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Review Article

Paramyxoviruses: The Lurking Pandemic Pathogens

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Abstract

The global impact of SARS-CoV-2 pandemic was devastating and since then the world has started looking for Pathogen "X" which might cause the next pandemic. Paramyxoviruses are mostly found in bat and are significant pathogens of interest. Of these, NiV and HeV should be source of concern for the international public health community. They possess characteristics that are associated with pathogens that cause pandemic. This review analyse these characteristics as basis for supporting WHO for including PMVs in their Priority Pathogen lists. The diagnostic and therapeutic interventions are also discussed.

Keywords: *Pandemics; Virus; Paramyxovirus; Zoonotic Diseases; Spillover; Bats*

Introduction

In December 2019, the world was awaken with the news of an outbreak of a disease which was later named coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). COVID-19 in Wuhan, China which later spread rapidly across the globe. It caused one of the most devastating pandemic encountered by humanity by affecting every facet of human life [1]. Based on these impacts on global affairs, the scientific community is preparing for pathogen X as the next pandemic pathogen.

This review is aimed at providing information on paramyxovirus as the possible next pathogen that would be the cause of pandemic. We would analyse the viral factors of NiV and HeV that would facilitate its potential in causing pandemic and discuss the predictive management of HVNs infection focusing on NiV and HeV.

The past pandemic

In order to understanding the potential of a pathogen to cause pandemic, it is important to draw some lessons from the past history. Below is the brief discussion of past pandemics.

The first well documented pandemic is the "Spanish Flu" which was caused by an Influenza subtype H1N1. The virus was transmitted from animal reservoir. It spread across the world rapidly and it has been suggested that poor hygiene and movements of troops might have played a role in its global spread [2]. Most studies undertaken to identify the virulence factor of influenza implicated viral surface protein, hemagglutinin (HA), polymerase protein, non-structural 1(NS1) protein and PB1-F2 [3-7].

The next pandemic was the Influenza A/H2N2 pandemic happened in 1957 which was caused by the reassortment of influenza A possessing H2 hemagglutinin and N2 neuraminidase from HA and NA, respectively. It also consisted of basic polymerase gene and the rest of the five viral genes were from previous H1N1 viruses [8]. At that time human did not have immunity to that strain which facilitated its spread across the world. It was estimated that approximately one million people died from this pandemic.

In 1968, the world experienced another pandemic due to influenza A/H3N2. This pandemic was due reassortment of human and avian influenza A virus. The following avian influenza virus genes: H3, HA, and PB1 reassortment with the human H2N2 viruses that were circulating at the time [9,10]. The reassorted virus (H3N2) encountered population that did not have any immunity against H3 thereby resulting in it spread around the globe. Like the 1957 pandemic, this also resulted in approximately one million deaths.

In 1977, A/H1N1 re-emerged to cause widespread outbreak. It was closely associated with the strains that circulated in the early 1950s, which suggest that it was accidentally released or due to vaccine trial with live virus that was not properly attenuated. However, the re-emerged virus did not replace the circulating virus instead co-circulated with A/H3N2. It should be noted that A/H1N1 did not cause pandemic however, the 2009 pandemic of H1N1 was totally different from H1N1 virus antigenically which enable it to evade the immune system and cause pandemic [11].

The 2009 A/H1N1 pandemic was as a result of reassortment of genes from human, avian, and swine influenza A virus. It was estimated that approximately 284 000 deaths was reported around the world. The 2009 strain of influenza displaced the earlier A/H1N1 viruses but not the circulating A/H3N2 viruses. Although A/H1N1 has been circulating around the world, it was not considered as agent of pandemic. However, the 2009 H1N1 was antigenically different enough to evade immunity thereby causing pandemic.

The 2003 SARS-CoV pandemic was regarded as the first pandemic of the 21st century [12]. It was estimated to have caused approximately 8422 cases and 858 deaths involving 32 different countries from November 2002 to August 2003. It was first reported in Foshan municipality, Guangdong province, China [13,56].

