MINI-REVIEW

# Nipah virus: a potential pandemic agent in the context of the current severe acute respiratory syndrome coronavirus 2 pandemic

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## Abstract

For centuries, zoonotic diseases have been responsible for various outbreaks resulting in the deaths of millions of people. The best example of this is the current coronavirus disease 2019 (COVID-19) pandemic. Like severe acute respiratory syndrome coronavirus, Nipah virus is another deadly virus which has caused several outbreaks in the last few years. Though it causes a low number of infections, disease severity results in a higher death rate. In the context of the recent COVID-19 pandemic, we speculate that many countries will be unable to deal with the sudden onset of such a viral outbreak. Thus, further research and attention to the virus are needed to address future outbreaks.



**Keywords:** Mutations, Nipah virus, One Health, pandemic, spillover, zoonotic diseases

**Original Submission:** 7 November 2020; **Revised Submission:** 23 February 2021; **Accepted:** 12 March 2021

**Article published online:** 19 March 2021

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## Introduction

The aetiologic agents of more than 60% of human infectious and emerging infectious diseases are of zoonotic origin [1,2]. Frequent outbreaks of emerging and reemerging zoonotic diseases that threaten to turn into pandemics are becoming characteristics of the Anthropocene [3]. For hundreds of years, viral zoonotic diseases like bird flu, swine flu, Rift Valley fever, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Ebola, Zika, Nipah and Henipa have created worldwide public health emergencies. These viruses can reemerge after a gap, then spread rapidly and kill millions of people [4,5]. The most common viral zoonotic epidemic is influenza, which is estimated to result in about 3 to 5 million cases of severe illness and 250 000 to 500 000 deaths globally every year [6].

Unfortunately, the coronavirus disease 2019 (COVID-19) pandemic, the most recent example of a zoonotic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the deadly outbreak since the 1918–20 Spanish flu. Emerging at the end of 2019 in Wuhan, China [7,8], COVID-19 is spreading in a relatively uncontrolled manner across the globe, infecting more than 100 million people and resulting in 2.4 million deaths as of February 2021 [9]. Previously, two coronaviruses, SARS-CoV and MERS-CoV, caused small outbreaks before the emergence of SARS-CoV-2 [10]. Apart from these reemerging coronavirus outbreaks, another zoonotic agent, the Ebola virus, recently emerged, infecting 16 000 people with a fatality rate of 40% to 60% in 2014 and 2018 [11].

According to the US National Institutes of Health guidelines for managing risky pathogens, both SARS and MERS are categorized in the risk 3 category group, while Ebola is in the risk 4 group, along with another zoonotic pathogen, Nipah virus (NiV) [12]. NiV is also classified as a potential bio- and agro-terrorism pathogen [13]. Previous outbreaks such as SARS



https://doi.org/10.1016/j.nmni.2021.100873

were controlled by a rapid global response, whereas Ebola and NiV could not establish any large outbreaks because of local initiatives or perhaps because of their intrinsic inability for mass transmission in a population [1]. However, despite undertaking several strict measures, the COVID-19 pandemic seems relatively unstoppable because, with time, new virus strains are emerging all over the world. Most of these epidemic and pandemic agents (e.g. SARS, MERS, SARS-CoV-2), including NiV, originated from bats, with cross-species transmission occurring via various intermediate hosts such as pangolins, rats, civets and camels [14–16].

NiV, a paramyxovirus, caused the first outbreak in Malaysia in 1998, followed by Bangladesh, India, Singapore and the Philippines [17]. Although Malaysia has not reported an outbreak since 1999, NiV outbreaks have been continuously reported from Bangladesh and India almost annually since 2001 [17–19]. Compared to other viral outbreaks, NiV infection has resulted in a lower number of cases and less human transmission, with a higher fatality rate of around 40% to 70% [20], which indicates that it may cause new outbreaks sooner or later. In 2019, researchers gathered in Singapore to discuss the historic outbreaks and the latest epidemiologic studies, vaccines and therapeutic developments for NiV research [21]. The discussion also reflected the understanding that this virus could become the next pandemic agent, with further studies urgently needed [13]. Many previous studies have also indicated that NiV has the potential to cause a pandemic or epidemic [5,20,22,23].

