Introduction
Malaysia (2°30'N, 112°30'E) is located in the heart of Southeast Asia with a population of approximately 27 million as of 2007. It is made up of Peninsular Malaysia and the Malaysian Borneo, which are separated by the South China Sea, divided into a federation of 13 states and three federal territories including the Kuala Lumpur Federal Territory. The majority of the population is concentrated in Peninsular Malaysia with approximately 20 million people living in this more developed area of the country. The local climate is tropical and characterized by annual monsoons from October to January.

Progressive development over the last 50 years since independence in 1957 has meant that infectious diseases have gradually ceased to be the leading cause of death, with chronic diseases such as cardiovascular disease, cancer, chronic respiratory diseases, and diabetes mellitus becoming...
more commonplace amongst the increasingly more affluent Malaysians. However over the last decade attention has once again been drawn to infectious diseases, with the emergence of new infections and the re-emergence of diseases previously well-controlled in the Asian region in general, and in Malaysia in particular.\(^2\) In Southeast Asia alone, the discovery of new human viruses that cause large and devastating epidemics, such as the severe acute respiratory syndrome (SARS) coronavirus and the highly pathogenic avian influenza (HPAI) H5N1 virus, have been reported. Unlike some countries in the region, Malaysia was spared from the outbreak of SARS coronavirus and has yet to identify the HPAI H5N1 infection in humans that adversely affected neighboring countries (although frequent outbreaks in poultry have been reported). Nevertheless, in the last decade, Malaysia has been battling different challenges caused by various known or novel zoonotic and non-zoonotic viruses identified for the first time in the country.

In this article we provide historical, epidemiological, clinical, and scientific insights into the emerging, re-emerging, and recombinant viruses identified in Malaysia between 1997 and 2007 (Figure 1). Although the discovery of novel viruses on some occasions may be explained partly as being an artifact of increased surveillance and reporting efforts in the country — the best example being the investigation of Nipah virus, which led to the incidental discovery of other novel zoonotic viruses — recent studies, taking into account various socio-economic, environmental, and ecological factors associated with the emergence of infectious diseases,\(^3\)–\(^6\) show that lower-latitude developing countries including Malaysia are particularly at risk of emerging infectious disease events due primarily to zoonotic pathogens of wildlife origin and vector-borne pathogens.\(^2\) Here, we discuss probable events that have been implicated in the appearance of these viruses, with the aim of strengthening the existing preventive measures and strategies for managing potentially new and unfamiliar diseases in the future.

### Enterovirus 71

Human enterovirus 71 (EV-71) and 11 other group A coxsackieviruses (CV-A) are members of the *human enterovirus A* (HEV-A) species from the *Enterovirus* genus of the *Picornaviridae* family. Enteroviruses are distributed worldwide and can be transmitted effectively through the fecal—oral route and to a lesser extent, by respiratory transmission. The great majority of enterovirus infections are asymptomatic, but some can lead to serious illnesses particularly in infants and the immunocompromised. Hand-foot-and-mouth disease (HFMD) in children is usually caused by enteroviruses such as CV-A10, CV-A16, and EV-71.

An epidemic of HFMD was first reported in Sibu, Sarawak (Malaysian Borneo) in April 1997,\(^7\)–\(^10\) followed by smaller outbreaks in Peninsular Malaysia in the same year (Figure 1).\(^7\)–\(^8\),\(^11\) More than 2600 children were infected. Most presented with a febrile illness and characteristic lesions on the palms, soles, and oral mucosa, but a small proportion, mainly children <6 years of age, presented with severe neurological complications such as aseptic meningitis, poliomyelitis-like acute flaccid paralysis, or fatal encephalomyelitis. Cardiopulmonary symptoms such as neurogenic pulmonary edema with secondary myocardial dysfunction leading to rapid cardio-respiratory decompensation were also reported. Twenty-nine children eventually succumbed to the disease in Sarawak\(^10\) and 12 in Peninsular Malaysia.\(^11\)

