fruit bats, and implementing quarantine and stock movement controls (Field et al., 2004; Mackenzie et al., 2003; Mackenzie and Field, 2004).

For NiV, the risk factors for epizootic emergence are essentially similar to those described above for HeV. However, there are important differences in the epidemiological features of NiV in Malaysia and Bangladesh. In Malaysia, NiV was readily transmitted between pigs and from pigs to humans. Human to human transmission of NiV was not a feature in the Malaysian outbreak (Chua et al., 2001a; Mounts et al., 2001). In contrast, the involvement of spillover hosts was not an obvious aspect of the outbreaks in Bangladesh and probably West Bengal (Chadha et al., 2006). In addition there has been epidemiological evidence to suggest that human to human transmission occurred in at least two of the epidemics in Bangladesh (Hsu et al., 2004; ICDDRB, 2005), as well as the outbreak in Siliguri, West Bengal (Chadha et al., 2006). In the

latter situation, nosocomial spread was implicated. The major risk factors in Malaysia and Singapore were associated with a close involvement with pig farming or infected pig carcasses, but in Bangladesh and Siliguri where there was no documented involvement with pigs, the risk factors were more difficult to clearly differentiate.

Control strategies in Malaysia have centered around good farm management practices with regular monitoring of herd health and early recognition of disease syndromes, clearly defined protocols for introducing new stock, and an ongoing disease surveillance program (Daniels et al., 2000; Field et al., 2004). In addition, decreasing the potential for fruit bat–pig interactions is also a major strategy to reduce the possibility of spillover events leading to disease emergence, and include simple measures such as removing fruit trees or orchards from the immediate vicinity of pig sheds, wire screening of open-sided pig sheds to prevent fruit bat access, and ensuring that roof run-off does not enter pig pens (Mackenzie et al., 2003; Field et al., 2004). It is also important that a rapid laboratory diagnostic capability is available with experienced veterinarians to interpret test results, and where necessary, to respond to and conduct outbreak investigations. In Bangladesh and West Bengal, the two most appropriate control measures at this time are to ensure all patients with possible NiV infection are barrier nursed with strict prevention of contact with visitors or other patients, and washing of all fruit for human consumption as well as ensuring all fruit juice is kept under conditions which restrict access to fruit bats.

Concluding Remarks

Since the emergence of HeV in 1994 in Australia, the last decade has witnessed multiple disease outbreaks caused by novel paramyxoviruses of bat origin. Of especial concern is the apparent human to human transmission of NiV in Bangladesh and India. Further investigation is warranted to determine the transmission routes of NiV, especially in the nosocomial setting. The possibility of human to human transmission becomes very important in all future control strategies. It also increases the potential for Nipah to become a disease of international significance.

Recent identification of bats as natural reservoir hosts of henipaviruses, MenV, Ebola virus, and SARS coronavirus highlights the importance of bats in emergence of zoonotic diseases. From the genetic diversity observed from limited genome sequences obtained so far, it is almost certain that other related viruses will emerge from *Pteropus* species or other fruit bats sharing the same or similar habitats. What we do not know is how genetically different they will be and whether they will be more or less transmissible to and among the human population. For example, the *Pteropus* sp in the western Indian Ocean are believed to have separated from other *Pteropus* sp more than 60,000 years ago. If one assumes that viruses coevolve with these hosts, one might expect that henipa-like viruses from these bats could be genetically very different from the ones isolated to date. This will undoubtedly have significant impact on our current diagnosis and control/prevention strategies.

It is therefore essential to focus our future research on a better understanding of virus diversity and distribution among fruit bats in different regions and on a better understanding of factors triggering spillover events and routes of transmission to and among human population. Wide international collaboration will be extremely important for such a multidisciplinary and multisite research endeavor.

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