Several factors are responsible for zoonotic outbreaks, such as intensive livestock farming and agriculture, using wildlife as food sources, clearing land for farming and grazing, human encroachment on wildlife habitats, international trading of exotic animals and urbanization, leading to more human–animal and environmental interactions [1,3]. Spillover of pathogens from an animal reservoir to humans remains a major factor in zoonotic outbreaks [3]. Anthropogenic activities are making zoonotic spillover more likely, consequently favouring some viral hosts of animal species [24]. Genetic factors are also responsible for zoonotic outbreaks, as many responsible viruses are RNA viruses, including influenza, SARS, MERS, Ebola [25] and the recent SARS-CoV-2. It has been found that the RNA viruses are the primary aetiologic agents of 44% of all emerging infectious diseases in the last decades, as they have exceptionally short generation times and fast evolutionary rates, which increase the likelihood of infecting new host species [25]. NiV is also an RNA virus, and because RNA viruses mutate so frequently, we cannot determine whether a novel NiV will emerge within the next 5 years or later. Because zoonoses place a significant burden on animal and human health, as well as on global economic growth, prioritizing disease control mechanisms is a major public health issue [26]. These emerging zoonoses are a global One Health issue that requires a holistic approach to control various key factors – socioeconomic, environmental and ecological – to reduce the burden of disease.

Considering all these points, we assume that NiV may result in a future outbreak, as this viral infection causes stage three zoonotic disease that have the potential to become a pandemic [21,22]. In this review, we focus on presenting some key points which indicate that NiV-like viruses are likely to become a next pandemic agent. Continuous investigation is therefore required for a better understanding of such zoonotic outbreaks.

## Nipah virus

NiV first emerged in Malaysia in 1998 [17]. The virus was named after a Malaysian village, Sungai Nipah, in Negeri Sembilan state, where it was first isolated from a case in a human [5]. On the basis of its unique genetic and biological characteristics, NiV is grouped into the *Paramyxoviridae* family and the *Henipavirus* genus [27,28]. The virus family also comprises viral pathogens such as measles, mumps, Newcastle disease, parainfluenza and Hendra virus [29]. It was thought that paramyxoviruses have a narrow host range and that human transmission events are rare [29]. However, henipaviruses and their recent emergence with high virulence and a broad host range are alarming. Although no cases of person-to-person spread have been found in Malaysia or Singapore, outbreaks from Bangladesh, the Philippines and India suggest that respiratory droplets of an infected person can transmit the virus, or that date palm sap contaminated by bats can transmit NiV to humans [19,30]. However, further research is needed to understand the dynamics of NiV's transmission from bats, pigs, and humans and from date palm sap to humans [5]. In NiV disease, the prevalent symptoms are fever, followed by altered mental status, headache, severe weakness, cough, difficult breathing, diarrhoea and seizures when encephalitis develops [5,20]. Mostly infected persons showed meningismus [31]. To date, 639 human cases of NiV infection have been reported from South Asia or South-East Asia, Bangladesh (261 cases), India (85 cases), Singapore (11 cases), the Philippines (17 cases) and Malaysia (265 cases) [17]. The overall fatality rate varies from 40% to 70%, while in the case of acute encephalitis, it can be 82% [17,19].

We know that the dynamics of such emerging infectious agents are unpredictable [32]. However, several factors are associated with any viral disease becoming a pandemic agent. In the case of NiV, its primary reservoir, genomic mutations, viral receptors, transmission speed and spillover from the animal source are some of the main factors that need to be dealt with and understood in order to monitor the next pandemic agent.

## Bat as primary reservoir of NiV outbreak

The main reservoir of NiV is fruit bats (*Pteropus giganteus*) [33], and the prime NiV outbreak area was Bangladesh, home of at least 33 bat species, commonly the big Indian fruit bats (*P. giganteus*), also known as flying fox. Reportedly, Bangladesh has the most cases of NiV disease, with scattered outbreaks throughout 2001 to 2014 [23]. With the geographical range of fruit bats extending from Pakistan to South and South-East Asia to South China and Australia [34], it is likely that NiV outbreaks may occur because bats are the primary reservoir of the virus.