**Figure 1** Zoonotic, non-zoonotic, and vector-borne viruses emerged in Malaysia between 1997 and 2007. The abbreviations for the viruses and their year(s) of emergence at various locations in Malaysia are shown. Viral outbreaks in Singapore during the same period are also indicated. HPAI H5N1, highly pathogenic avian influenza subtype H5N1; NIV, Nipah virus; CHIKV, chikungunya virus; EV-71, enterovirus 71; HIV-1 CRF33_01B, HIV type 1 circulating recombinant form (CRF33_01B); MelV, Melaka virus; TiV, Tioman virus; PulV, Pulau virus; SARS-CoV, severe acute respiratory syndrome coronavirus.
EV-71 was isolated from neuronal or non-neuronal samples from most of the infected children, including those who succumbed to the infection, suggesting its role as the etiologic agent. Different lineages of EV-71 subgenotypes C1 and C2 and two previously undefined subgenotypes B3 and B4 were identified in these outbreaks, with novel subgenotype B3 being the most prevalent strain in Sarawak in 1997, particularly among patients with the milder form of HFMD. Further outbreaks occurred in 2000 and 2003 in Sarawak where newly identified subgenotypes B4 and B5 were predominant. Interestingly, phylogenetic and recombination analyses revealed that some EV-71 strains isolated in the 1997 outbreak were intertypic recombinant involving EV-71 subgenotype B3, CV-A16, and various HEV-A species. These recombinant strains were isolated from uncomplicated HFMD cases and were thought to have reduced viral fitness and adaptation to host immunity compared to the parental strains. The pathogenic potential and clinical attributes of these recombinants, however, are not well understood.

Subsequent to the first outbreaks in Malaysia, several large EV-71-associated HFMD outbreaks were also reported across the Asia Pacific region: in Taiwan in 1998; in Western Australia in 1999; in Singapore, Japan, Korea, and Taiwan in 2000; in Vietnam in 2005; and in China in 2008. Despite the occurrence of numerous HFMD and EV-71 outbreaks worldwide since 1969, no outbreaks involving fatal cases of brainstem encephalitis and neurogenic pulmonary edema have been reported, except for those in Malaysia, Taiwan (which claimed 78 lives), and recently in Vietnam and China. This shows that the past decades EV-71 may have evolved to become more pathogenic than its ancestral strains. In the meantime, the synergistic potential exerted by other infectious agents in the pathogenesis of the disease cannot be ruled out. This includes the description of acute flaccid paralysis caused by adenoviruses and echovirus 7-associated encephalomyelitis during these outbreaks. Furthermore, a prospective study conducted during the 2000 and 2003 HFMD outbreaks in Sarawak showed that co-infection with another enterovirus or adenovirus among children with EV-71 was common.

Diverse EV-71 subgenotypes determined from different genomic regions indicate that multiple EV-71 lineages have been circulating in the Asia Pacific region since 1997, with each subgenotype causing distinct outbreaks of varying clinical manifestations and neurovirulence. Driven by such complexity, it has not been possible to identify a single neurovirulent genotype nor its pathogenic mechanisms associated with the severe neurological outcomes — although recent studies have suggested that subgenotype B5 and particular subgenotypes from the genogroup C are linked with neurological complications. Continued molecular epidemiological surveillance is essential to delineate the temporal trends of EV-71 transmission, the neuropathogenic potential of its subgenotypes, and to plan for effective clinical interventions plus preventive measures.

**Nipah virus**

In September 1998, an outbreak of respiratory illness and encephalitis with low morbidity and mortality rates occurred among pigs in commercial farms (initially presumed as porcine respiratory and encephalitis syndrome) in the Kinta district of Ipoh, Perak state in Peninsular Malaysia. Later in the month, a group of workers linked with pig farming presented with acute febrile encephalitis that was associated with a high case fatality rate. The disease affecting humans was initially diagnosed as Japanese encephalitis (JE), which is endemic in Malaysia, prompting health authorities to attempt to contain the outbreak based on preventive measures against JE in the Kinta district and also throughout the country. The infected pigs in the Kinta district were presumed to be disease-free and eventually transported to pig farms and abattoirs in other states in Malaysia, and also to neighboring Singapore.