COVID-19 is the current pandemic that was first reported in Wuhan China. By 10/03/2023, 676, 609, 95 total cases and an estimated 6,881,955 COVID-19-associated deaths was reported with an approximate 13,339,000,000 vaccine doses administered around the globe (https://coranvirus.jhu.edu/map.html). Almost every country around the world experienced the devastating impact of COVID-19. COVID-19 was the third outbreaks to be associated with coronaviruses [14]. Due to its global impact, the World Health Organization (WHO) declared COVID-19 a "global health emergency" on 31 January 2020 and later declared it a "pandemic health" on 11 March 2020.

World health organization priority pathogens

Due to the 2014-2016 epidemics, the WHO identified some emerging pathogens with potential of causing public health emergency which has few countermeasures to enable the world mount sufficient preventive or therapeutic interventions [15]. Currently, the WHO priority viral pathogens includes COVID-19, Crimean-Congo haemorrhagic fever, Ebola virus disease and Marburg disease, Lassa fever, Middle-East respiratory syndrome coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviruses Rift Valley fever, Zika fever, Mpox, and Disease X which is unknown pathogen not currently affecting humans but could be a potential source of pandemic due to its zoonotic risk, global warming, mode of transmission, tropical deforestation, or other factors. The WHO's Research and Development (R&D) Blueprint is a global strategy that promotes rapid activation of research and development activities during epidemics and pandemics (https://www.who.int/teams/blueprint/).

Characteristics of potential pandemic virus

Before COVID-19, the scientific community have been issuing warnings about the potential of coronaviruses to cause pandemic. By then they had evaluated the characteristics of these viruses and found that they are emerging viruses with significant public health

concern. Viruses have been the cause of the most pandemics which suggests that they are potential source of the next pandemic. Viruses are divided into RNA or DNA, with DNA viruses known to consist of viruses that have coevolved with humans over long period of time; although there are some few exceptions such as pox and herpesviruses [16]. The RNA viruses on the other hand are different because most of them that infects human are of also zoonotic in nature, which suggests they have the ability of infecting vertebrate hosts apart from humans. In addition, most of them that are not zoonotic but may have evolved recently and having zoonotic origin. This makes RNA viruses pathogens of interest when it comes to studying pathogens as priority agents in terms of epidemic or pandemic. About 180 species of RNA viruses infect human, however this number can be regarded as an underestimation because new RNA viruses are being identified due to advances in technology. This discovery is at about two per year; although some data showed that the number of undiscovered species may be lower than predicted [16-18]. But the suggestion is there are still quite a number of species out there that need to be discovered.

The RNA viruses can be grouped as those who infect: humans or non-humans. Of these viruses, 160 species are known to infect human with approximately 89% considered as zoonotic. The non-human RNA virus in most cases infects other mammals and rarely birds. The remaining viruses are considered "specialist human pathogens" because they naturally infect humans; for e.g. hepatitis B which can coevolve with human over a long period of time and human immunodeficiency virus (HIV) [17]. When one considers the ability to infect humans, the RNA viruses have the ability of easily infecting humans. This is based on the fact that the genomic stability of RNA viruses is less than that of DNA viruses thereby giving RNA genome flexibility. Spillover is therefore highly possible. However, some DNA viruses such as smallpox and Mpox seem to challenge this consensus [19,20].

Location of replication of the viruses is another trait that is associated with pandemic. It has been suggested that viruses that possess have ability to spread widely are more likely to replicate in the cytoplasm of the cell which permit entry into the nucleus thereby limiting its zoonotic ability resulting in it becoming strongly associated with its natural host [17]. RNA viruses' replication tends to be cytoplasmic while DNA viruses possess nuclear replication cycle. However certain viruses also challenges this dichotomy; for e.g. smallpox, a DNA virus with the ability of causing pandemic has a cytoplasmic cycle while influenza virus, a RNA virus also causing pandemic possess nuclear replication cycle [21,22].

Other traits that can influence the ability of a pathogen to cause pandemic include segmented genome, smaller genome size, and high host viremia as seen in vector-borne flavivirus. With segmented genome, this can lead to novel genetic reassortment as seen in flu virus's segment while large genome inhibits mutation [23].

Based on the above mentioned characteristics, consistent with the recommendation of WHO priority pathogens, most RNA viruses should be pathogens of high priority in terms of causing the next pandemic because of their spread via respiratory route, cytoplasmic replication and increased ability to mutate. However, other DNA viruses that are known to also cause pandemic should not be neglected.

