

Perspectives

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A New Era of Global Disease Emergence

The International Response to Nipah Encephalitis Virus

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Abstract

Since the culmination of SARS in 2003, the world has been awakened to the surreptitious and often fatal reality of viral emergence on a global scale. The WHO, as the leading governing body in global public health, has recognized the need for heightened surveillance of emerging pathogens. The Nipah Encephalitis virus, a lethal zoonotic paramyxovirus, has been identified as a source of potential pandemic disease and thus a threat to the health security of the international community as a whole. An interdisciplinary, multi-lateral approach is needed to understand the changing nature of this deadly pathogen from a microbiological to societal level, and in concert, prepare for a possible public health emergency of international concern.

Introduction

SARS (severe acute respiratory syndrome), the first emerging and readily transmissible disease of the 21st century, rocked the global community and the international public health infrastructure by setting off several deadly and unexpected outbreaks beginning in November of 2002.¹ While the area categorized by the World Health Organization (WHO) as the Western Pacific Region fell victim to the greatest number of these attacks, the world watched in fear as the unidentified viral pneumonia left China's Guangdong province and began its deadly spread throughout the mainland and around the world. On July 5, 2003, the WHO declared that all known human-to-human transmission had ceased, but not before the epidemic claimed nearly 800 lives. What followed the culmination of SARS in

2003 was not a feeling of success but rather one of fear—fear of the realized ineptitude of the international community to respond to novel disease emergence.¹ Since then, the international health care field has been awakened to the surreptitious and often fatal reality of viral emergence on a global scale. Furthermore, the WHO, as the leading governing body in global public health, has recognized the need for heightened surveillance of emerging pathogens.² Nipah Encephalitis virus, a lethal zoonotic paramyxovirus, has been identified as an exemplary source of potential pandemic disease spread and thus a threat to the health security of the entire international community.³ Given the renewed emphasis on disease surveillance following the unexpected SARS outbreak in 2003, the international community must embrace the lessons learned from managing the SARS

outbreak and apply an interdisciplinary, multi-lateral approach to effectively understand and respond to the rapidly changing nature of this novel pathogen.

Understanding the Pathogen

Nipah virus (NiV), initially misdiagnosed as Japanese Encephalitis virus, was first recognized in 1999 during an outbreak of encephalitis (inflammation of the brain) at pig farms and slaughterhouses in Malaysia and Singapore.⁴ It has since claimed over 100 human lives, and Nipah virus has been confirmed as the etiologic agent of several additional small-scale outbreaks in South Asia with case-fatality rates exceeding 75% (See Table 1).⁵ NiV infection manifests as severe illness, characterized by encephalitis, respiratory illness and death (See Table 2).⁶ Pathologic studies from recent outbreaks identify endothelial cells and neurons as major cellular targets of NiV.⁷ These studies reveal that infection is most prominent in the central nervous system, where diffuse vasculitis is noted in the cerebral cortex and the brain stem of humans.⁸ In addition, pathologic examination of pigs has shown extensive involvement of both the upper and lower respiratory tract, suggesting that respiratory secretions from infected pigs are likely to be a rich source of the infectious virus.⁹ Evidence of NiV infection has also been found in several other animal species, including dogs, cats and horses.¹⁰ Given that there is currently no vaccine or treatment option available for NiV infection, scientists are eager to understand the mechanisms of its viral pathogenicity and immune evasion.

The virus' utilization of an intermediary pig vector has varied between regional outbreaks, indicating a bimodal nature of NiV transmission.¹¹ The initial encephalitis outbreak in Malaysia was confined to a cluster of patients associated with pig farming. During this outbreak, humans were infected through direct contact with infected fluids of pigs such as urine, saliva, pharyngeal or bronchial secretions; however, no secondary human-to-human transmission was confirmed.¹² The outbreak subsequently spread to various regions of Malaysia and Singapore due to the movement of infected pigs.¹³ Fruit bats of the Pteropid species were initially identified as the natural host reservoir and, given their close proximity to pigsties, it has been suggested that contamination of food and water supply by bat urine is the most likely mode of bat to pig transmission.¹³ While use of a pig vector was characteristic of the 1999 Malaysia/Singapore outbreak, all subsequent outbreaks in Bangladesh and India have been associated with direct infection from bats to humans, with significant human-to-human transmission as well. The bimodal nature of viral transmission suggests either a mutating virus or a changing global ecology that facilitates viral access to human populations. Further research is needed to understand the exact determinants of viral host jumps.

