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JAPANESE ENCEPHALITIS/ NIPAH OUTBREAK IN MALAYSIA

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Over a 35-week period from 29 September 1998 to 31 May 1999, 265 cases of viral encephalitis were reported to the Ministry of Health, Malaysia. The cluster of cases occurred at four localities and started in the Kinta district of Perak on 29 September 1998. The cases spreaded 200-km southward to the Sikamat and Bukit Pelandok areas with the movement of infected pigs. The last case with an onset on 29 May 1999 was reported at Sungai Buloh, Selangor. There were 105 fatalities due to the outbreak with a case fatality rate of 39.6%. Those who were discharged were recalled for follow-up at least seven times a year to study the pathophysiology of the disease and to follow up clinical progression.

Initially this outbreak in Kinta district was treated as an outbreak of Japanese Encephalitis. Japanese Encephalitis (JE) is endemic in Malaysia with sporadic outbreaks of this disease occurring in the last few years. There were a total of 529 cases of JE reported over a ten year period, that is from 1988 to 1998. The number of JE cases ranged from 9 to 91 per year with an average of 53 cases annually. Sarawak had the highest proportion of cases, 208 (39.3%) followed by Perak, 85 (16.1%), and Penang, 46 (8.7%). There were 35 fatalities over the 10 year period ranging from 0 to 10 deaths per year with an average of 3 deaths annually. As such the diagnosis of JE was top on the list of possible causes of encephalitis because of the endemicity of JE in the country, the clinical presentation, laboratory findings and the epidemiological picture of the disease occuring among workers dealing with live pigs. Initially pigs were reported to be healthy which is common in a JE outbreak.

However, exclusion of other possible causes of infection was done by the Institute for Medical Research (IMR). Laboratory investigations were also carried out for dengue, enterovirus, influenza, pseudorabies from the viral group, rickettsiae and leptospira from the bacterial group and mycoplasma from the fungal group. All these agents have been known to cause encephalitis in humans. Investigations for all the above diseases were negative except for JE. Specimens confirmed to be JE were sent to WHO Collaborating Centres for Tropical Diseases at the University of Nagasaki, Japan, which reconfirmed the earlier findings.

Various control measures were then taken to combat the outbreak in Kinta district and throughout the country proactively. Those included health education of pig farmers regarding good animal husbandary, larviciding, fogging of pig farms and dwellings of pig farmers to kill adult mosquitoes. The affected areas were classified into priority area 1 comprising of 8,125 farmers and workers living in the farms and priority area 2 comprising 381,638 people living within 2 km radius from the farms. This was done for the purpose of JE vaccinations. JE immunizations were given to all the people in the priority area 1 and children below 15 years old in priority area 2. Altogether 152,210 people were vaccinated from 27 October 1998 – 7 October 1999 and that included not only the outbreak areas but also the rest of the country. There were 1,579 pig farms in the country of which 13,031 inspections were carried out. 18,286 fogging were done on farms and 403,837 fogging were done on affected homes. 200,000 pamphlets and information booklets on JE were printed and distributed. 24,652 pig farmers and workers were examined for signs and symptoms of the disease by active case detection.

When the outbreak spread to Sikamat Negeri Sembilan, body fluid from human cases were forwarded to the microbiology laboratory of University Malaya for diagnosis. A researcher from the University of Malaya found a new virus from the cerebrospinal fluid of one of the patients. This was then sent to Fort Collins in Colorado, USA for testing. This finding of a new virus was confirmed by the Centers for Disease Prevention and Control (CDC) Atlanta on 18 March 99 and was announced by the Ministry of Health, Malaysia on 19 March 99. This virus belongs to the Paramyxovirus group with similarity to Hendra virus that was first discovered in Australia in 1994. In the previous outbreak, race horses and 2 persons whose work involved close contact with horses were taken ill. One of these two subsequently died of severe respiratory infection. A second incident occurred in Mackay, 1000 km north of Brisbane, where a farmer was infected and died of meningoencephalitis after a latent period of 13 months. In the Australian outbreak, the most likely wildlife involved would be either birds or fruit bats.

Paramyxovirus is a group of enveloped RNA viruses whose members have been shown to cause animal and human infection. There are several new viruses belonging to this Paramyxovirus family.

Molecular studies done on the new virus isolate showed a 21% difference in the nucleotide sequence and an 11% difference in the amino acid sequence compared to the Hendra virus. The new virus was subsequently named Nipah, from the name of the river and village from where the virus was first isolated.

Twelve experts from CDC, Atlanta, two from Commonwealth Scientific and Industrial Research Organisation (CSIRO), Geelong and one from Animal Research Institute, Queensland were invited to assist in the control and investigation of the outbreak. Later three Japanese laboratory experts and epidemiologists were also invited to review the laboratory works and surveillance mechanisms. In addition, four consultants from WHO and one from OIE also visited the country to review the outbreak and control measures taken. Two veterinary experts from Germany also assisted the Ministry of Environment in advising long term plan for environmental control of the pig rearing industry.

