

REVIEW

Epidemiology, surveillance and control of Nipah virus infections in Malaysia

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Abstract

The outbreak of Nipah virus, affecting pigs and pig-farm workers, was first noted in September 1998 in the north-western part of peninsular Malaysia. By March 1999, the outbreak had spread to other pig-farming areas of the country, inclusive of the neighbouring country, Singapore. A total of 283 human cases of viral encephalitis with 109 deaths were recorded in Malaysia from 29 September 1998 to December 1999.

During the outbreak period, a number of surveillances under three broad groups; Surveillance in Human Health Sector, Surveillance in Animal Health Sector, and Surveillance for the Reservoir Hosts, were carried out to determine the prevalence, risk of virus infections and transmission in human and swine populations as well as the source and reservoir hosts of Nipah virus. Surveillance data showed that the virus spread rapidly among pigs within infected farms and transmission was attributed to direct contact with infective excretions and secretions. The spread of the virus among pig farms within and between states of peninsular Malaysia was due to movement of pigs. The transmission of the virus to humans was through close contact with infected pigs. Human to human transmission was considered a rare event though the Nipah virus could be isolated from saliva, urine, nasal and pharyngeal secretions of patients. Field investigations identified fruitbats of the Pteropid species as the natural reservoir hosts of the viruses.

The outbreak was effectively brought under control following the discovery of the virus and institution of correct control measures through a combined effort of multi-ministerial and multi-disciplinary teams working in close co-operation and collaboration with other international agencies.

Keywords: nipah virus, encephalitis, epidemiology, surveillance, fruit bats, pigs

INTRODUCTION

Nipah virus, a novel paramyxovirus within the family *Paramyxoviridae*, closely related to Hendra virus, emerged in the suburb of Ipoh, the capital city of Perak state in north-western part of Peninsular Malaysia in 1998.¹⁻⁴ The virus caused an outbreak of severe febrile encephalitis which carried a high mortality rate in humans, encephalitis and respiratory diseases but with a relatively low mortality rate in pigs. The illness in pigs was initially thought to be of Classical Swine Fever and the deaths in humans were thought to be due to Japanese encephalitis virus. The outbreak subsequently spread to other parts of the country and Singapore in 1999.¹⁻⁵ The

outbreak in Singapore ended with prohibition of importation of pigs from Malaysia while the outbreak in Malaysia ceased with institution of new control measures based on the discovery of this novel virus that led to the culling of over a million pigs. This presentation describes the epidemiology and control of Nipah virus outbreak and infections, various surveillances undertaken to determine the prevalence and risks of infections in both animal and human populations as well as the natural reservoir host of the virus.

Epidemiology of Nipah virus outbreak and infections

An outbreak of febrile encephalitis among pig farm workers was officially noted in September

1998 in the suburb of Ipoh, the capital city of Perak state, situated in the north-western part of Peninsular Malaysia.¹⁻⁴ It was apparently preceded by the occurrence of illnesses and excessive mortality in pigs in three pig-farming areas in the same affected suburb, beginning with farms in the Ampang village and subsequently involved neighbouring farms in Tambun and Ulu Piah. From this epicenter, the outbreak spread to other pig farms within the state of Perak and by December 1998, southward to pig farms in Sikamat which is situated in the state of Negeri Sembilan.¹⁻⁴ By February 1999, the outbreak had gained its foot hold in pig farms within the Bukit Pelanduk district inclusive of Sungai Nipah village in the state of Negeri Sembilan, the country's biggest pig-farming region.¹⁻⁴ By March 1999, the outbreak was noted in Sepang and subsequently Sungai Buloh within the Selangor state.¹⁻⁴ During that period, the outbreak had also spread into Singapore through importation of live pigs from Malaysia.⁵

During the outbreak, the Ministry of Health Malaysia recorded a total of 283 cases of viral encephalitis with 109 deaths from 29 September 1998 to December 1999.⁶ Of the 283 cases of viral encephalitis, 265 cases were classified as acute Nipah encephalitis (based on detection of anti-Nipah virus IgM and/or virus isolation), 10 were diagnosed as late-onset Nipah encephalitis, and 7 had neither detectable anti-Nipah IgM nor positive isolation of Nipah virus. A 42-year-old Indian male abattoir worker from Shah Alam, Selangor state was the only patient admitted to University Hospital Kuala Lumpur during the outbreak that was conclusively laboratory-confirmed as Japanese encephalitis (JE). The laboratory confirmation was based on pair-serum samples of sero-conversion to JE virus but negative on Nipah virus isolation and serology. Of the 109 deaths, two patients were due to late-onset Nipah encephalitis and the other two had neither detectable specific Nipah-IgM nor positive Nipah virus isolation at the time of death during the acute phase of illness. Of the 283 cases of viral encephalitis with 109 fatalities, the state of Negeri Sembilan recorded the highest number of cases (231) and fatalities (86), followed by Perak with 28 cases and 15 deaths while Selangor state had 24 cases and 8 deaths.⁶ Other states did not report any human Nipah cases or deaths. The overall case-fatality rate was 38.5%. The majority of patients were from 21 to 60 years of age (88.1%). The largest number of cases (45, 15.9%) occurred in the 40-