Understanding the Response

In order for the international community to front a comprehensive and effective response to an emerging zoonotic disease of this severity, there must first be an examination of human behaviors and practices that have changed patterns of animal-human interactions. Once scientists understand the biological pathways affecting Nipah emergence, they must then explore the viral/host constructs that facilitate transmission from human-to-human, in order to model the potential extent of the impact and spread. This information will allow decision-makers to more confidently allocate resources to prevent outbreaks, and in the instance of an outbreak, such data will prompt effective response measures of containment and control.¹⁴

Immunopathology reports suggest that bats can harbor NiV without detrimental consequence to their own well-being; thus, it can be assumed that bats in the South Asian region may have carried this virus for years, and only when they interacted with humans or domesticated animals did the virus jump species. Many disease ecologists point to agricultural intensification and specific agricultural practices for possibly increasing the frequency of pathogen emergence from wildlife to human populations.¹⁵ To understand the ecological determinants of Nipah viral host-jumps, it

Table 1: Chronology of NiV Outbreaks³

| Year | Country | State | Cases | Deaths | CFR |
|------|------------|-------------|-------|--------|------|
| 1999 | Malaysia | Multiple | 265 | 105 | 40% |
| 1999 | Singapore | Singapore | 11 | 1 | 9% |
| 2001 | India | West Bengal | 66 | 49 | 74% |
| 2001 | Bangladesh | Meherpur | 13 | 9 | 69% |
| 2003 | Bangladesh | Naogaon | 12 | 8 | 67% |
| 2004 | Bangladesh | Rajbari | 29 | 22 | 76% |
| 2004 | Bangladesh | Faridpur | 36 | 27 | 75% |
| 2005 | Bangladesh | Tangali | 12 | 11 | 92% |
| 2007 | Bangladesh | Thakurgaon | 7 | 3 | 43% |
| 2007 | Bangladesh | Kushtia | 8 | 5 | 63% |
| 2007 | India | West Bengal | 5 | 5 | 100% |
| 2008 | Bangladesh | Manikgonj | 3 | 3 | 100% |
| 2008 | Bangladesh | Rajbari | 8 | 3 | 38% |
| 2010 | Bangladesh | Faridpur | 17 | 15 | 88% |
| 2011 | Bangladesh | Rangpur | 35 | 8 | 38% |
| 2012 | Bangladesh | Joypurhat | 17 | 17 | 100% |

is essential to examine the spatial and temporal patterns of agricultural production in peninsular Malaysia prior to and at the time of the initial outbreak.¹⁵ Juliet Pulliam, an expert in ecological modeling of outbreaks, found that between the early 1970s and the late 1990s the correlation of expansion of large-scale pig farming and mango production in peninsular Malaysia allowed for a unique opportunity for pigs and fruit bats to come into intimate contact.^{15,15} The pig farm where Nipah first emerged contained over 30,000 pigs, with fruit trees surrounding the perimeter of the pen.¹⁶ Mangoes, jackfruit and durian were grown on the index farm, while other farms in the area grew primarily pomelos, which are not eaten by the Pteropus species of fruit bats. The close proximity of pigsties to fruit bat feeding sites facilitated this cross-species transmission of NiV from bats to pigs.¹³ Pigs are commonly referred to as the "virus mixing bowl" because they contain viral receptors that bind to viruses native to multiple different species. Thus, pigs can often be infected with a virus from one species, help it undergo viral reassortment, and then subsequently act as amplifier hosts, enabling infection of humans through direct contact with infected fluids (such as urine, saliva, pharyngeal and nasal secretions).¹⁷ The circumstances of the 1999 Malaysian outbreak indicate that the virus demands a large pig population to maintain itself for several months, with several possible viral introductions, before spreading to human populations (See Map 1).²⁴ After the initial outbreak, the movement of infected pigs spread the disease to various regions of the country and to Singapore.¹³