From the studies carried out by the experts, it was confirmed that the new virus is transmitted among pigs and can be transmitted to human through close contact with body secretions of the infected pigs. The clinical signs and symptoms of the Nipah disease were also documented in the outbreak. In humans, the cases typically presented with fever, headache, altered sensorium, myalgia, drowsiness, fits, jerky movements, weaknesses of the limbs and other signs and symptoms indicating involvement of the brain and brain stem. The incubation period of the illness was between 10 to 15 days. The disease involved those who had direct contract with the infected live pigs. These were farm workers, farm owners and families who worked in the farm, lorry attendants and lorry drivers who helped in moving pigs from farms to lorries and from farms to abattoirs, and abattoir workers. They were mostly young adult Chinese males. The disease in pigs was characterised by acute fever with respiratory involvement (laboured breathing, loud dry cough) and sometimes nervous signs (muscle tremors, spasms in more advanced cases) in all age classes. Sows and boars sometimes died acutely. The disease in pigs was highly infectious.

Further control measures were then instituted. Farmers were evacuated from the infected areas and infected farms were quarantined. A public announcement about the outbreak was made and extensive health education was carried out to advise high-risk groups on self-protection when dealing with pigs. The most effective means of protection was the use of protective clothing and improved personal hygiene. A 24-hour disease control operating room was established at the Ministry of Health which included representation from other ministries. Similar operations rooms were established at state and district levels where outbreak occurred.

Enforcement of existing Prevention and Control of Infectious Disease Act 1988 was done to facilitate evacuation and culling of pigs in the affected farms. Among the Public Health Interventions that were instituted was the isolation of cases and barrier nursing. This is to minimise exposure within the ward as well to optimize nursing and medical observation. All patients suspected of having Nipah virus were placed in a special wards with close monitoring (24 hours) by special teams consisting of medical specialists, medical officers, physiotherapists, occupational therapist, counselors and others. Its susceptibility to soap and common household detergents helped in the prevention of infection amongst the high risk groups.

Special protocols and guidelines were produced which included those for management of suspected viral encephalitis cases; autopsy examination for Nipah infection; transport and disposal of dead bodies due to Nipah infection, occupational exposure to Nipah virus, and chemoprophylaxis for people exposed to Nipah virus. Intensive health education especially for the target groups was also started through the mass media, television, radio, schools and others. Posters, pamphlets, health education material in the various languages were produced and distributed. Ministry of Health had set up its web site and hotlines to provide information to the general public. The health education materials for the special groups included the farm workers, abattoir workers and those involved in the trading and transport of pigs. Advice was given on the need to wear protective clothing, gloves, masks, goggles, boots and long sleeved shirts. As the virus was easily destroyed by soap and detergents, those involved in the handling of pigs were advised to wash themselves thoroughly with water and soap or normal detergent. Similar advise was given for items used for cutting meat, vehicles involved in transportation and slaughter houses.

Cullings of pigs was carried out in two phases. Phase 1 involved areas where there were outbreaks. A total of 1,000,000 pigs were culled. The culling of pigs started from 20 March 1999 and was done in a systematic way in focal areas. These included the affected farms and all those farms within the 10km radius (buffer zone). Phase II involved surveillance in all the other pig farms throughout the country. This process was carried out for three months and farms where three or more samples were tested positive were considered as positive farms and all the pigs in the affected farms were culled. The farms within 500m radius of the infected farms were quarantined immediately as high risk farms and given priority for sampling and testing. Farms under high risk were releases upon 2 negative serology reading.

During the beginning of the outbreak period, the government faced difficulty in getting co-operation from the pig farmers to release their pigs to be culled. Several meetings were held with the pigs farmers in order to obtain their full co-operation. The Minister of Health gave a full support on this as he himself had a meeting with the Pig Farmers Associations. The Minister had given them encouragement and reassurance especially with regards to the financial assistance on the pigs culled. The culling process then was carried out smoothly.

During the outbreak period, the majority of cases (93%) reported among those involved directly in the pig farming industries. This included pig farms workers (41.9%), pig farm proprietors (38.5%), housewives staying on the pig farms (5.7%), students staying on pig farms (3.4%), those involved in trading and transporting of pigs (7%), those involved in culling operations (1.9%), and an abattoir worker (0.4%). 12 cases occurred among others who were not directly involved in pig industry but found working or living in the close vicinity of the pig-farms.

The majority of cases occurred among the age group of 40 to 49 years old (26.4%) followed by 30 to 39 years old (25.7%), 50 and above (21.9%), 20 to 29 (18.5%). These are the active age groups involved in pig-farming industry. Only 6.4% of cases occurred among the age group 10 – 19 years old and 1.2% among children below 10 years old.