For a pathogen to be able to cause pandemic, significant global population should be immunological naïve so that the pathogen can have a high number of susceptible people to infect. In addition, intervention measures such as broad-spectrum antiviral agents and vaccines are not be available. In addition, the pathogen should have the ability of evading the immune system which permits the development of productive infection.

The pathogen should be able to use human receptors that would enable its transmission thereby infecting majority of humans. The receptors can be used for organ tropism thereby leading to severe disease such as respiratory tract, faecal-oral route and arthropod vector, for e.g. in COVID-19, the virus used ACE2 receptor to enter human host while it entry mechanism is dependent on cellular transmembrane protease serine 2 which enable it to have high transmission rate suitable for global outbreaks while vector-borne viruses are good in

infecting humans but poor in transmission [18,24]. However, it should be noted that although humans are regularly prune to infection with vector-borne viruses, some of these viruses do not easily adapt to new host.

The virulence of pathogen capable of causing pandemic is another important trait. It is postulated that high virulence of a pathogen is associated with high case-ratio fatality (CRF) and pathogens has been termed 'virulent' if it has high CRFs. SARS-CoV and HIV-1 can therefore be regarded as virulent while parainfluenza virus and rhinovirus are not regarded as virulent [18]. However, with pandemic the CRF should not be exceedingly high for a pathogen to cause pandemic. This is because by killing many of its hosts, the pathogen would run out hosts for it to it to continue surviving [24].

In addition, the reservoir of the pathogen is another important characteristic with the data suggesting that viruses acquired from certain reservoirs are virulent. For e.g. SARS-CoV-2, Proal., *et al*. found that the virus persists in tissue as reservoir and this mechanism of reservation is associated with post-acute sequelae of COVID-19 [25]. In Ebola virus disease, new outbreaks have been reported among individuals carry the virus in their reservoirs years after acute infection [26]. In addition, source of the pathogen can determine its ability to cause pandemic; for e.g. primates vs. nonprimates or birds vs. mammals. Some highly virulent human viruses such as HIV-1 can be acquired from primates who are close relatives to humans. Other virulent viruses are acquired from hosts that are distantly related to humans for e.g. H5N1 influenza virus [18].

Paramyxoviruses as potential agent of pandemic

The family *Paramyxoviridae* (Table 1) consists of segmented negative-sense RNA viruses that are enveloped. The genome is approximately 14.6 and 20.1 kb. They have a wide range of hosts that includes mammals, birds, fish, and reptiles. The International Committee on Taxonomy of Viruses (ICRV) classified *Paramyxoviridae i*nto 4 subfamilies, 17 genera, and 78 species (http://ictv.global/report/paramyxoviridae).

Characteristics	Description
Typical member	Measles virus, Ichinose-B95a (AB016162), species *Measles morbillivirus*, genus *Morbillivirus*
Virion	Enveloped, pleomorphic (mostly spherical) virions with a diameter of 300 - 500 nm enclosing a ribonucleoprotein
Genome	Negative-sense, non-segmented RNA genomes of 14.6 - 20.1 kb
Replication	Cytoplasmic, by the virus ribonucleoprotein complex, involves replication of antigenome and transcription of 6 - 8 positive-sense mRNAs
Translation	Cytoplasmic, by cellular machinery from capped and poly-adenylated mRNAs
Host range	Mammals, birds, fish, and reptiles
Taxonomy	Realm Riboviria, phylum *Negarnaviricota,* class *Monjiviricetes*, order *Mononegavirales*, currently 4 subfamilies, 17 genera and 78 species

Table 1: *Characteristics of members of the family Paramyxoviridae (Source: ICTV).*

Paramyxoviruses (PMVs) consist of divergent genera that include measles virus (*Morbillivirus)*, human parainfluenza viruses (Orthorubulavirus*, Respirovirus*), mumps virus (*Orthorubulavirus*), Nipah and Hendra viruses (*Henipavirus*) which are important human pathogens of international public health importance. They have different mode of transmissions. Measles virus are transmitted via human-to-human while mumps and parainfluenza viruses are transmitted through airborne route or fomites; henipaviruses (HNVs) are usually transmitted by direct contact of infected bodily fluids such as saliva, urine, and respiratory secretions [27]. HNVs consist of zoonotic Hendra virus (HeV) and Nipah (NiV) virus which are known to be highly pathogenic in domestic animals and humans when

there is spillover from their natural hosts (bats). Recently a divergent virus, Angavokely (AngV) was isolated and characterized from urine samples of wild Madagascar fruit bat [28]. All experienced human cases of HeV were reported in Queensland, Australia [29] while NiV has been outbreaks have been frequently reported in South Asia and Southeast Asia [54].