Pertinent ecological information obtained from the initial outbreak of Nipah in Malaysia and Singapore must prompt policy and public health interventions focused on controlling disease amplifiers, namely agricultural intensification, movement into previously uninhabited areas, human/animal interchange and climatologic and other environmental factors that influence viral shedding of the host. In order to prevent future outbreaks of NiV, the WHO must implement fruit bat surveillance initiatives to monitor the flying ranges of these species. According to the Institute of Medicine's expert committee on emerging disease surveillance, improved surveillance is particularly important when the risk of outbreaks in humans is largely determined by the epidemiology of infection in the host reservoir.¹⁴ In regions prone to viral introduction, environmental surfaces believed to have high risk of contamination with Nipah virus, such as pigsties, date palm sap collection pots and fruits that may have been in contact with Pteropid bats, must be selected for viral sampling. Human resources and field capacity are essential in order to conduct surveillance of zoonotic pathogens in animal reservoirs that may be difficult to reach. Improvement and development of such field capacity will greatly improve the ability to predict where the next zoonotic disease will emerge.¹⁴

In addition to understanding the context of viral introduction into human populations, researchers must consider viral/host constructs, such as patient care practices, host susceptibility factors and strain variation to understand the mechanisms of human-to-human spread.¹⁸ Stephen Luby and colleagues from the International Center for Diarrheal Disease Research in Bangladesh propose that three factors are likely to contribute to higher frequencies of person-to-person transmission in Bangladeshi outbreaks. First, respiratory disease associated with Nipah infection was both more common and more severe in Bangladesh than that of Malaysia and Singapore, offering more opportunities for transmission via respiratory droplets. Second, the personal care typically provided to ill and dying relatives in Bangladesh is characterized by close physical interaction, increasing contact with the patient's saliva. Third, all Nipah viral strains from human cases in Malaysia and Singapore were genetically similar, whereas strains in Bangladesh were quite diverse; thus, these strains could possess characteristics that facilitate human-to-human transmission.¹⁹

Given the emergence of new strains of Nipah virus, proposed to be highly capable of human-to-human transmission, the WHO must encourage the constant collaboration of expert virologists, microbiologists, pathologists, immunologists and physiologists to decipher the rapidly changing constructs of the virus. Luckily, new technologies such as advanced polymerase chain reactions and high-throughput sequencing have enabled the scientific community to identify novel pathogenic strains and increase the rate and frequency of mutation detection.¹⁴ It is then crucial that the WHO act as a liaison between the scientific and public health communities in order to relay all pertinent information regarding new discoveries.²⁰

The New Era of Global Disease Emergence

Nipah virus is just one of over 40 new diseases that have emerged since the 1970s, including Ebola, Hantavirus Pulmonary Syndrome, Venezuelan equine encephalitis, Hendra virus and Avian influenza. Three quarters of all emerging infectious diseases are a result of zoonosis—a microbial jump from an animal reservoir to a human population.¹⁶ The majority of recent discoveries of new human pathogens are viruses associated with other mammalian hosts; a few are associated with birds, and only rarely are they associated with other classes of vertebrates.²¹ The rate of emergence of these wildlife-origin zoonotic diseases also appears to have increased significantly over the past six decades, with pathogens of wildlife origin representing the majority of all emerging pathogens

since the 1990s.²² As the ecology of the world changes and people begin to move into formerly uninhabited areas, their domesticated animals increasingly come into contact with local pathogens and subsequently act as vehicles for transmission to human populations.²³ Preventing and controlling emerging zoonoses requires identification of processes that drive cross-species pathogen transmission.²⁴ Broad, interdisciplinary approaches focused on data from specific emergence events are crucial for early identification of fatal epidemics and can illuminate emergent processes that may be applied to other emerging pathogens.²⁵

Given the commonality of many conditions surrounding novel disease emergence, it is imperative to draw themes from such events and to identify lessons learned from the management of these crises. In the wake of SARS, Nipah Virus and other significant novel pathogen outbreaks, public health officials point to four managerial factors that play a significant role in the effectiveness of control operations. These four critical disease response and control tactics are 1) early detection and communication of accurate, complete and timely information by affected governments and international administrative bodies; 2) rapid contact tracing, quarantine and isolation of infectious patients to prevent “super-spreading” events; 3) international partnerships to manage a localized outbreak and prevent development of a global pandemic; and 4) clearly reasoned, well-planned and effectively managed response plans that take into account national economic consequences for affected countries.