## Virus mutations

The mutation rates of RNA viruses are a million times higher than those of their hosts [35]. Like influenza A virus, over the past 100 years, four flu pandemics have been reported by mutated influenza A virus strains: 1918 H1N1 Spanish flu, 1957 H2N2 Asian flu, 1968 H3N2 Hong Kong flu and 2009 H1N1 swine flu [36]. Interestingly, all these diseases are also classified as zoonotic diseases, with birds being the main reservoir of such viruses [37].

In the case of NiV, to date, two different strains have been reported [38]. Phylogenetic analysis has revealed similarities with the *Henipavirus* genus exclusively with the Malaysian NiV strain. Apart from the W protein, the phylogenetic relationships between the nucleoprotein (N), V protein and surface glycoprotein were slightly dissimilar to the sequences of the Bangladeshi NiV isolates [38]. Strains were named NiV Bangladesh ($NiV_B$) and NiV Malaysia ($NiV_M$) according to the differences in viral properties [5,39]. In addition, $NiV_M$ has no trace of human-to-human transmission, whereas $NiV_B$ can be transmitted directly between humans, thus making it the ghastliest infection, as Bangladesh has reported more cases and deaths than any other country's outbreaks [40]. $NiV_B$ is more likely infectious than $NiV_M$, and it will not be surprising that the virus will mutate further, thereby producing a new strain to which humans will be vulnerable.

## Zoonotic spillover

Although NiV was initially found in a fruit bat, the virus became established in domestic pigs and caused a major outbreak in Malaysia. Virus spillover from a primary reservoir (bats) to intermediate hosts (pig) to humans is still poorly understood [41]. The virus spillover is capable when successful transmission enables an animal pathogen to develop infective stages in a human [41]. However, virus spillover depends on several factors such as disease dynamics in the reservoir host and density of the transmitted population [42]. Luby *et al.* [43] analysed NiV spillovers of a few cases reported in Bangladesh from 2001 through 2007 and concluded that NiV-infected patients with severe respiratory symptoms were more likely to transmit NiV than others. They hypothesized that a *Pteropus spp*. bat shedding NiV can occasionally infect one or more persons, and the infected individuals initiate the epidemic chain by spreading the virus via person-to-person transmission. The study had many limitations, so more studies with larger sample sizes and using systematic surveillance are necessary to confirm this theory [23].

## Attachment that regulates the host

Virus–receptor interaction plays a key regulatory role in the selection of the viral host, tissue tropism and pathogenesis [44]. The virus–receptor binding is highly specific, which is necessary for initiating successful infection by a given virus in the host. For instance, according to published reports, the current pandemic agent SARS-CoV-2 uses human angiotensin-converting enzyme 2 (ACE2) receptor, which is mainly available in arteries, heart, kidneys and intestines, as very common; therefore, the virus can initiate rapid transmission and various comorbidities [45]. Because it is expressed by a wide range of animal species (except rat and mouse), it helps cross-species and human-to-human transmission [15]. The NiV receptor ephrin (B2/B3) is found in almost all tissues, thus increasing its availability to develop infection [46,47]. The ephrin (B2/B3) disseminates the virus, which is an essential step in reaching and infecting different cell types [48,49]. Naturally, dissemination of NiV occurs in the host via blood; ephrin (B2/B3) on leucocytes helps NiV bind with leucocytes [50]. As a result of the high expression of NiV receptors in the central nervous system, NiV has the highest neurologic disease potential – which is often lethal [51]. Development of outbreaks from any zoonotic agent to a human population needs available specific receptors, as viruses will only infect if they find cells that display their specific receptors, which successfully promote virus particle internalization [52].

## Speed of virus spread

The basic reproduction number (R0) estimates the speed at which a disease can spread in a population. The R0 is crucial to understand the transmission rate in the study population. The value of R0 may provide useful insight into an outbreak,

permitting national-level preparedness schemes to be constructed to tackle the scenario [53]. The first estimations were published online by early May 2009 during an H1N1 outbreak in Mexico [53,54]. A R0 value greater than 1 indicates a potential increase of the infection transmission in the population, while a value less than 1 indicates that the infection will reduce its spreading ability, although exceptions exist [55]. A systematic review indicated median R0 values of 1.80, 1.65, 1.80 and 1.46 for influenza outbreaks in 1918, 1957, 1968 and 2009, respectively [55].

