

Published: June 30, 2023

**Citation:** Daniel R. Lucey, 2023. 4 Origin Scenarios if a Nipah Virus outbreak occurs outside South/SE Asia, Medical Research Archives, [online] 11(6). <https://doi.org/10.18103/mra.v11i6.3942>

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DOI  
<https://doi.org/10.18103/mra.v11i6.3942>

ISSN: 2375-1924

## RESEARCH ARTICLE

### 4 Origin Scenarios if a Nipah Virus outbreak occurs outside South/SE Asia

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#### ABSTRACT

Nipah virus is a bat-borne zoonotic RNA virus discovered in Malaysia during an 1998-1999 outbreak that involved pigs, fruit bats, and humans in Malaysia (1). Clinical manifestations are primarily encephalitis and pneumonia. The case fatality rate of symptomatic cases is 40%-70%. Survivors can have severe neurologic sequelae (2-5). There are no licensed vaccines, antiviral drugs, monoclonal antibodies, or point-of-care rapid diagnostic tests, although extensive work on vaccines and monoclonal antibodies is underway (6). Person-to-person transmission, including a small number of superspreading events, has occurred in Bangladesh and India (7-9).

From 1998-2023 all reported outbreaks have been in either southeast (SE) Asia (Malaysia, Singapore, the Philippines), or south Asia (Bangladesh, India) (2, 7-10). It is likely that a future Nipah outbreak, and possibly widespread epidemic, will occur outside south/SE Asia, whether elsewhere in Asia such as China, or on another continent. When it does, then as with the COVID-19 pandemic, multiple questions will be raised regarding the origin of the epidemic. Each of the following four (4) main scenarios could be anticipated to account for the origin of such a geographically-unprecedented Nipah epidemic during analysis on Day 1 of the event by national and international organizations.

### **Scenario 1: Accidental Infection in a Nipah virus Field Researcher or a Traveler**

In September 2022 the World Health Organization (WHO) published a landmark document<sup>11</sup> titled, “Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual use research”. Annex 2 offers three “Case studies for responsible life sciences research on high-consequence pathogens”. Along with “chemical synthesis of poliovirus cDNA” and “1918 pandemic influenza reconstruction” is a case study<sup>11</sup> titled, “Environmental surveillance for Nipah virus”.

Two types of environmental surveillance for Nipah virus from Pteropus species fruit bats are listed. These are: (1) spreading tarpaulins on the ground beneath trees where the fruit bat species (pteropus) that can be infected with Nipah virus roost, and then pooling the collected samples from the tarpaulins before testing for Nipah virus; (2) capturing and then testing individual bats for Nipah virus e.g., via blood, throat, and urine specimens. The WHO case study specifies the pandemic risk of such work below (boldtype added for emphasis):

*“Criticism of environmental surveillance research tends to focus on **the risk posed to society if a field researcher is infected with a pathogen with pandemic potential.** The risk of viral exposure is most prevalent when collecting samples directly from living wild animals. These risks can include needle sticks while taking blood samples, exposure of animal excreta to open wounds, and bites or scratches from improperly anaesthetized animals. The first environmental surveillance collection method limits the risks posed by needle sticks and bites or scratches, but the data quality is sacrificed as a result. Lower data quality may reduce the impact the study results can have on preventing or mitigating Nipah virus spillover events. The second environmental surveillance collection method produces high-quality and specific data, but the risk to field researchers is considerably increased. **The unintentional infection of a researcher with Nipah virus has the potential to result in a global pandemic if proper precautions are not followed.**”<sup>11</sup>.*

In the hypothetical Day 1 outbreak analysis, this scenario could be initiated by the accidental infection of one or more field researchers and potential person-to-person spread of Nipah virus in at least two ways. The first is if the field researcher is working in a location in south/SE Asia and then that individual, or someone infected by them, travels to a location elsewhere in Asia such as China, or somewhere outside Asia altogether. A second scenario that can be envisioned and anticipated is if the infected field researcher is

working in a location where Nipah-infected bats exist outside south/SE Asia.

