Nipah virus is an emerging zoonotic pathogen that causes severe febrile encephalitis resulting in death in 40% to 75% of human cases. Nipah virus is considered a biosafety level-4 pathogen and is listed as a select agent with high risk for public health and security due to its high mortality rate in people and the lack of effective vaccines or therapies. The natural reservoir for Nipah virus and related members of the genus *Henipavirus* are fruit bats of the genus *Pteropus*. Nipah virus emerged in Malaysia in 1998 as a porcine neurologic and respiratory disease that spread to humans who had contact with live, infected pigs. Research reviewed in this paper suggests that anthropogenic factors, including agricultural expansion and intensification, were the underlying causes of its emergence. Nipah virus has caused five subsequent outbreaks between 2001 and 2005 in Bangladesh. Here, it appears to have spilled over directly from bats to humans, and person-to-person transmission is evident suggesting a heightened public health risk.

Introduction

Emerging infectious diseases (EIDs) are a significant threat to public health globally [1]. Of those diseases considered to be emerging, approximately 75% are zoonotic (ie, are able to naturally be transmitted between animals and humans) [2•]. The underlying causes of these disease emergences involve changes to human social behavior (eg, drug use, travel and trade), to demography (eg, urbanization) or to the environment (eg, landuse changes) [3,4,5••]. For zoonotic EIDs, anthropogenic landuse changes and other factors that affect the contact between animals and humans are particularly important [6,7]. Deforestation, agricultural expansion, global travel, trade in wildlife, and other anthropogenic factors can lead to increased interaction among humans, domestic animals, and wildlife, increasing the opportunities for pathogens to be exchanged among these groups [8]. Because of this close connection among the environment, humans, domestic animals, wildlife and their pathogens, a broad ecologic perspective is useful to understand the reasons for zoonotic disease emergence.

Nipah virus—like severe acute respiratory syndrome coronavirus, HIV, and highly pathogenic avian influenza—is a salient example of a wildlife pathogen that emerged in human populations causing a lethal disease. Nipah virus is a recently discovered paramyxovirus belonging to a new genus (*Henipavirus*) within the family *Paramyxoviridae* (Order: *Mononegavirales*, subfamily *Paramyxovirinae*) [9]. The first member of this genus to emerge was Hendra virus in 1994 in Australia [10]. Nipah virus caused a large outbreak in humans in Malaysia during 1998 to 1999 and is responsible for five subsequent outbreaks in Bangladesh between 2001 and 2005 [11,12,13••]. Both viruses appear to have fruit bat (*Pteropus* species) reservoirs [14•,15], and both initially emerged via domestic animal amplifier hosts (horses for Hendra virus; pigs for Nipah virus), although some of the recent outbreaks in Bangladesh may have involved direct transmission between bats and humans [13••].

In this review we summarize the clinical aspects and pathology of Nipah virus encephalitis. We discuss information on the epidemiology of this pathogen in its natural reservoir and current hypotheses on the factors responsible for its emergence in Malaysia and, more recently, in Bangladesh. Finally, we discuss the potential for future emergence of Nipah and related viruses in Asia, Australia, and elsewhere.

Clinical and Epidemiologic Features of Nipah Virus in Humans: Malaysia 1998 to 1999

Nipah virus emerged in Malaysia in 1998 to 1999 as a porcine respiratory and neurologic disease and was transmitted to humans [11]. The outbreak of encephalitic
disease in pigs spread through peninsular Malaysia as infected animals were shipped between farms from north to south and into Singapore. There were a total of 265 human cases of Nipah virus infection in Malaysia and a further 11 in Singapore [16]. Of those infected, nearly 40% (105) died. Almost all cases were directly associated with the pig industry, suggesting that Nipah virus in Malaysia is either unable or unlikely to spill-over from its reservoir directly to humans. This was subsequently supported by a serologic survey of Tioman Islanders who live in close proximity to the population of the Island fruit bat *Pteropus hypomelanus* from which Nipah virus was isolated. This survey did not find evidence of exposure to Nipah virus in any of the 153 people tested, suggesting that the risk of direct transmission from bats to humans is low [17]. The origins of the outbreak were in a large, intensively-managed pig farm in Ipoh, Malaysia, where the first known pig and human cases occurred as early as January 1997, prior to the large outbreak in the Nipah region of Malaysia [11,14•] (Field et al., unpublished data).

Nipah virus causes severe acute febrile encephalitis with virus infiltrating most major organs and endothelial cells [18•]. Laboratory tests used to make a definitive diagnosis include viral isolation, immunohistochemistry (IHC), polymerase chain reaction (PCR), and serology [18•]. In fatal cases of acute Nipah virus encephalitis, there was an 81% correlation between serology and IHC [18•]. Retrospective diagnosis of Nipah virus used a case definition that included contact with pigs or other infected animals and inhabiting a known outbreak site [19].