Two months later in December 1998, a similar outbreak was detected in Sikamat town, and then by February 1999 in Sungai Nipah village and the town of Bukit Pelandok, all within the city of Seremban in the state of Negeri Sembilan located in central Peninsular Malaysia. Approximately 70% of the infected patients were of Chinese ethnicity and were directly involved in pig farming activities (as pig farmers and workers). Those affected had had direct contact with pigs in the 2 weeks before the onset of illness, suggesting direct viral transmission from pigs to humans with a short incubation period. These patients presented with an acute illness with fever, headache, dizziness, vomiting, and reduced levels of consciousness, before rapidly progressing to severe encephalitis that was associated with a high mortality rate. Up to 25% of cases had concomitant respiratory syndromes. A similar outbreak was then reported in Singapore among abattoir workers who had handled infected pigs imported from Malaysia.

In early March 1999, a novel paramyxovirus responsible for the outbreak was isolated from the cerebrospinal fluid of an encephalitic patient from Sungai Nipah village, and was later named the Nipah virus (NiV). The discovery of NiV played a critical role and was an important turning point in controlling the outbreak. Strong evidence showed that transmission of NiV to humans was through close contact with infected pigs, and affected those directly involved in pig farming activities such as assisting in pig breeding and birthing of piglets, those administering injections or medications to pigs, and those handling dead pigs. This led to an immediate halt in direct handling and transportation of pigs within the country and subsequently the culling of over a million pigs. Initially, NiV was also described among healthcare workers, although this was uncommon. The overall case fatality rate for the outbreak reported by the Ministry of Health was 38.5%; 109 fatalities from 283 cases of viral encephalitis.

Genetic characterization revealed that NiV is closely related to the Hendra virus (HeV), a paramyxovirus species causing severe respiratory disease in horses and humans in Queensland, Australia, which first emerged in 1994. The full-length genome sequences of NiV and HeV are approximately 18 kb, significantly longer than the average size of 15.5 kb of other viral genomes from the *Paramyxovirinae* subfamily. NiV and HeV also share similar genomic organization, both having increased nucleotide length of the 3' non-coding region in most of the genes. Taking together the close phylogenetic relationship of NiV and HeV plus its distinct divergence and little immunological cross-reactivity with other established genera within the *Paramyxoviridae*, the two geographically remote viruses were classified as belonging to a new genus — *Henipavirus*. (Figure 2).
The discovery of NiV as the causative agent of severe febrile encephalitis in humans and the identification of pteropid fruit bats as the natural hosts has helped regional as well as international scientific communities to be better prepared with management strategies for similar emerging zoonotic diseases, as witnessed in the recent NiV-associated encephalitis outbreaks in Bangladesh. 

The pursuit of the natural host of NiV led to the unexpected discovery of another novel zoonotic virus in 1999. On an island about 25 km off the eastern coast of Peninsular Malaysia, a new virus of the *Paramyxoviridae* family called the Tioman virus (TIV) was identified. TIV was isolated from pooled urine samples of free-living variable flying foxes (*P. vampyrus*), and other species of the order Chiroptera, suggesting widespread infection of NiV in the bat population in Peninsular Malaysia. A novel method of collecting free-living fruit bat urine samples using plastic sheets was then adopted, and eventually NiV was isolated from urine samples and swabs from fruits partially eaten by the variable flying foxes (*P. vampyrus*), Malayan flying foxes (*P. hypomelanus*), and other species of the order Chiroptera, suggesting widespread infection of NiV in the bat population in Peninsular Malaysia. 

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### Tioman virus

The first sporadic outbreak of chikungunya virus (CHIKV) infection occurred between late 1998 and early 1999 in Port Klang, Kuala Lumpur. Fifty-one patients living in low-cost housing in the Klang Valley presented with fever, headache, malaise, and myalgia. The rash, which appeared on the second to third day of illness, usually started on the lower legs and spread upward, sparing the palms and soles. The rash persisted for an average of 5 days and was pruritic. The median duration of illness was 10 days. 