Henipavirus, a pathogen of interest

Henipaviruses has several characteristic making it a very significant threat to global health including: 1. Its natural reservoir is the fruit bat (*Pteropus genus*) which is found spread across Asia and Africa and this play a significant role in spillover events; 2. The viruses can be transmitted from bats to human either directly or through domestic animals; 3. The transmission can be through human-to-human transmission; 4. Spillover has occurred frequently among highly populated areas such Africa; 5. They are associated with high mortality rate among humans greater than 40 - 75% for NiV (in comparison to COVID-19 pandemic which has a mortality of 1 - 2%); and 6. There are no antivirals agents or vaccines available to tackle the disease [30-32]. This suggest that based on the above stated factors, NiV is of importance to global public health. Clinical manifestation of NiV infection in human includes encephalitis, vasculitis, and myocarditis with infected individuals showing symptoms including confusion and drowsiness which can advance to coma. In some cases, residual neurological complications have been reported among survivors [33]. Figure 1 represents a diagrammatic representation of clinical manifestations of NiV infection in humans, swine, and equine.

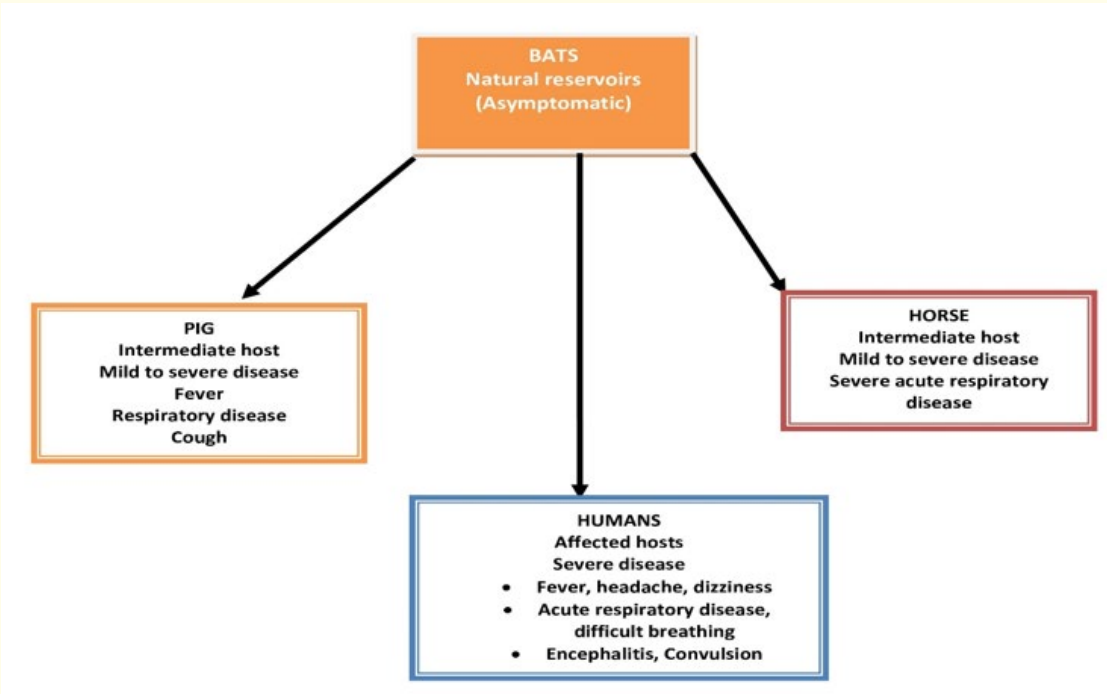

Figure 1: *Clinical manifestations of NiV infections. Bats are the natural reservoirs without any symptoms. The two intermediate hosts: horse and pigs shows different symptoms while among humans, there is presentation of severe diseases which includes acute respiratory disease, encephalitis, and convulsion.*