The predominant symptoms in Malaysian patients were fever, headache, altered mental state, vomiting, and loss of consciousness [19]. Myoclonus, areflexia, and tachycardia were among the signs that indicated brain stem dysfunction and central nervous system (CNS) involvement. Less than 20% of patients presented with coughing or other upper respiratory signs, despite the presence of virus in the upper respiratory tract [19]. Coughing was a more prominent feature (40%) in cases of fatal acute Nipah virus encephalitis [18•]. The relatively low occurrence of coughing may explain the lack of human to human transmission in the Malaysia outbreak. Relapse of Nipah virus encephalitis occurred in 12 acute encephalitis survivors (7.5%) and delayed onset (average 8.4 months) occurred in 10 cases (3.4%). Of these 22 late-onset and relapse cases, four died and the rest had persistent neurologic deficits [20].

In cases of acute fatal Nipah virus encephalitis, the virus was identified in the CNS, lungs, kidneys, spleen, lymph nodes, and endothelial tissue of the smaller blood vessels [18•]. Typical lesions included widespread vasculitis, particularly in the CNS, heart, lung, and kidney, with multinucleated giant endothelial cells sometimes present in these organs. Viral inclusion bodies were present in the cytoplasm and nuclei of neuronal cells. Viral antigen was seen by IHC staining in the blood vessels of most organs, particularly where vasculitis was present. Many of the pathologic findings of acute fatal Nipah virus encephalitis are common to other encephalitic diseases; however, the presence of syncitial multinucleated endothelial cells is characteristic of Nipah and Hendra virus infection [18•].

There have been no new cases of Nipah virus reported in Malaysia or Singapore since the 1998 to 1999 outbreak.

**Nipah Virus Outbreaks in Bangladesh**

Five outbreaks of human Nipah virus infection have been recognized in Bangladesh between 2001 and 2005. To date, 102 human cases of Nipah infection have been documented in Bangladesh; 76 (75%) of these were fatal. Epidemiologic data suggest four major differences between the outbreaks in Bangladesh and those in Malaysia and Singapore: 1) Nipah virus has spilled over into the human population repeatedly in five independent outbreaks; 2) spillover appears to be seasonal; 3) spillover occurred without livestock amplifier hosts; and 4) there is strong evidence of human-to-human transmission. Genetic characterization of the Nipah virus isolated from humans in Bangladesh in 2004 showed it to be distinct from the Malaysian strain, with the two viruses having approximately 92% nucleotide sequence homology [21].

All five outbreaks occurred between the months of January and May [13••,22–24]. There is no evidence for livestock amplifier hosts between pteropid bats and humans in the Bangladesh outbreaks. Pigs are uncommon in Bangladesh, though a pig herd was present in Naogaon 2 weeks before the outbreak [13••]. Contact with a sick cow was significantly associated with illness in the Meherpur outbreak (odds ratio [OR] 7.89; 95% CI 2.2–27.7). The cow was not tested for Nipah virus, and so it is still unclear what role domestic animals play in Nipah virus transmission in Bangladesh [13••]. Among 10 birds, 6 pigs, 4 dogs, 2 shrews, and 4 rodents tested in Meherpur and Naogaon, none had antibodies to Nipah Virus [13••].

In Bangladesh there is evidence of person-to-person transmission of Nipah virus [13••,23]. In the first outbreak, in the Meherpur district, the index patient died 6 days after developing symptoms. Five other persons in the household developed Nipah virus disease 10 to 18 days after the index case, and nine of the 13 infected people in this outbreak were relatives of the index case. Living with an infected person was a risk factor for illness (OR 4.80; 95% CI 2.2–9.1) in the Naogaon outbreak (odds ratio [OR] 7.89; 95% CI 2.2–27.7). The cow was not tested for Nipah virus, and so it is still unclear what role domestic animals play in Nipah virus transmission in Bangladesh [13••]. Among 10 birds, 6 pigs, 4 dogs, 2 shrews, and 4 rodents tested in Meherpur and Naogaon, none had antibodies to Nipah Virus [13••].

In Goalando in January 2004, the head of one household became ill, followed 2 weeks later by his wife and three eldest daughters. All died of Nipah virus infection. In Faridpur between February and April 2004, the virus appears to have undergone four transmission cycles in people [23]. The most recent Nipah outbreak occurred in the Tangail District in north central Bangladesh in January
2005. Among 12 persons who met a case definition of outbreak-associated encephalitis, 11 (92%) died [23].

Most patients presented with fever and central nervous system symptoms, and a severe respiratory illness was reported in some [24]. This was not a finding in the Malaysia outbreak, and may explain some of the human-to-human transmission.