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### Phylogenetic analyses

Phylogenetic analyses show that TIV and MenV are clustered in the *Rubulavirus* genus with up to 85% amino acid similarity in the nucleocapsid (N) gene between the two viruses (Figure 2). The N protein shows significant sequence homologies with other *Rubulavirus* members, including the mumps virus (approximately 50%). Human disease caused by TIV has not been documented thus far, although possible human infections, as determined by the presence of antibodies against TIV among the island inhabitants, have been observed. Animal experiments have demonstrated that TIV is neurotropic causing necrosis in the cerebrum and hypothalamus in intracerebrally-inoculated mice, and is capable of causing mild disease in pigs, mainly by affecting the lymphoid tissues.
and squatter estates presented with fever, polyarthritides of the small joints of the hands and feet, transient maculopapular rashes, myalgia, and arthralgia. The clinical symptoms resembled those of the more ubiquitous classical dengue fever; this posed an initial challenge in diagnosing the disease since dengue virus is endemic in the country.79

Chikungunya virus (chikungunya, from the root verb kun-gunya) means to ‘dry up or become contorted’ in Makonde language in Tanzania65) is related to group A arboviruses. CHIKV is an Alphavirus from the Togaviridae family that shares the same vectors responsible for spreading dengue virus, namely Aedes aegypti and, to a lesser extent, Aedes albopictus, which are the common peridomestic mosquito species in the Southeast Asia region. Studies conducted in the 1970s detected antibody against CHIKV among the rural populations in Malaysia, indicating the presence of CHIKV infection.81,82 However, until recently, outbreaks causing human diseases have not been reported.

Seven years after its first appearance, new CHIKV infections re-emerged in Bagan Panchor (about 50 km from Ipoh), Perak between March and April 2006.83,84 More than 200 villagers in a fishing community were infected with CHIKV strains derived from a common ancestral lineage from the 1998/99 outbreak, but this recent outbreak had a notably higher number and rate of infections. This outbreak coincided with the largest ever CHIKV epemics affecting the Indian Ocean territories between 2005 and 2006, where in Reunion alone more than 266 000 people, about a third of the total population, were infected. In India, an estimated 1.4 million human cases were reported during 2006. In these outbreaks, a substantial proportion of patients also showed unusual clinical manifestations, including severe neurological symptoms and fulminant hepatitis.85,86 Although unclear, plausible explanations for the re-emergence of CHIKV in this region include tourism and migration labor (Malaysia is greatly dependent on migrant workers from neighboring countries where CHIKV is endemic76), viral mutation, and CHIKV introduction into a naive population.87 Phylogenetic evidence has shown that the contemporary Malaysian strains isolated in 2006 were, however, distinct from the epidemic strains reported in the Indian subcontinent (2005—2006), suggesting that CHIKV is indeed endemic in Malaysia.83 Since the concurrent re-emergence of CHIKV in the Indian Ocean region and Malaysia seem to be unrelated, it is possible that other factors could have played an important role in driving these outbreaks. Climate anomalies, for instance, may have favored the mosquito vectors and consequently facilitated CHIKV emergence in these areas.88,89

**Pulau virus and Melaka virus**

During the search for NiV in fruit bats on Tioman Island in 1999, another novel virus, initially thought to be a bat paramyxovirus, was identified. While serological tests excluded the presence of a paramyxovirus, further electron microscopic, serologic, and phylogenetic investigations established the fusogenic agent as a reovirus.90 Designated as Pulau virus (PulV) (pulau denotes ‘island’ in the Malay language), PulV is a dsRNA virus displaying the typical ultrastructural morphology of a reovirus. PulV formed large syncytium in Vero cells and showed serologic reactivity against Nelson Bay virus (NBV), another known bat Orthoreovirus isolated from the Australian flying foxes (Pteropus alecto).91 To date, PulV has not been associated with any human diseases, and very little is known about the host range, pathogenesis, and epidemiology of this newly recognized virus.

