

Editorial

Zoonotic viruses discovered and isolated in Malaysia: Do they pose potential risks of zoonosis?

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In order to focus and prioritise its efforts under its R&D Blueprint, the World Health Organization in 2018 has developed a list of diseases and pathogens that have been prioritised for R&D in public health emergency contexts. Disease X was included in this list to represent a hypothetical, unknown disease that could cause a future epidemic.¹ Besides the pathogen that causes Disease X, several viruses such as Ebola virus, Nipah virus, Influenza virus, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and others are being listed as potential candidates that may be associated with pandemic outbreaks in the future. Therefore, viral zoonosis that may be caused by one of these pathogens including Pathogen X in the future, is being investigated and monitored by scientists and public health practitioners around the globe.

Most scientists and policy makers claimed that viral zoonotic outbreaks are related to increased human activities interacting with wildlife.² Increases in population density through urbanisation and the globalisation of transportation systems have eventually led to significantly increased exposure frequency of humans to wildlife and the global mobility of humans. In addition, agricultural capacity, animal husbandry and widespread deforestation have intensified in response to the demands of industrial development, urbanisation and rising human population densities.^{3,4} In fact, humans have been increasingly encroaching on wildlife habitats,

which are believed to be the reservoir of most viral diseases, resulting in high spill over events to the human population.

This paper aims to recapitulate the list of viruses that were discovered and isolated in Malaysia and outline the potential threat of zoonosis among these viruses. These viruses are divided into two categories: 1) arboviruses, and 2) non-arboviruses to iterate the transmission route of these viruses.

Arboviruses

Many arboviruses are zoonotic, infecting a wide variety of arthropods, other animals including birds in their sylvatic habitats and humans as incidental hosts. Over many years, arboviruses have evolved balanced relationships with these sylvatic hosts. Thus, morbidity and mortality are rarely seen in these sylvatic animals when they are infected by arboviruses.² Below is the description of arboviruses that were discovered in Malaysia.

Under the family of *Flaviviridae*, several notable viruses had been isolated from *Culex* and *Aedes* mosquitoes in Malaysia. Kunjin virus (KUNV) was first isolated from *Culex alienus*, *C. pseudovishnui*, and *C. annulus* in 1966.⁵ KUNV which is genetically more closely related to West Nile virus, has not been reported to be associated with any infections in Malaysia. There is also no serological study being conducted in Malaysia. Dengue virus (DENV) was first isolated from a Malaysian patient in 1954⁶ and subsequently isolated in *Aedes* mosquitoes. To date, all dengue serotypes

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(DENV-1– DENV-4) have been reported in Malaysia, with potential sylvatic transmission between animals and humans.⁷ Similarly, *Japanese encephalitis virus* was isolated from a patient⁸ and later shown to be transmitted by *Culex* sp in Malaysia.⁹ Zika virus (ZIKV) was isolated from *Aedes aegypti* in 1966 with subsequent serological prevalence indicating ZIKV had been circulating in Malaysia without any outbreaks being documented.^{10,11} Tembusu virus (TMUV) was isolated from *Culex tritaeniorhynchus* mosquitoes in 1955.¹² There is a concern of TMUV being a potential zoonotic virus with serological evidence of anti-TMUV among farmers, even though TMUV is primarily associated with poultry outbreak. On the other hand, Langat virus (LGTV) is a tick-borne virus isolated in 1956 from *Ixodes granulatus* ticks of rats.¹³ Although LGTV is considered avirulent in rodent and human populations, it can induce encephalitis in experimentally infected mice when the virus is inoculated intra-cerebrally.¹⁴ However, there have been no reports of human infections. Jugra virus and Carey Island virus are novel flaviviruses isolated from *Cynopterus brachyotis* (lesser short-nose fruit bat) in 1969 and 1970, respectively.¹² To date, there are no known human diseases related to both viruses and the vectors involved in their transmission are still unidentified.