The WHO Global Outbreak Alert & Response Network (GOARN) points to the critical importance of early outbreak detection to ensure that the most appropriate experts reach the field in the least possible time to carry out effective outbreak control activities.²⁶ While GOARN and other bio-surveillance institutions work to identify indicators of an unexpected biological event, countries prone to emerging infectious disease must also have the diagnostic capability to identify in-country pathogen emergence.²⁷ The Committee on International Science, Engineering and Technology Policy recommends the installation of sophisticated laboratory capabilities in high-risk settings in order to upgrade local capacity to identify and respond to infectious disease emergence. The integration of modern technologies (such as electronic medical records, advanced BSL laboratories, secure sample transport systems, rapid tests/diagnostics and proper telecommunication systems) into an outbreak preparedness framework for countries at risk would drastically improve the ability to report real-time data to health governing bodies. While installation of such technologies is a costly endeavor, it should be considered an investment in health security and a necessary asset to prevent even greater human and economic losses. If in-country capacity is reached, then the WHO and member states should hold countries accountable for failures in conveying straightforward, reliable information in a time of crisis.¹ In China, for example, SARS was allowed to spread unreported for at least three months before the national government acknowledged the situation developing in the southern Guangdong province. Given limited time, major city centers such as Hong Kong and Beijing were unprepared for the influx of sick patients and therefore were unable to adequately treat and save lives. However, once SARS was reported, and the WHO Regional Office in Manila was appointed to coordinate response efforts in the region, electronic communication allowed the Regional Office to constantly update information and synchronize reporting and recommendations.¹

Given the multitude of unknown variables in situations of emerging infectious disease, scientists and public health officials have acknowledged the importance of learning quickly from the available data. Often times this data comes in the form of epidemiological or biostatistical records. It is essential that this data be used immediately to create epidemiological links and identify at-risk areas or highly infectious individuals who may be infecting others at alarming rates. Data from epidemiological investigations into the Nipah virus outbreak in Siliguri, India in 2001 suggest that 45 of 60 case-patients (75%) were health care workers with a history of hospital exposure to patients infected with Nipah virus.¹¹ Such alarming incidences of nosocomial spread pose major threats

Table 2: Clinical Manifestations of NiV⁶

| Species Affected | Characteristics |
|------------------|--|
| Humans | <ul style="list-style-type: none"> • Fever • Migraine • Vomiting • Emphysema • Encephalitis <ul style="list-style-type: none"> may relapse after recovery • Meningitis • Disorientation • Neurologic Deficits <ul style="list-style-type: none"> may persist after recovery • Coma • Death |
| Pigs | <ul style="list-style-type: none"> • Coughing <ul style="list-style-type: none"> sounds as if pig is barking • Open-mouthed breathing • Abnormal posturing • Convulsions |

to health care workers and public health infrastructure.¹⁸ In addition, during the 2005 Bangladeshi NiV outbreak, scientists from the International Center for Diarrheal Diseases in Bangladesh reported that 33 of 36 case-patients became ill after close contact with an infected person, 22 of whom were directly infected after contact with “patient F,” a proposed “super-spreader” of NiV.¹¹ “Patient F,” a local religious leader, became ill after he returned to his village in March of 2004, and subsequently transmitted NiV to 22 of his family members and followers during the course of his illness. The “super-spreading event” of Patient F is very similar to the one seen in SARS in 2003 when a 33-year-old infected male entered Amoy Gardens, a large seven-block apartment complex, and subsequently infected an astounding 329 residents.¹ Such an event is likely derived from the classical explanatory triad of host, agent and environment, in which an agent primarily causes disease, but its distribution, signs and severity are highly influenced by host and environmental factors. Both the “super-spreading events” of SARS and that of the Bangladeshi outbreak in 2004 are indicative of a lack of early diagnosis and infection control. It is thus essential to conduct contact-tracing early on, in order to identify highly infectious individuals quickly, and efficiently implement appropriate protocols of isolation in order to curtail further infection.