More recently in 2006, another novel Orthoreovirus named Melaka virus (MelV) associated with acute respiratory disease in the human was identified.92 MelV was isolated from an adult male who developed a high fever and acute respiratory symptoms. Icosahedral viruses similar to those of the Orthoreovirus genus were noted on microscopic examination of mammalian cell lines infected with MelV, and serological studies of the patient serum showed neutralization activity against PulV. Nucleotide analysis of the small (S) segments revealed a close genetic relationship of MelV to PulV and NBV, and clustering within the Orthoreovirus genus subgroup III of the Reoviridae family. In the meantime, two adolescent children of the index patient also developed fever (without respiratory symptoms) approximately 6 days after the onset of his illness. Interestingly, epidemiological investigations of the index case revealed that about one week before he developed the illness, he had a bizarre exposure to a bat that flew into his living room for a short period. Subsequently, antibodies against MelV were detected from the family members including his wife who was asymptomatic. Although direct evidence of bat-to-human transmission of MelV has not been documented, the role of the bat as a possible reservoir of MelV has not been ruled out. MelV is believed to be the first Orthoreovirus associated with acute respiratory disease in the human.92

**HIV type 1 (clade CRF33_01B)**

Since the first cases of AIDS reported in 1986,93 the rise in HIV/AIDS in Malaysia has continued unabated. As of December 2007, a total of 80 938 HIV type 1 (HIV-1) infections have been identified, while 10 334 people have died of AIDS-related illnesses nationwide. Of these, 72% were injecting drug users (IDUs), followed by 16% transmission via heterosexual route (Figure 3a). It has been suggested that the early epidemic was a spillover from Thailand, located at Malaysia’s northern border. Malaysia is currently defined as a country with a ‘concentrated’ HIV-1 epidemic, based on relatively low rates of infection in the general population as measured by a prevalence of less than 0.1% among women attending government antenatal clinics, and seemingly isolated high prevalence rates among high-risk groups such as IDUs and female sex workers. In 2003 it was reported that Malaysia had the fifth fastest growing HIV infection rate in the Asia Pacific region, with the infection rate doubling every three years (http://www.unicef.org/aids/).

HIV-1 exhibits tremendous genetic diversity that is driven by high rates of mutation and recombination, coupled with high viral turnover and the persistent nature of infection.94–97 By these mechanisms, HIV-1 group M, which is largely responsible for the global pandemic, diversified into 11 subtypes and four circulating recombinant forms (CRFs). Five strains of CRFs have been reported so far in Asia: CRF01_AE, CRF15_01B, and CRF34_01B in Thailand and CRF07_BC and CRF08_BC in China. In addition to CRFs,
various types of unique recombinant forms (URFs) that are detected in a single individual or a single epidemiologically-linked cluster have been identified in the region, where multiple lineages of HIV-1 strains co-circulate in the same population.

The evolution of the HIV-1 epidemic in Malaysia produced a unique lineage when a distinctive recombinant strain emerged in 2003. Phylogenetic analyses of the HIV-1 protease and reverse transcriptase genes found 19% CRF01_AE/B intersubtype recombinants (a recombinant involving CRF01_AE and subtype B of Thai origin) amongst antiretroviral-naïve patients in Kuala Lumpur, all having a recombination profile different from other previously described CRFs. Designated as HIV-1 CRF33_01B from near full-length genome analyses (Figure 3b), this novel CRF was disseminating at a significant proportion among various high-risk populations, especially among the IDUs. Wide distribution of CRF33_01B involving all major ethnic and risk groups has provided evidence that extensive bridging of HIV-1 transmission between different risk groups has occurred in Malaysia.