The epidemiological data highlight the significance of NiV. It was first described between 1988 and 1999 in Malaysia in pigs which resulted in cases encephalitis in pig farmers. The outbreak resulted in 105 human mortalities, with 265 reported cases in Malaysia and 1 case fatality while in Singapore, 11 cases were reported among abattoir workers [34]. However, 2001, a different strain of the virus was described in Bangladesh and named NiV-B. It was responsible for cases of encephalitis. Since then, Bangladesh have been experiencing NiV outbreaks almost every year with the recent being January 2023 and 14 February 2023 in which 15 cases were reported and eleven associated fatalities (Figure 2). Bangladesh reported that local death due to NiV infection is about 73%. This is a sufficient number to cause global concern [35].

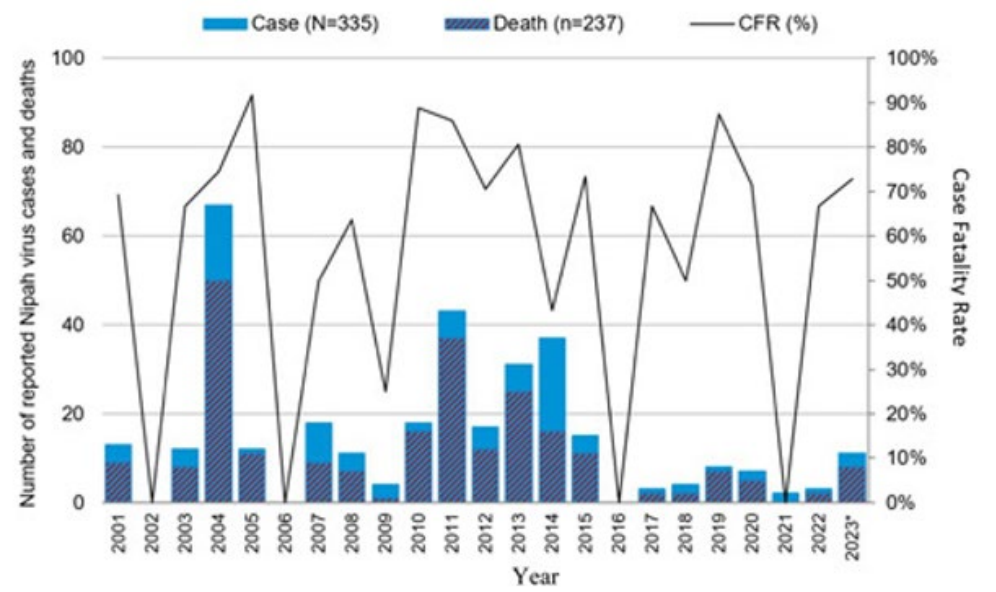

Figure 2: *Number of reported NiV morbidity and mortality from 2001 to 2023 in Bangladesh (Source: Bangladesh Ministry of Health and Family Welfare).*

Apart from Bangladesh, NiV cases have been reported in India in 2001 with a reported 66 cases and 45 associated mortalities while a smaller number (6 cases) was reported in Nadia district of West Bengal in which the fatality was 100%. In 2018, there was an outbreak in regions in South India and in 2019, a single case of NiV infection was reported in Kerala and in 2021, NiV associated encephalitis was confirmed in a boy in Kerala who later died from the disease [33,36,37] and in Philippines in 2014 involving 17 human cases of which ten infected showed history of close contact with either horses or meat of horse was consumed. The CFR was 82% [36].

HeV, just like NiV also have the same natural reservoir (bat) and has been associated with fatal diseases in human and horses. Transmission of HeV to horse can be via the excretions of HeV-infected bat, especially through urine. In addition, it can also be transmitted to humans from horses via excretions or bodily fluids. Different clinical manifestations have been reported in humans including mild influenza-like symptoms and severe disease such as fatal respiratory disease or neurological symptoms. HeV also have no antiviral agents or vaccine for humans [38].

HeV was first reported among horses in 1994 in Brisbane, Australia with symptom of severe respiratory disease which led to 14 horses to die and their trainer. There were 7 horses and one person that were infected but they didn't succumb to the infection. However, it

should noted that the first described case of HeV was few months before the cases in horses which also included an individual who later developed encephalitis and succumb to the infection after 13 months [39]. Since the first cases in Brisbane, there have been further 64 outbreaks in Australia which led to 104 equine fatalities [38].