44 year old age group, followed by the 30-34 and 25-29 age groups with 39 (13.8%) and 37 (13.1%) cases, respectively.⁶ More than half (69.6%) of the encephalitis cases were Chinese followed by Indians (17.3%), and Malays constituted only 2.1% of all cases. A large proportion of cases (231, 81.6%) occurred among males and the majority (70%) were those who were directly involved in pig-farming (pig farm owners and workers).⁶

So far, only fruitbats of Pteropid species under the suborder *Megachiroptera*, family *Pteropodidae* has been identified as the natural reservoir hosts of henipaviruses.⁷ The natural reservoir hosts of Nipah virus in Malaysia are the *Pteropus vampyrus* and *Pteropus hypomelanus* whereas *Pteropus lylei* besides *P. vampyrus* and *P. hypomelanus* are identified as the reservoir hosts of Nipah virus in the Indochina region.⁷⁻¹¹ The *Pteropus giganteus*, being the only *Pteropus* species which is widely distributed throughout Bangladesh, parts of Myanmar and India, and along the eastern part of Africa inclusive of Madagascar has been identified as the reservoir hosts for the Nipah virus.^{12,13} On the other hand, the four species of Pteropid fruitbats (*P. alacto*, *P. poliocephalus*, *P. scapulatus*, *P. conspicillatus*) are the reservoir hosts of Hendra virus in Australia.^{14,15}

Nipah virus is contagious, highly virulent and capable of infecting several mammalian species in nature and under experimental conditions. Field investigations in Malaysia suggest an interplay of multi-factorial events such as reduction of wildlife habitat due to deforestation, prolonged El Niño-related drought, severe haze from anthropogenic forest fires in Indonesia, mixed agro-pig farming practices and traditional design of pig-sties led to virus spillovers via contaminated fruits from fruitbats to pigs as early as 1997.¹⁶ In the infected farms, the disease spread rapidly among pigs. Transmission between pigs in the same farm is attributed to direct contact with excretions and secretions such as urine, saliva, pharyngeal and lungs secretions. The possible mechanical transmission by dogs and cats, the repeated use of same needles or equipment without further sterilization after each use for health intervention and artificial insemination and sharing of boar semen within a farm are also being implicated. The spread of the virus among pig farms within and between states of peninsular Malaysia was due to movement of pigs.¹⁷ Field investigations show farms that did not receive animals with suspected infection

remained free from infection although some of these farms were located fairly close to an infected farm.¹⁷ The transmission of the virus to humans was through close contact with infected pigs.¹⁸⁻²¹ There was significant association between Nipah virus infection and performing activities involving close contact with pigs, such as processing of piglets (clipping tails, tagging ears), administering injection or medication to pigs, assisting in the birth of piglets, assisting in pig breeding (collection of semen from boars and artificial insemination of sows), and handling of dead pigs.¹⁷⁻²¹ In the Malaysian Nipah virus outbreak, human to human transmission is considered a rare event though the Nipah virus could be isolated from saliva, urine, nasal and pharyngeal secretions of patients.^{22,23} However, transmission of the virus from infected human to human and from infected dogs to human has also been documented.²³ Unlike the Malaysian outbreak, in most outbreaks in Bangladesh, it appears that viral transmission from bats to humans occurs without involvement of intermediate animal hosts, and human-to-human spread is an important mode of transmission of the virus in Bangladesh and India.^{12,24,25}

Experimental transmission studies of Nipah virus among pigs carried out in the Australian Animal Health Laboratory, Geelong, Australia, establish that pigs could be infected by both oral and parental inoculation with the excretion of virus via oro-nasal routes. Infection is noted to spread quickly to the in-contact pigs.²⁶ Experimental infection of Pteropid bats with Nipah virus in the same institution shows that the infected bats excrete the virus and seroconvert without evidence of illness. However, mode of virus transmission and virus persistent in the bat population in the wild is far from clear.

Control of Nipah virus outbreak and infections

As soon as the outbreak was recognized in late 1998, various control measures based on control of JE epidemic were intensively taken by the Ministry of Health Malaysia. Intensive inspection of pig farms and surveillance of JE vectors using the Center for Disease Control Light Traps in the pig-farming areas were carried out.⁶ From 27 October 1998 to August 1999, a total of 13,031 pig farms were inspected and vector control based on chemical fogging of pesticides were carried out on 18,586 pig farms and 403,837 houses in the vicinity of the pig farms.⁶ A 4-dose JE vaccination schedule

for those in Priority I Areas (39,978 pig-farm workers) and 3-dose JE vaccination schedule for those in Priority II areas (children less than 15-years-old living in the vicinity) was planned.⁶ A total of 644,615 doses of JE vaccines with a value of RM16,575,565.00 were purchased by the Ministry of Health for mass vaccination of the target groups.⁶ Extensive educational materials and guidelines on personal hygiene and JE control and prevention were distributed to pig farm workers and the population living in the vicinity. Electronic media such as national radio and TV channels were actively engaged to disseminate information on the prevention and control of JE outbreak.⁶ Despite government intensive effort, the outbreak continued to spread and intensified.