Getah virus (GETV), an *Alphavirus* under the family of *Togaviridae*, was first isolated in Malaysia in 1955 from *Culex gelidus* mosquitoes.¹⁵ GETV is primarily reported among outbreaks in both horses and pigs. Even though there are no reports of any illnesses associated with this virus, anti-GETV antibodies have been reported in humans and this raises the concern of potential zoonotic infection of GTV, similar to TMUV. Other alphaviruses such as Bebaru virus (BEBV) and Sindbis virus (SINV)

have been isolated in Malaysia, but they have not been associated with clinical infections, except a single case of mild fever attributed to SINV.¹⁶ BEBV was first isolated from *Culex* sp and *Aedes butleri* in Rantau Panjang, Malaysia. Antibodies against Chikungunya virus (CHIKV) were detected in Malaysia in the 1970s^{17,18} prior to the CHIKV outbreak in Malaysia in 1998. There is concern that CHIKV may be endemic to Malaysia due to the fact that this virus shares the same vector, *Aedes* mosquitoes with DENV.

Non-Arboviruses

Malaysia has experienced a fair share of zoonotic outbreaks from 1998-1999. The emergence of Nipah virus (NIV) in Malaysia had caused tremendous human suffering especially among those involved in pig-farming, excessive economic loss and led to a near collapse of the local swine industry.¹⁹ NIV, under the family *Paramyxoviridae*, had been shown to have originated from the *Pteropus* sp, large fruit bats (also known as flying foxes) in Malaysia and accidentally transmitted into the swine population prior to being transmitted to humans.¹⁹ Surveillance of NIV in Pulau Tioman in 1999, has led to the isolation of another novel paramyxovirus, namely Tioman virus (TioPV). To date, there are no known human diseases related to TioPV, even though, anti-TioPV antibodies were detected among Tioman island inhabitants.²⁰

Besides TioPV, pteropid bats were found to harbour Pulau virus (PRV2P) in 1999.²¹ PRV2P is a member of *Pteropine Orthoreovirus* (PRV), under the family of *Reoviridae*. Under the genus PRV, PRV3M (Melaka virus), PRV4K (Kampar virus) and PRV7S (Sikamat virus) had been isolated from Malaysian patients who presented with disease spectrum ranging from influenza-

like illness to acute respiratory distress. Chronologically, PRV3M and PRV4K were discovered in 2006 while PRV7S was discovered in 2010.^{22, 23, 24} PRV infections in patients in Japan and Hong Kong had history of travel to South East Asia, further indicating that the spill over event from pteropid bats to human population is limited to specific geographical regions.

Besides fruit bats, insectivorous bats such as *Rhinoplus* sp (horseshoe bats) had been documented to harbour bat SARS-like and MERS-like coronaviruses which are genetically closely related to human SARS and MERS coronaviruses, respectively.²⁵ SARS-CoV2 is also claimed to have originated from bat SARS-like coronavirus isolated from *Rhinoplus affinis* (intermediate horseshoe bat).²⁶ The possibility of an intermediate host facilitating the emergence of the virus in humans has already been shown with civet cats acting as intermediate hosts for SARS-CoVs, dromedary camels for MERS-CoV, and pangolin hypothesised for SARS-CoV2. COVID-19 caused by SARS-Cov2 was first identified in Malaysia on 25 January 2020 with early sporadic cases. Subsequently, several waves of SARS-CoV2 infection eventually resulted in COVID-19 becoming endemic in Malaysia. On the other hand, a novel canine coronavirus, which was isolated from a hospitalised pneumonia patient in East Malaysia in 2020²⁷, showed its ability to cross species barrier, infecting humans. In parallel, the one-health approach zoonosis surveillance in wild and domesticated

animals performed by the Department of Wildlife and National Parks and Department of Veterinary Service, respectively had reported novel animal coronaviruses and paramyxoviruses being mostly detected in wild animals in Malaysia in comparison to domesticated animals (data in PREDICT reports).

The above-mentioned viruses that were discovered and isolated in Malaysia illustrate a broad range of zoonotic viruses from different genera and families that are lurking in the dark and may pose potential risk to public health in the future. In the event if one of these viruses jumps among species and is able to be transmitted from human to human, the potential risk will become a real threat to humans. The zoonotic viruses described here are not an exhaustive list and may not be exclusive only to Malaysia. Several zoonotic viruses such as influenza virus, rabies lyssavirus and rotavirus C that were identified as causative agents in several outbreaks in Malaysia were not described here as the zoonotic origin of the viruses were not determined after the outbreaks.

In summary, Malaysia, a mega biodiversity country, appears to be a hot spot encompassing a broad range of zoonotic viruses. These viruses are naturally isolated away from humans by environmental ecosystems that provide a buffer zone. Strong evidence has linked biodiversity losses to emergence of zoonotic diseases in the human population. Protecting biodiversity is vital in protecting the environment, which is integral to Malaysia's future.

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