One of the important characteristics of HNVs especially NiV as a potential agent of the next pandemic is it ability to cross species which has been reported on many occasions, resulting to infections among human and animals who have limited person-to-person transmission [40]. NiV transmission to humans takes place in areas where bats, pigs, and human come in close contact to each other. Human rears pigs for business in areas surrounded by farms and plant-fruit bearing tress. The bats are attracted to the fruits where while consuming the fruit drops saliva on partially eaten fruit which are then consumed by domestic animals leading to spillover of infection in the domestic animal which are then transmitted to humans. This was experienced in the Malaysia outbreak. NiV infection in humans can take place through either by intermediate hosts or directly to humans from bats which can then result in human-to-human transmission. More studies are needed to understand the transmission dynamics of the NiV and HeV from bats, pigs and humans as well as from contaminated fluids such as date sap to humans. The transmission dynamic of emerging pathogens can be unpredictable however with NiV; it possesses certain characteristics that facilitate it becoming pandemic pathogen including genomic mutation, viral receptors, spillover, and mode of transmission.

The genome of PMNs consists of non-segmented, single-stranded (-) sense RNA which is spherical in shape. It consists of six structural proteins: nucleocapsid, phosphoprotein, matrix, fusion, glycoprotein and polymerase. When compared to other *Paramyxoviridae*, HNVs have a larger genome approximately 18.2 kb. The extended length is due to many long 3' untranslated regions (UTRs) of nucleocapsid, phosphoprotein, fusion, and glycoprotein mRNAs. The genome of HNVs just like other PMVs consistently exhibits polyhexameric length which is based on the "rule of six", a requirement for efficient genomic replication under mRNA editing properties of the PMNs genome. The PMNs P locus is associated with transcription features which are shared among all members of the *Paramyxoviridae.* The P gene's role in translation of additional accessory protein in the locus before translation or an overlapping open reading frame in the P gene itself. Of interest is that almost all HNVs consist of conversed mRNA editing site where inserting extra guanine residues leads to translation of V and W, accessory proteins associated with viral antagonism and immune evasion [28,36,41,42]. The P gene also consists of an overlapping ORF that is also associated with immune evasion [41]. The glycoprotein is associated with receptor binding while the fusion protein is responsible for fusion of viral envelope to the target cellular membrane. The M protein is responsible for viral assembly and budding from the host cell plasma membrane. The genomic features of HNVs increases its prospect of causing pandemic because it has exceptionally high mutation rate which can be million times higher than in their hosts. For e.g. with NiV, there are two strains, NiV Bangladesh (NiV_B) and NiV Malaysia (NiV_M) named based on the viral properties. Furthermore, NiV_M is not associated with human-to-human transmission while NiVB is associated with direct human-to-human transmission making it the most dangerous infection [43]. Therefore it can be suggested that NiV_B is more infectious than NiV_M and it has the potential of further mutation leading to the development of new strains for which human will be susceptible and if human-adapted strain are to infect any communities with high population and global interconnection, it would rapidly spread across the globe as witness in COVID-19 [43,54].

HNVs can be transmitted (Figure 3) from bat to horses and from horse to human when they come into direct contact. Although there has not being direct human-to-human transmission of HeV, direct human-to-human transmission has been reported for NiV especially if exposed for more than 12 hours (38). HNVs can be been recovered from oral fluids, urogenital fluid, faeces, and uterine fluids which increases it dynamics for multiple transmission including exposure to excreta, uterine fluids, ingesting contaminated foods by saliva, and mating [44]. Furthermore, roost size is elevated seasonally during mating and birthing periods, which suggests that transmission, can be increased when the seroprevalence is below the herd immunity thresholds. Previous studies focusing on NiV and HeV in *Pteropus* species on transmission dynamic gave inconclusive results and in some cases contradictory results. For e.g. in NiV, HeV, Marburg and some bat coronaviruses, seasonal spike was linked with seasonal spike in infection that concurs with annual or semi-annual simultaneous birth

pulses; in NiV, seasonal shedding was notices in *Pteropus lylei* in Thailand while seasonal spike were reported in *Eidolon dupreanum* in Madagascar and it was concurrence with the periods of pregnancy. In Australia bats, the prevalence of HeV was shown to be associated with ongoing interepizootic phases. During this phase, viral shedding was found to be highly increased [30].