The discovery of Nipah virus as the correct aetiological agent of the outbreak was pivotal and also the turning point in changing the direction of control measures from JE to Nipah virus. In 17 March 1999, the Cabinet Task Force Committee was set up during the Parliamentary Cabinet meeting. The Cabinet Task Force Committee was chaired by the Deputy Prime Minister with direct involvement of Ministers of 7 Ministries (Health, Transport, Primary Industry, Public Works, Housing and Local Government, Agriculture, and Finance) and Deputy Ministers of 3 Ministries (Information, Defense, and Home Affairs).⁶ The Secretariat for the Cabinet Task Force Committee was chaired by the Director-General of Health. State Outbreak Committees and District Outbreak Committees were also set-up in respective states and districts affected by the outbreak.⁶ Policies, terms of reference, roles and responsibilities of each respective ministry were drafted for smooth and co-ordinate operation. At the same time, the National Operation Room was set up and chaired by the Minister of Health to co-ordinate all the outbreak control and prevention operations.⁶

The Department of Veterinary Services under the Ministry of Agriculture was empowered under the Animal Ordinance 1953 to cull all diseased and in-contact pigs and potentially Nipah virus infected pigs through the following processes: Legislation, Logistics, Enforcement and Movement Control of pigs, Financial Assistance/Compensation, and Mass Culling and Depopulation of diseased farms.⁶ Mass culling of all diseased and in-contact pigs and potentially infected pigs were carried out by shooting and burial in deep pits followed by decontamination using alkaline quick lime. During the stamping

out operation, an estimated 901,228 pigs from 896 farms were destroyed from 28 February 1999 to 26 April 1999. A further 50 pig farms were destroyed under the national swine surveillance. Approximately 1.1 million pigs were culled in total to control the outbreak.⁶

Following laboratory confirmation of the presence of Nipah virus in respiratory secretions and urine of patients, extra precaution to wear appropriate personal protective equipment were subsequently taken by all health-care providers and in-contact patients' relatives to prevent the possible human to human transmission of Nipah virus.²²

Surveillance of Nipah virus infections

During the outbreak period, a number of surveillances were carried out by local medical epidemiologists, veterinary epidemiologists, wild-life researchers, medical and veterinary virologists, physicians, army personnel, biostatisticians and state epidemiologists in collaboration with international and WHO experts of respective disciplines.⁶ The main goal was to determine the prevalence, risk of virus infections and transmission in human and swine population as well as the source and reservoir hosts of Nipah virus. It was essentially divided into three groups; Surveillance in Human Health Sector, Surveillance in Animal Health Sector, and Surveillance for the Reservoir Hosts. The surveillance in human health sector covered three categories, namely, Disease Surveillance, Patient Surveillance and High Risk Group Surveillance. Disease surveillance studied the mode of transmission and risk of infections, clinical features of diseases as well as the pathology and pathogenesis of disease. Patient surveillance looked into occurrence of complications, neurological sequelae, social and economic supports. High risk group surveillance covered pig-farm workers and their families, lorry drivers and attendants, abattoir workers, pork sellers, pig cullers, health-care providers, veterinary officers (public and private) and field workers, stable workers and others in a Polo Club, laboratory staff, and general population in nearby villages of affected pig farms.⁶ Surveillance in animal health sectors was divided into surveillance of swine population under the comprehensive National Swine Testing and Surveillance Programme and surveillance for evidence of Nipah virus infections in peridomestic (birds, rats other rodents) and domestic animals (horses, dogs, cats, goats and poultry). The National Swine

Testing and Surveillance Programme covered surveillance programme for all pig farms, surveillance programme for abattoirs by random blood sampling, and testing protocol for high risk farms. High risk farms were categorized as those with a history of human disease or animal disease, and/or positive test result from abattoir surveillance programme.⁶

Surveillance for the reservoir hosts of Nipah virus was made easier with specific focus on bats by the findings that Nipah virus was closely related to Hendra virus and fruitbats (flying-foxes) of Pteropid species had been established as the reservoir hosts of Hendra virus. Initial field work by Mohd Yob *et. al.* showed that a high percentage of flying-foxes of the species *Pteropus hypomelanus* and *Pteropus vampyrus* found in Malaysia had antibodies reacting with Nipah virus (31% and 17% respectively) though no Nipah virus was isolated from any of the necropsied tissues.⁸ The isolation of Nipah virus from the partially eaten fruits and urine of *P. hypomelanus* by Chua *et. al.* corroborated that flying-foxes are the natural hosts of Nipah virus and also shed some light on the possible mode of virus spillover from its reservoir hosts to pigs or other animals.⁹ The novel approach of collecting saliva and urine samples from bats has not only contributed to the establishment of flying-foxes as the natural reservoir of Nipah virus but has opened up a new way of collecting clinical samples of bats for study of infectious or potentially infectious microbes and viruses from bats such *Waddlia chondrophila*, Tioman virus, Pulau virus, SARS coronavirus, Ebola virus, Marburg virus and other potential novel bats' viruses.²⁷⁻²⁹

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