We recently observed a unique parallelism of the transition in molecular epidemiological features of HIV-1 epidemics between Thailand and Malaysia. In the early phase of the Thai epidemic, two HIV-1 strains, CRF01_AE and subtype B, were circulating relatively independently among different risk populations. CRF01_AE was distributed among persons at risk of sexual exposure, while subtype B was distributed mainly among IDUs. Co-circulation of CRF01_AE and subtype B in Thailand presented opportunities for inter-clade recombination to take place (a common feature for HIV-1), and has led to the generation of various forms of CRF01_AE/B recombinants. A similar molecular epidemiological trend has been observed in Malaysia. Studies conducted in 1992–1997 showed that CRF01_AE and subtype B were prevalent among 81% of heterosexuals and 55–92% of IDUs, respectively. However, recent studies have documented the gradual dilution of non-recombinant pure subtypes and the establishment of CRF33_01B as the emerging epidemic strain in Malaysia. Besides expanding rapidly within the country, further molecular epidemiological surveillance has shown that CRF33_01B spread across the border to Singapore in 2005 (Paton NI and Sun YJ, personal communication). Such genetic complexity and dynamicity of HIV-1 provides opportunities for new recombinants to develop and spread within Malaysia and also in the region, thus presenting new challenges to disease diagnosis and treatment, particularly in the development of antivirals and vaccine candidates.

Highly pathogenic avian influenza (H5N1)