Shedding of the viruses from bat and their survival in environment is important for spillover and associated with transmission of HVNs. Some Pteropus bats can migrate and interrelated colonies then form meta-population thereby allowing the virus to be reintroduced into susceptible population. Furthermore, reappearance was reported in wild bat such as *P. vampyrus* and *E. helvum*. This aids NiV to last regionally when the immunity of the local population is high. These suggest that birthing period, demographic and immunological factors plays roles in the transmission dynamics of HVNs [30,45]. The effect of such free-living bat population on transmission dynamics in HVNs needs further elucidation.

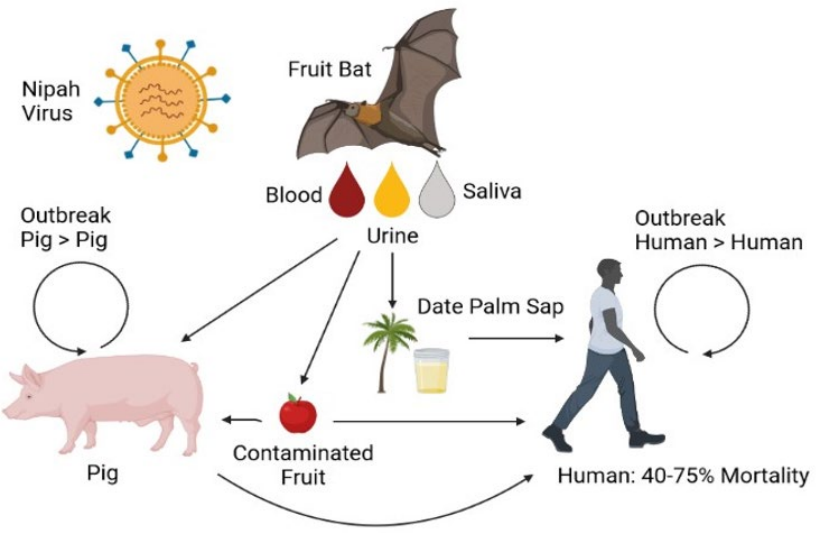

Figure 3: *Diagrammatic representation of different route of NiV transmission. Mortality among human is 40 - 75% (Source: Jenner Institute).*

Till date, outbreaks have been reported in Australia, Bangladesh, India, Malaysia, Philippines, and Singapore which involved not more than thousand cases in total. However, the CFRs for HVNs infection are high (can reach 100% in some cases). Of concern is the fact that the geographical range of *Pteropus* bat species which enable it to survive is extensive and covers almost half of the world's population. The reproductive number (R_0) is the measure of speed by which a disease can spread in population. Ro is essential is understanding the transmission dynamics. R_0 for HeV is yet to be elucidated but it is suggested to range from 0.19 to 0.59 in a nosocomial setting and corpse-to-human transmission [46]. Generally, it is estimated that NiV can be associated with three fatalities in four people infected (https://www.gavi.org/vaccineswork/next-pandemic/nipah-virus).

The viral receptor plays significant role in viral transmission because of the importance of the viral-receptor interactions. In COVID-19, it was established that the human ACE2 receptor which is found in arteries, heart, kidneys, and intestine are consistent so the virus can commence rapid transmission and several comorbidities [47]. ACE2 receptor is expressed by wide range of animal species so it aid in cross-species and human-to-human transmission. Similarly, in NiV infection, the virus possesses ephrin (B2/B3) receptor which has

been found in almost all tissue increases its prospect of initiating infection. The receptor aid in the spread of the virus which is required a step for infecting different cell types. Since outbreaks from zoonotic pathogens to human population is dependent on the availability of specific receptor, viruses can infect specific to the cells, possession of ephrin receptor aid NiV internalization process which is essential for transmission [43].

Diagnostic approaches for HVNs

Diagnosis of NiV infection is based on clinical symptoms. However, this method is limited by the wide range of clinical manifestations observed in NiV infection. Some techniques have been suggested that would facilitate diagnosis of NiV infection include virus isolation, nucleic acid amplification testing such as NAAT, PCR, and sequencing and serological approach such as ELISA, cell-fusion assay and virus neutralization assays.