### **Scenario 2: Animals Known or Unknown to Infect Humans**

Another scenario hypothesizes that the infection occurred from an animal to a human. For example, in the first-recognized Nipah outbreak of 1998-1999 in Malaysia pigs on large commercial pig farms constructed in rural areas were infected by fruit bats carrying the virus. Persons in contact with the pig farms, or abattoirs, became infected. Infected pigs transferred to different places in Malaysia, and Singapore, also resulted in more pig and human infections<sup>1</sup>.

In 2014 the first and still only reported Nipah outbreak occurred in the Philippines on the southern island of Mindanao. Filipino public health officials reported in 2015 that horses were infected in two villages in Ninoy Aquino province and then horse-to-horse and horse-human infections occurred<sup>10</sup>. It was suggested that humans might have been infected through consumption of undercooked horse meat<sup>10</sup>. Until this outbreak it was not clear that humans could be infected by Nipah-infected horses. Thus, additional still-unrecognized animal species might exist that can transmit the virus to humans (see also next scenario). Unlike rabies virus, direct infection of humans by bats has not been established.

### **Scenario 3: Food or Drink**

A third scenario hypothesizes that Nipah virus-infected food would be the source of an outbreak. This scenario could include direct consumption and infection of humans via the food. Implicated Nipah-infected food to date includes mango (in the Malaysia 1998-1999 outbreak, but not implicated to date anywhere outside Malaysia), and date palm sap in Bangladesh, including a liquor (“tari”) made from fermented date palm sap<sup>12</sup>.

Alternatively, it could involve consumption of the virus-infected food by an animal e.g., pigs or horses or other susceptible animals, or even an unrecognized susceptible animal species in a part of the world outside of south/SE Asia.

An example of the latter occurred with a different virus in 2003 in the USA. Prairie dogs were infected for the first time with mpox (then called “monkeypox”) in pet dealerships in the USA following importation of mpox-infected “exotic pets” (e.g., African giant pouched rats, dormice, and rope squirrels) from Ghana<sup>13</sup>.

“Food-borne transmission of Nipah virus in Syrian hamsters” was reported in 2014 by US researchers<sup>14</sup>. Important caveats, however, include

that the “food” was a laboratory-prepared artificial date palm sap to which the virus was added in a laboratory setting. Of note, some hamster-to-hamster transmission was observed after this food-borne infections.

#### **Scenario 4: Laboratory-Related**

It must be emphasized that currently there are no reports or published studies on Nipah virus and any type of research variously referred to as “gain-of-function (GoF)”, “dual use research of concern (DURC)”, or “enhanced potential pandemic pathogens (ePPP)”. Moreover, there are no reports of serial passage of Nipah virus in any susceptible animal species e.g., ferrets, Syrian hamsters, or African Green Monkeys.

Nevertheless, such research could occur in one or more laboratories worldwide. This hypothetical concern was acknowledged briefly in a 1,028-page document<sup>15</sup> discussing a wide spectrum of GoF research and policy issues that was published online in the US in 2016 by Gryphon Scientific:

*“Similar techniques to those used in GoF experiments could be leveraged for other pathogens to create a highly transmissible strain of an already deadly virus (like the Hendra and Nipah viruses)...”* page 217 of 1028.

Examples of concern regarding potential use of a Nipah virus with genetically-enhanced transmissibility occurred in two hypothetical simulation exercises in the USA in 2016 and 2018. The first scenario imagined a bioterrorism attack on Washington, DC and four states<sup>16</sup>

*“...during our Independence Day celebrations. Many of our own colleagues and staff fell ill and died. Thousands more were killed in coordinated attacks in allied nations in the days that followed. The attack here in Washington, D.C. used aerosol delivery devices we could see, but did not know contained dangerous organisms. We discovered later that other attacks had already begun elsewhere in the Nation, using methods we have yet to identify that spread the disease among livestock in rural communities. Delays in recognition – because most veterinarians and physicians had never seen Nipah virus – meant animals and people were sick for more than a week before we realized what had happened. And now we are being told that the virus, which in nature does not spread easily among people, was genetically modified to increase its ability to spread from animal to animal, animal to person, and person to person.”*<sup>16</sup>.