Therapeutics and Vaccines
During the 1998 to 1999 outbreaks of Nipah virus in Malaysia, ribavirin was administered to patients presenting with acute, Nipah virus encephalitis. Ribavirin treatment was associated with a 36% reduction in mortality among those diagnosed with Nipah virus encephalitis as compared with a control group of patients who were treated prior to the availability of ribavirin or who refused ribavirin [25]. Although ribavirin therapy may have been somewhat effective, there are currently no commercially available vaccines or approved therapeutics for Nipah virus. Nipah and Hendra virus have homologous attachment glycoproteins that are associated with virus to host-cell binding (G) and fusion (F), suggesting that these viruses may utilize common host-cell receptors [26,27]. Ephrin-B2 was recently identified as a cell-surface receptor that permits both Nipah and Hendra virus viral fusion and cell entry. Ephrin-type receptor proteins are found in most human tissues. Ephrin-B2 is highly expressed in vascular and respiratory tissue, which is where Nipah virus was commonly found in patients who died from Nipah virus encephalitis [18•,28•]. Fusion inhibitors that block the expression of Ephrin-B2 could be used in future vaccines or therapeutic agents of clinical benefit [28•].

Nipah Virus in Pig Amplifier Hosts
In contrast to the predominance of neurologic symptoms in humans, pigs infected with Nipah virus commonly presented with an acute febrile severe respiratory and neurologic syndrome, with signs varying depending on the age of the pig [29,30]. The most obvious clinical feature in young pigs was a severe, nonproductive cough, sometimes called a “barking cough.” Neurologic signs included tremors, hind-end weakness with spastic paresis, and general ataxia. Boars and sows presented with a similar syndrome that included excessive flow of saliva, nasal discharge, and abortion primarily in early-pregnancy sows [29]. Nipah virus is thought to be highly infectious among pigs, most likely spread through aerosolization of virus due to coughing and mechanical contact with oronasal secretions. This is presumed to be the primary mechanism of transmission to humans as well, although virus was isolated from pig urine and feces [29]. In some pigs, virus was present in the CNS despite a clinically normal appearance [30]. Sub-clinical infection occurred in pigs during the outbreak, and pigs were able to transmit the virus during sub-clinical infections [31]. Experimental infections also showed that pigs can maintain Nipah virus sub-clinically and are able to transmit the infection in this state [31]. The infection rate among pigs was close to 100%, and mortality was between 1% and 5% [29].
and in turn, these species at the northern extent of their range are known to mix with *P. giganteus*, whose distribution extends eastward (from Thailand and Burma) across to India and Bangladesh [36,37]. Molecular characterisation and phylogenetic analyses suggest that both Hendra and Nipah viruses have co-evolved with their fruit bat hosts from an ancient, common ancestor [38,39]. As would be expected for such a long co-evolutionary relationship, henipaviruses have relatively low pathogenicity in their fruit bat reservoir hosts. Australian fruit bats (*Pteropus poliocephalus*) experimentally inoculated with Hendra virus in some cases developed sub-clinical infections [40], and no clinical signs were reported in bats inoculated with Nipah virus (Halpin et al., unpublished observations).

Ecologic change, rather than evolution of a new strain, is the most plausible key factor in the emergence of Hendra and Nipah viruses. The available molecular data suggest little variation in the known isolates of both viruses. Data on many fruit bat species suggest that populations in Australia and Southeast Asia are in decline [41]. Anthropogenic activities, primarily habitat loss and hunting, have been identified as major threats to their populations [37]. Deforestation for agricultural land, commercial logging, or urban development and hunting for sport, consumption, or crop protection is widespread in the region and results in loss of feeding habitat or abandonment of roosting sites. A scenario emerges of fruit bat populations under stress, of altered foraging and behavioral patterns, and of closer proximity to human populations [42].

At the time Nipah virus emerged, there was limited information available about the current distribution of *P. vampyrus* in Peninsular Malaysia [41,43]. The population of *P. vampyrus* in Peninsular Malaysia has likely declined in recent times due to habitat loss and hunting [41,43,44]. Anecdotal evidence suggests that *P. vampyrus* moves from Sumatra to Malaysia and it seems likely that the population is contiguous to some extent [43]. Deforestation is severe in Sumatra, and it is likely that this has also led to a lowering of the total reservoir population, and perhaps a change in migration patterns. Loss of natural food resources through deforestation may have made *P. vampyrus* more dependent on cultivated fruits such as durian, rambutan, langsat, and jambu air [43]. These fruits were cultivated on and near the farm where the index cases of Nipah virus were found [45].
The Causes of Nipah Virus Emergence

Pathogen emergence may be addressed by answering two essential questions: “why here?” and “why now?” The “why here” aspect of Nipah virus’ emergence is explained by the intersection of commercial fruit production with intensive pig-farming and resident fruit bat populations in the area surrounding the index farm of the 1998 to 1999 outbreak [45]. At the time of the outbreak, fruit trees were routinely planted in close proximity to pig sties. Planting orchards provided additional income for farmers, but an unintended result was the attraction of flying foxes onto their properties. On the large pig farm where Nipah virus infection first occurred in pigs and then humans (the “index farm”), branches from fruit trees frequently hung over the pig enclosures [45]. The isolation of Nipah virus from chewed fruit dropped by bats suggests that ingestion of bat saliva- or urine-contaminated fruit by pigs at the index farm may have led to the spillover of the virus into pigs [45].