The initial PCR assay was developed with N gene and was found to be highly specific and could detect NiV viral RNA in samples from hamsters that were infected with NiV. However, this assay could not detect HeV viral RNA [48]. Reverse-transcriptase PCR (RT-PCR) has been developed that targets N, M, or P segments of the genome. Other PCR assays that have been developed include conventional RT-PCR, and real-time RT-PCR (qPCR). However RT-PCR has been found to be thousand time more sensitive than conventional PCR [49]. In addition, PCR assay targeting NiV N gene can be utilized in phylogenetic studies.

Serological assay can be used in detecting NiV antigens and immune responses such as IgM and IgG against the antigen. IgM measurement can be used for detecting active infection because anti-IgM in serum increases after nine days of illness while IgG can be used for epidemiological studies and surveillance because IgG persist long after an individual is well. IgM ELISA is usually used as first-line NiV diagnostic test which is followed by confirmatory treat; for e.g. serum neutralization and PCR assays. Due to the 90% similarity between NiV and HeV N and G proteins as well as 30% difference in their P protein, polyclonal antibodies have been developed that targets both NiV and HeV antigens. It can also be used in differentiating NiV and HeV. One prospect is utilizing ELISA tests reagents to lateral flow format which can used for faster results as rapid detection tests (RDTs). There are still no RDTs for HVNs for humans and animal [49]. However, uses of serological confirmation assays are limited by the use of live NiV thereby requiring BSL-4 facility [50].

Multiplex immunoassay approaches have been developed for differential diagnosis using beads coated with NiV and HeV proteins. Two strategies were utilized: binding assay that differentiate the two viruses and inhibition assay that detect and differentiates the two viruses' neutralising antibodies [49,51].

Electron microscopy and immune-electron microscopy can also be beneficial as it can be utilized in determining the structure of NiV (and HeV) and also evaluating viral antibody interactions. NiV grows well in Vero cells which are shown by formation of syncytia and plaques on the cell monolayer. In addition, immunohistochemistry is used for identify viral agent [49].

Therapeutic interventions

One lesson we learned from COVID-19 is the essence of preparedness therefore we have to start addressing NiV as the possible pathogen with pandemic capability. Currently, treatment of NiV infection is by supportive care and management of symptoms such as acute encephalitis syndrome [52]. Ribavirin has been recommended by the Infectious Diseases Society of America for treating NiV encephalitis but *in vitro* and *in vivo* studies gave conflicting result in terms of efficacy. A study by Lipin., *et al*. suggested that favipiravir can has very good inhibitory activities against NiV [53]. When evaluated in Syrian hamster animal models, it was found to treat the animals when administered daily for 14 days. However, more studies are needed to identify the best therapeutic doses, the period of treatment and the routes after infection [43].

Others have also suggested the use of monoclonal antibody m102.4. In May 2020, m102.4 was given to a mother and her daughter on compassionate grounds. They were exposed to HeV from infected horse and both of them did not develop HeV infection. But there have been questions whether the treatment was effective or whether the patients didn't even get infected. Intensive efforts should be channelled towards developing vaccine or effective antiviral agents for NiV and HeV.

In order to be ready, there is urgent need to engage in research that could lead to the development of potent antiviral agent and/or vaccine. International collaboration would be an ideal platform for such collaboration.

Conclusion

HVNs consist of some highly pathogenic emerging zoonotic viruses. HeV and NiV are the most studied but other HVNs such as AngV have been identified which have the potential of spillover, one of the characteristics for pathogens capable of causing pandemics. NiV and HeV are BCL-4 viruses with no antiviral agents or vaccine. HVNs are agent of interest in terms of causing the next pandemic. A lesson we have learned from COVID-19 is preparing for the next pandemic and because HVNs are mostly found in bats, we should focus our attention and effort to them. They possess relevant characteristics that makes them virus of interest. We need to develop antiviral agents or vaccine to mitigate against the potential global effect of NiV and HeV pandemics and that preparation must start now. COVID-19 caused devastating impact on health and economies around the globe. This "rat race" between man and pathogens would continue since they are not new phenomenon and we need to be prepared to enable us triumph over this lurking pathogens.

Conflict of Interest

Both authors do not have any conflict of interest to report.

Use of Artificial Intelligence

Authors confirms that no aspect of artificial intelligence was used during preparing this article.

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