The highly pathogenic avian influenza (HPAI) H5N1 virus that originated in southern China in the mid-1990s, was respon-
Effective controls, the 2007 outbreak was
H5N1 persistence (117) is important to counter possible re-
tic ducks (thought to be the potential reservoir and source of
continued surveillance of avian populations including domes-
by implementing a stricter ban by the authorities on cock
Peninsular Malaysia. Such public health threats — that
(cited in the introduction and spread of HPAI H5N1 in
affected countries (i.e., Thailand and Indonesia) have been impli-
ment) that could lead to the generation of an influenza strain
enhanced transmissibility among humans, possibly trig-
ger a pandemic.113
In Malaysia, the first ever outbreak of HPAI caused by
subtype H5N1 was reported in August 2004 in a village in
the state of Kelantan located approximately 22 km from the
Thai border in northeastern Peninsular Malaysia.114,115
The virus, discovered in fighting cocks smuggled from a
neighboring country, was transmitted mainly among the
local village chickens. Molecular analysis showed that the
H5N1 strain was highly homologous to the H5N1 strains
previously isolated from Thailand and Vietnam. A few
weeks following the first outbreak, eight other outbreaks
were reported, largely affecting poultry in villages located
around the index case. In these outbreaks, no human cases
or deaths were reported and the disease was brought under
control by depopulation and quarantine/clinical surveil-
ance of poultry and birds within a 1-km and 10-km radius of
the index case, respectively, coupled with restrictions
on the movement of birds and their products to other
states.115
In February 2006, fresh outbreaks of HPAI H5N1 emerged
over a wider geographical area involving villages in Kuala
Lumpur and the states of Perak and Pulau Pinang along the
more industrialized western coast of Peninsular Malay-
sia.115 Phylogenetic analysis of the H5 and PB2 genes
revealed that the H5N1 strain isolated from infected vil-
lage chickens, ducks, and quails was different from that of
the 2004 outbreak and was highly similar to the H5N1 isolates from Indonesia and China, suggesting different
H5N1 lineages were introduced into the country, possibly
by the poultry trade rather than through migratory
birds.116 Although these outbreaks were brought under
control through effective disease control and preventive
efforts, including the culling of about 60,000 birds, a
similar outbreak re-occurred in another village in Selangor
state not far from Kuala Lumpur in June 2007.115 Through
effective control measures, the 2007 outbreak was
resolved several months later.
In Malaysia, cock fighting is a popular albeit illegal activity
among village folks. Fighting cocks smuggled from neighbor-
ning countries (i.e., Thailand and Indonesia) have been impli-
cated in the introduction and spread of HPAI H5N1 in
Peninsular Malaysia. Such public health threats — that
increase the risk of infection in humans — could be avoided
by implementing a stricter ban by the authorities on cock
fighting and smuggling activities in the country. In addition,
continued surveillance of avian populations including domes-
tic ducks (thought to be the potential reservoir and source of
H5N1 persistence117) is important to counter possible re-
occurrence or re-introduction of HPAI H5N1, a phenomenon
that is not uncommon in the Southeast Asia region.118
Discussion
Over the last eleven years, between 1997 and 2007, Malaysia
has witnessed the unprecedented appearance of eight novel
viruses that have never been documented in the country
before (Table 1). The majority of these viruses, such as EV-71,
NiV, CHIKV, and HIV-1 recombinant, have caused serious
human infections and/or deaths of varying magnitudes and
are of epidemiological importance, whereas others have yet
to be known to cause widespread human diseases (e.g., MelV
and HPAI H5N1) or cross into a wider range of susceptible
hosts (e.g., Tiv and PulV). Factors leading to this emergence
are not entirely understood but various features associated
with such a trend — including socio-economic, environmen-
tal, and ecological factors1—6 — have been hypothesized.
Unlike entrovirus infections that usually occur in densely
populated areas, where hygiene levels are poor and food or
water supplies may be contaminated, conditions that favor the
fetal—oral route of transmission, more complex attributes, be
it of the environment, viral hosts/vectors, or humans, have
been associated with the emergence of the other novel viruses
in Malaysia. For instance, early studies implicated the effects
of the El Niño/Southern Oscillation (ENSO) phenomenon in
1997/98 in the emergence of NiV.119 Directly preceding these
outbreaks, Malaysia experienced a severe drought resulting
from the El Niño conditions (the largest and warmest to
develop in the Pacific Ocean in the past century). The situation
was aggravated by the excessive haze produced by the aggres-
sive slash-and-burn deforestation activities in Indonesia. This
series of environmental and human events may have affected
the natural habitat of the atheropid bats, forcing their migra-
tion and subsequent encroachment into fruit orchards sur-
rrounding the pig-farming area, resulting in the unanticipated
introduction of NiV from its natural host to pigs as the amplify-
ing host. Recent investigations, however, refuted the effect
of ENSO and showed evidence that NiV is frequently present in
fruit bats in Malaysia, and that its spillover — from bats to pigs
and subsequent transmission to human — was largely a chance
event that might have occurred as a result of increased habitat
encroachment and agricultural expansion by humans, con-
founded by the temporal and spatial dynamics of both the
virus and hosts, and the hosts (pigs) immunity against NiV
infection.119—121 In fact, similar anthropogenic drivers have
been linked to outbreaks in Malaysia, Bangladesh, and India,
raising concerns that these countries, which are currently
experiencing promising economic growth, are still at risk of
NiV re-occurrence should unrestrained deforestation and agri-
cultural intensification activities not be closely regulated.
Overlapping the NiV epidemic was the first sporadic out-
break of Aedes mosquito-borne CHIKV infections in Kuala
Lumpur in 1998. The arbovirus then re-emerged seven years
later in northern Malaysia, coinciding with the drought-assoc-
ated CHIKV outbreaks affecting countries cresting the
Indian Ocean,88 by far the largest CHIKV epidemic on record.
The cause of the disease outbreaks remains multifactorial.
Previous lessons have suggested that increased tourism, viral
adaptation, and host immunity,87 plus importation of migrant
workers from countries where CHIKV is endemic,78 may play a
substantial role in the spread of the virus to humans, although
the effect of a warmer climate has also been reported.88 As a
whole, such a climate abnormality of prolonged drier-than-
average conditions may be critical in introducing new viruses