It has been reported that the R0 value for SARS and MERS was around 2.5 [56] and 1 respectively [57], which also varied depending on country populations. However, for SARS-CoV-2, the value is about 2.5 to 2.6 in earlier studies, which increases up to 5.7 [58–60]. For NiV, the R0 value is 0.48 [22], but like MERS, it has a low R0 value and high mortality rates. However, it is known that if the R0 value remains less than 1, the number of cases will diminish and the pathogen will eventually disappear as a result of a drop in its ability to spread further. Many pathogens fail to become endemic in people because the susceptible hosts are limited, so the R0 can be correlated with host density. For example, most NiV outbreaks are reported from villages in Malaysia, Bangladesh and India, where the normal density of the population is low; this may be a reason why large outbreaks are not observed [17]. Another reason for the low R0 value may be its infrequent spillover due to the host's death, as person-to-person transmission is impossible. Thus, zoonotic infectious diseases with high death rates often result in a low incidence rate [61].

As the disease progresses, the R0 value may change depending on different variables such as geographical area, population, interval periods and data collection accuracy, so the R0 value might help with implementation of several interventions, but it requires extensive study because a mutation of an existing virus may result in a failure to predict its spreading vulnerability, which was evident in the COVID-19 pandemic [53].

## Latest antiviral treatment

Since coronavirus outbreaks such as SARS and MERS, small trials with existing antiviral drugs have been conducted to observe their effectiveness. The COVID-19 pandemic has hit its 1-year mark, and fortunately, two categories of vaccine (BNT162b2 and mRNA1273) are now available against COVID-19, which are reported to be 95% effective [62].

Attempts were made to repurpose drugs such as chloroquine and remdesivir as successful treatment options for COVID-19 through a small-scale trial. For chloroquine, clinical studies demonstrating beneficial effects are lacking, although remdesivir was founded to be safe; one US Food and Drug Administration programme reported few adverse events and good patient tolerance of the drug [63].

The COVID-19 outbreak has taught us that NiV should be addressed now, as it has pandemic potential but lacks specific antiviral drugs or vaccines that are presently effective against the virus [64,65]. In 2008, the Infectious Diseases Society of America recommended short-term treatment of NiV encephalitis with the antiviral drug ribavirin, but ribavirin's efficacy against NiV is not well understood; it results in teratogenicity in animals, its dosage treatment is undefined and there are several adverse effects related to long-term treatment [66]. Recent studies suggest that favipiravir has the highest antiviral activity against NiV [67]. In Syrian hamster animal models, the drug could fully treat the animals with 14 days' daily administration, but further studies are needed to optimize the therapeutic doses, routes and timing of treatment after infection [65,68].

In an animal model, a monoclonal antibody, m102.4, against the G protein of NiV was found to be effective, but human trials remain to be conducted [68–70]. Although the development of vaccine and treatment options against NiV is highly warranted, it is unlikely to be prioritized in the context of the current COVID-19 epidemic. Thus, deep investigation towards developing vaccines or potential antiviral drugs against NiV is highly warranted.

## Conclusion

For about 22 years, a *Henipavirus* strain, NiV, has occasionally emerged, with several outbreaks in different areas killing many people. Scientists have speculated that NiV is likely to be the next pandemic agent after COVID-19. A focus on a One Health approach on animal–human–environment interfaces is urgently needed to combat future outbreaks. Approaches should consider surveilling animal health or management of animal farms; monitoring human and environment health; increasing food safety and food security associated with zoonotic disease; checking environmental aspects such as deforestation and sustainable land use for managing biodiversity; and engaging in global-level participation or collaboration.

Creating or maintaining scientific momentum as well as investing in studies dealing with viruses and vaccine development should be a concern for world leaders and policy makers. The ongoing unimaginable coronavirus pandemic has shattered the world's economy and highlighted the limitations of healthcare systems. Out of 215 countries, only a few are capable of dealing with the pandemic with full healthcare facilities to treat millions of patients. Although we can never know what the next

epidemic will be, preparation for the worst, including NiV, will reduce morbidity and mortality.

## Conflict of interest

None declared.

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