The “why now” aspect of Nipah virus emergence is more challenging. A recent paper hypothesized that spill-over was a one-time event driven by a severe El Niño Southern Oscillation drought and anthropogenic forest fires in Indonesia that forced migration of Nipah virus–infected bats to Malaysia [45]. This hypothesis implies that bats were newly arrived in the Ipoh area in early 1998, just prior to the outbreak, leading to the emergence of Nipah virus. Our surveillance and tracking data suggest that Pteropodid bats are consistently found in the Ipoh area, even in nondrought years and that P. vampyrus regularly move between Sumatra and mainland Malaysia in the absence of severe climatic conditions or haze (Epstein et al., unpublished data). Furthermore, several Nipah virus encephalitis cases associated with the index farm were retrospectively diagnosed as occurring in early 1997, prior to the El Niño–related drought (Field et al., unpublished data). Thus, the “why now” of Nipah spill-over must be considered as largely random: transmission from flying foxes to pigs, and subsequent pig-to-human transmission, may have occurred on multiple occasions over an unknown time span.

The presence of Nipah virus encephalitis cases before the main outbreak and the largely random nature of the timing of spillover raise an additional question in relation to Nipah virus emergence: “Why was it noticed in 1998 to 1999, when it had gone unnoticed before?” The answer to this question appears to have two parts and again hinges largely on chance events. First, models show that spillover of the virus from bats to pigs on an intensively managed farm such as the index farm leads to a large epidemic in pigs that quickly burns itself out [46]. Such an epidemic would be expected to produce few human cases, and those that occurred would be highly clustered in both space and time. The cluster of cases on the index farm in 1997 follows this pattern. Subsequent reintroduction of the virus from bats into the pig population could have a variety of effects, depending on the timing of the spillover. The scenario that best explains the difference between the series of cases in 1997 and the 1998 to 1999 outbreak is that the virus was reintroduced into the pig population whereas a large proportion of the sows retained antibodies from previous exposure. Unlike young pigs, which are usually sent to market within 6 months after birth, sows are kept in the population up to 5 years for breeding purposes. After approximately 6 months, therefore, no previously exposed young pigs would remain in the population; sows and pigs young enough to maintain maternal antibodies, however, would be immune to infection. The difference in the force of infection compared with the earlier epidemic would permit the virus to circulate endemically within the pig population [46]. The long-term maintenance of the virus on a single, large pig farm would allow plenty of opportunity for spread beyond the index farm, producing more widespread cases in both pigs and humans.

Finally, there was another chance event: that some of the infected pigs from the Ipoh area were sold to farms in the south, probably as a “firesale” response once farmers perceived a link between sick pigs and people. In southern Peninsular Malaysia conditions increased the rates of pig-to-human transmission and led to a large-scale outbreak in humans. Once the human cases reached a large number, it became clear that the disease was epidemiologically distinct from Japanese encephalitis, which was originally thought responsible for the outbreak, and a novel etiologic agent was sought.

Conclusions

The wide distribution of Nipah virus antibodies in Pteropus fruit bats across South and Southeast Asia suggests that these bats harbor Nipah or related viruses across their range. Some of these viruses are likely to be highly lethal and able to transmit from human to human, as seems to have occurred in Bangladesh. The distribution of Pteropus ranges from Madagascar eastward across the Indian Ocean islands, South Asia, Southeast Asia, Australia, and much of the Pacific islands, and includes some of the most densely populated regions on Earth. Clearly, this suggests a serious potential for larger epidemics in the future. As seen with the severe acute respiratory syndrome, air travel can rapidly expose diverse populations to respiratory illnesses originating in remote locations.

There is a need for novel therapeutic and vaccine strategies against Nipah and related viruses to limit future epidemics. Other strategies may include curtailing anthropogenic activities that increase interactions between fruit bats, domestic animals and people. Spillover in Bangladesh may have occurred from people eating fruit from trees or drinking date palm juice also utilized by bats [13••,22]. In Malaysia, deforestation, planting of fruit orchards and the development
of intensive pig farms created the right conditions for a sustained Nipah virus outbreak. Our new understanding of the conditions and mechanisms of transmission of Nipah virus may provide the basis for these intervention strategies to protect human and animal health.

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