Emerging and re-emerging viruses in Malaysia 313
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<td>Novel bat paramyxovirus, closely related to Hendra virus</td>
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<td></td>
<td>Menangle virus</td>
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<td></td>
<td></td>
<td>Human infections and diseases in experimentally infected animals</td>
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<td>have been reported</td>
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<tr>
<td>Tioman virus</td>
<td>Paramyxoviridae</td>
<td>Rubulavirus</td>
<td>–ssRNA, enveloped</td>
<td>1999</td>
<td>Tioman Island</td>
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<tr>
<td>Pulau virus</td>
<td>Reoviridae</td>
<td>Orthoreovirus</td>
<td>dsRNA, non-enveloped</td>
<td>1999</td>
<td>Tioman Island</td>
<td>Novel bat Orthoreovirus</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>No human/animal disease reported</td>
</tr>
<tr>
<td>HIV type 1 (clade CRF33_01B)</td>
<td>Retroviridae</td>
<td>Lentivirus</td>
<td>Reverse-transcribing ssRNA, enveloped</td>
<td>2003</td>
<td>Kuala Lumpur</td>
<td>Novel recombinant descended from subtypes B and CRF01_AE</td>
</tr>
<tr>
<td>Highly pathogenic avian influenza H5N1</td>
<td>Orthomyxoviridae</td>
<td>Influenzavirus A</td>
<td>–ssRNA, enveloped</td>
<td>2004</td>
<td>Kelantan</td>
<td>Widespread among all major risk groups</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Outbreaks confined to poultry and have been linked to fighting</td>
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<td></td>
<td></td>
<td></td>
<td>cocks smuggled from neighboring countries</td>
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<tr>
<td>Melaka virus</td>
<td>Reoviridae</td>
<td>Orthoreovirus</td>
<td>dsRNA, non-enveloped</td>
<td>2006, 2007, 2009</td>
<td>Kuala Lumpur; Perak; Pulau Pinang; Kuala Lumpur; Melaka</td>
<td>Novel bat Orthoreovirus associated with acute respiratory disease in the human</td>
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into the country, although more research is certainly needed to validate this relationship.122

The discovery of bat-associated NiV (a Henipavirus), TIV (Rubulavirus), and PulV and MelV (both within the Ortho-
erovirus genus) has highlighted the significant role that bats play as important reservoir hosts of emerging viruses.123,124

Although yet to cause severe, widespread human outbreaks, medical and research institutions should adopt a proactive approach in understanding and managing the potential threats posed by these viruses. This includes conducting large-scale surveillance to determine the prevalence, both in bats and humans of these viruses (as in Bangladesh, for example, during the recent NiV outbreaks62,68,69), establishing
diagnostic systems in public health laboratories that include the diagnosis of these viruses, and reviewing the traditional/medicinal practice of drinking fresh bat blood or eating improperly cooked bat products among certain rural

HIV is among the most genetically diverse human pathogens. In addition, co-circulation of two or more HIV-1 subtypes in any population can lead to co-infection in individuals and consequently generate recombinant strains,106,107,126
as occurred with clade CRF33_01B in Malaysia, a fact that further increases the genetic plasticity of HIV-1. The possible phenotypic advantage inherited from recombination among different HIV-1 clades remains uncertain.

However, it has been reported that HIV recombinants may have enhanced replicative capacity and transmissibility or higher risk of disease progression compared to its parental strains,127,128 as reflected by the high prevalence of such recombinants in particular populations with risk practices. Further genetic diversification of HIV-1, which will add further to the problems in the development of antivirals and vaccines, could be reduced by limiting the incidence of infections among the high-risk groups and among those who are already infected.

As Malaysia progresses towards becoming a developed country in the new millennium, a number of zoonotic, non-zoonotic, and vector-borne viruses have been reported for the first time in the country. Although a decade has past, the potential health threats faced by the population are far from over. In fact, the momentum with which these diseases are spreading has intensified over time, as seen by the exponential increase in the annual HIV/AIDS incidence in Malaysia and elsewhere in the world, the temporal persistence of EV-71 infections, the sporadic expansion of CHIKV worldwide, the broad regional distribution and aggressive NiV outbreaks in Bangladesh and India, and the re-occurrence of highly pathogenic H5N1 avian influenza in poultry and humans. Taken together, indispensable lessons learnt from the past plus current understanding of the probable circumstances leading to disease emergence suggest calls for better preparedness to deal with impending infectious disease risks.

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References