The second hypothetical scenario was a tabletop exercise held on May 2018 in Washington, DC called “Clade X”. In this scenario,

on another continent certain genes from Nipah virus were inserted into a known respiratory-transmitted highly contagious virus. This hybrid virus was termed “clade X”. In this extreme-case scenario the resulting pandemic began in Europe and South America and eventually resulted in 150 million deaths<sup>17</sup>.

The potential for accidental infection with Nipah virus of humans and/or animals associated in any way with a laboratory is of perhaps enhanced concern given the ongoing three-year controversy<sup>18</sup> regarding the origin of SARS-CoV-2/COVID-19, given its first report in Wuhan, China. The World Health Organization Scientific Advisory Group on Origins of Novel Pathogens (WHO SAGO) has addressed this issue<sup>18</sup> and continues to do so as of 2023.

This hypothetical Day 1 outbreak scenario analysis might be considered by the WHO SAGO of international experts if an unusual Nipah virus epidemic occurred. Their involvement would be especially likely if the earliest-recognized location of the outbreak was outside of south/SE Asia, and particularly if it was in Wuhan or elsewhere in Hubei province, China. Importantly however, given the growing number of BSL-4 laboratories worldwide that might work on Nipah virus, including ones in the USA, Europe, Asia and likely elsewhere, then high vigilance for optimal biosafety is essential everywhere worldwide and not only in China.

At the large international Nipah virus conference held in Singapore December 9-10, 2019 researchers from around the world gave presentations on what had been learned, and what still needed to be learned, over the 20 years since the discovery of Nipah virus.<sup>19</sup> Abstracts of the presentations are still available in a 67-page online document. One of the final abstracts (on page 65 of 67) was by the renowned virologist at the Wuhan Institute of Virology and Editor-in-Chief of the journal *Virologica Sinica*, Dr. Zhengli Shi<sup>19</sup>. This abstract included the following statements: *“Nipah represents a priority pathogen for the Wuhan facility, due to 1) its ability to infect animals and humans; 2) its high mortality in humans; and 3) the prevalence of henipaviruses and henipa-like viruses in countries of Southeast Asia, including China. Work on Nipah is divided into six work packages: 1) NiV pathogenesis; 2) Epidemiology; 3) Development of a DC-based prophylactic mucosal vaccine; 4) Therapeutics development; 5) Diagnostics development; 6) Biostatistics analyses.”*<sup>19</sup>

Although there have not been any reported human or animal cases of Nipah virus infection in China, a review article on Nipah<sup>20</sup> published in 2018 in *Virologica Sinica* by five authors from the

Wuhan Institute of Virology stated that “NiV is also distributed in China...”. However, the reference cited<sup>21</sup> did not report Nipah virus itself, but only antibody to Nipah or a related virus in bats in China.

Nevertheless, if a first-ever Nipah outbreak occurred in China and particularly near Wuhan, whether in humans or animals (e.g., pigs in the city of Ezhou, approximately 40km from Wuhan where large numbers of pigs are raised in 26-storey buildings<sup>22</sup>), then on the first day of the recognition of the outbreak all four scenarios discussed above could prove relevant.

### Conclusion

This paper serves as an anticipatory guide to four origin scenarios on a future day 1 of the first-ever Nipah virus outbreak anywhere in the world e.g., China, Europe, the Americas, or Africa,

that is outside of past outbreaks in south/SE Asia. As has occurred with the ongoing origin controversy of SARS-CoV-2/COVID-19 since at least January 25-26, 2020<sup>23</sup>, each of the potential natural and laboratory-related Nipah virus origin scenarios discussed in this paper should be rapidly considered in order to control and stop the outbreak. A part of such a rapid investigation should also include searching retrospectively for unrecognized cases of Nipah, as illustrated by retrospectively identifying the earliest known cases of another coronavirus, the Middle East Respiratory Syndrome (MERS), in Zarqa, Jordan in April 2012<sup>24</sup>.

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