The WHO has asserted that emerging infectious diseases of the 21st century “represent a global threat that will require a coordinated global response.”²⁸ David Fidler, an expert in global health law and infectious disease research, notes that “the threat [of emerging infectious disease] is global because a disease can emerge anywhere on the planet and spread quickly to other regions through trade and travel... Experts grappling with these diseases no longer consider that the pursuit of a strictly national public health policy is adequate.”²⁹ Particularly in impoverished, densely populated regions of the world, a lethal virus with capacity for person-to-person transmission could rapidly spread before public health authorities can implement effective control measures. Larry Gostin, a public health law scholar, states, “Such a spread would provide a seed for a substantial regional, even global, public health emergency. While certain countries may be prone to the propagation of disease, rarely does disease remain contained in the country in which it originated.”³⁰ It is essential, then, that the WHO take the lead in mediating the response efforts on behalf of the international community. Upon notice of an event, a WHO-selected international team must be deployed to the site, where the team can integrate and coordinate all activities in support of the affected nation and the existing public health infrastructure.²⁶ In addition, it is the responsibility of member states to collaborate as well as provide technical and financial support. Within countries, the ministries of health should take the lead as the country’s primary reference point and work with higher levels of government and other ministries to update their respective administrations of all information coming in from the WHO. In the case of SARS, an impressive amount of goodwill surfaced during the outbreak, and government agencies generally set aside differences to ensure cooperation. The Director of the US Centers for Disease Control and Prevention announced several times that her organization would yield all decision-making to the WHO and would work in collaboration with other countries to assist in their response plans.¹ In anticipation of future outbreaks, the multi-national collaborative effort demonstrated in the case of SARS should be seen as an example of how the international community should coordinate response activities. The WHO should draw up a resolution that codifies this model, which can then be used as a directive for future outbreaks.

While the perception of risk drives multi-country support for aggressive action to contain disease spread, this same motive can facilitate an overly aggressive response with potentially devastating economic repercussions for affected countries. Upon the initial outbreak of Nipah Virus in 1999, Singapore banned the import of pigs from Malaysia, and the international community pressured

Map 1:
Surveillance Locations for Nipah Virus in Peninsular Malaysia



the Malaysian government to take swift action to prohibit the exportation of the virus to other countries. In response, the Malaysian pig industry was decimated with the culling of more than one million Malaysian pigs and the destruction of 1,004 pig farms. While some may consider the response successful in prohibiting a potential pandemic, it came at the cost of 36,000 jobs and \$120 million in lost export revenue.¹⁶ Similarly, during the outbreak of SARS that infected some 10,000 individuals, the health impact was infinitesimal compared to the economic impact suffered by many of the countries in the South Asian region. In addition, the social disruption and economic losses caused by SARS traveled well beyond the outbreak sites. According to the WHO, “news about the disease jolted stock markets. Economic growth projections had to be lowered. Commerce suffered in distant countries that depended on Asian goods and manufacturing capacity. Travel to affected areas plummeted, causing losses of about US\$10 billion to airlines with Asian routes.”³¹ The disproportionate scale and nature of this impact has caused concern that outbreaks of more serious diseases could deal devastating blows to the global economy.³¹ While priority should be given to the containment of disease, effective response plans should take into consideration the national and global economic consequences before strategies are implemented.

In today’s globalized world, the flying range of fruit bats or their proximity to pig farms does not sufficiently forecast where and when this human-to-human transmissible pathogen will appear. Pathogens alone do not have the capacity to jump species, infect thousands and spread to far regions of the world. Pandemics are in fact social phenomena whereby pathogens utilize settings and systems put in place by humans, commonly known as disease factories, to evolve and invade previously uninhabited terrain.³² Given that diseases will inexorably spread to neighboring countries, regions and even continents, states should work in concert to protect the global community from emerging threats that affect the security of all nations.³⁰ Sustained, long-term surveillance at both the local and regional levels is required for rapid detection of and response to potential outbreaks. In the case of Nipah virus, further research is needed to understand the geographic range of the animal reservoir, as well as mechanisms of animal-animal, animal-human and human-human transmission. Efforts to develop effective

strategies for containment and prevention of this and other viruses are needed, and guidelines must be distributed to all high-risk settings in the region and around the world.

Dr. Shigeru Omi, regional director of WHO's Western Pacific Region, states, "in looking back, I believe that one of the lessons that SARS taught us is that public health around the world has entered an era where it will need to be on constant guard against threats of emerging infectious disease."¹ While many would say that the interconnectedness of global societies is a trademark of a highly advanced and developed world, this system also renders the global population extremely vulnerable to the spread of infectious disease across populations and boundaries.³⁰ In 1999 the Nipah virus was regarded as a scary yet containable virus, and a communicable disease unique to Malaysia and Singapore. However, after repeated outbreaks indicative of a rapidly changing pathogen, public health authorities are beginning to recognize the seriousness of Nipah viral emergence and are prioritizing targeted global surveillance.^{32,33} Public health and research entities from around the world have taken on the challenge of understanding the drivers of newly emerging infectious disease as well as the context in which they arise. Interdisciplinary approaches are needed in order to understand the dynamics of Nipah virus from a microbiological to societal level in order to prepare for the future of NiV infections and their implications for the global public health community.

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