The majority of cases (82.6%) involved males but this is due to the fact that more males are involved in this industry. Racial breakdown of the cases shows 70.6% involving Chinese, 17.0% among Indians and 11.3% among others who are mainly foreign workers. Incidentally there were three cases (1.1%) involving Malays. It is to be noted that the pig industry largely involved the Chinese.

During the outbreak period, the Ministry of Health and the Department of Veterinary Services carried out many epidemiological studies. The sero-survey among 713 abattoir workers was conducted in 11 states in Peninsular Malaysia. Four hundred and thirty five (61%) worked with pigs, 241 (34%) worked in the ruminant section, while the remainder worked in other sections of the abattoirs. None of those who worked in the ruminant section reacted to the Hendra antigen. Seven workers who worked with pigs were found to be reactive (1.6%). Two of the workers worked in the receiving units, one was a gardener who helped in herding pigs and cleaning the abattoir, one worked in the slaughtering area removing the urinary bladder, one bathed live pigs, and sometimes helped in slaughtering, one was an administrative worker helping with the stamping, gambrelling and herding of pigs, and one in the delivery section, packing pork for export. High attack rates were found among those herding live pigs (17.6%), bathing live pigs (15.4%), removing urinary bladder (12.5%) and gambrelling (11.1%).

A total of 1,412 army personnel who were involved in the pig culling operations were investigated. The mean duration of exposure was nine days. The activities in which the soldiers were involved included shooting pigs (63%), herding, hitting or carrying live pigs (61%) and carrying dead pigs (26%). Seven (0.5%) were reactive to the Hendra antigen. Six of them had borderline values. All had IgM response to the Hendra antigen, and none had IgG response. (SNT on those who were reactive is being conducted by the CDC. No result has been received till the time of this report). The transmissibility from pigs to army personnel involved in culling operations is low.

There is evident of infection occurs in other domestic animal, notably cat, dog, horse and goat. It is believed that infected pigs were the source of infection for these species, and that all are effectively 'dead-end' hosts. Flying foxes are suspected to be a natural reservoir and subsequently evidence of infection were also present among the flying foxes. Active surveillance for infected pig farms through

blood sampling and testing is continuing. In addition, further research on the natural reservoir and the natural history of the virus and the mechanism and risk factors for infection is being conducted. At a farm in an infected area, 2 of the 47 polo horses were found to have Nipah virus antibodies and were euthanised. All racehorses in the country were tested negative. The study also found out that more than 50% dogs captured in one of the infected areas were positive to Nipah virus by IgG capture ELISA using Hendra antigen. In addition , results showed that one of the 23 cats studied in outbreak areas was positive. Out of 99 flying foxes tested, 15 were found to be positive to the virus neutralisation test for the Nipah virus. To date serum samples from rats trapped in infected areas have all been negative.

The Hendra antigen assay was initially developed utilizing the serum of a patient who survived Hendra virus infection in Australia. This test appears to offer the earliest indicator of infection to the new Hendra like virus. As laboratory work progresses and as additional tests become available more definite results will be obtained. With the help of laboratory investigations, sera from the pre vaccination blood survey in Ipoh were screened for the Nipah virus. Six of the sera from viral encephalitis cases in 1997 were found positive for IgG and this suggests that the virus was already circulating in the farm in 1997.

After one year of study and follow up, there were 12 patients who had relapses of Nipah infection. These patients had either neurological symptoms after an initial illness without re-exposure to the pigs, or long latency from the initial exposure to the virus to the development of neurological symptoms. Seven of the cases were pig farmers, four were family members and one was a pig farm worker. The onset of symptoms during relapses was acute. The signs and symptoms were fever 8 (53%), headache 8 (53%), focal neurological signs 8 (53%), seizure 7 (47%), dizziness 4 (26%), reduced consciousness 4 (26%), and myoclonus 1 (8%). It was noted that 2 of these patients died, 3 patients developed cognitive impairment, 2 developed cerebellar signs, dyphasia (1case) and opthalmoplegia (1 case).

The outbreak brought about a lot of implications to the pig rearing industry in Malaysia as well financial implication to the Government. The export of live pigs to Singapore has stopped since March 1999. Other financial implication included payment to pig farmers whose pigs have been culled, prevention and control of the existing outbreak as well the prevention of any future outbreak of similar in nature. Continuous monitoring and surveillance of the existing pig industry, surveillance of those who were found to have antibodies including continuous follow up of discharged patient to be carried out and maintained. The Ministry of Health will be given funds to upgrade the existing laboratory services in order to strengthen technical capability and capacity in disease surveillance in emerging and re-emerging communicable diseases. The Ministry of Health is requested to build few Biosecurity Level (BSL) 3 laboratories in order to be prepared for future handling of the outbreak of this nature. Allocations were also approved to strengthen bio-security level in specified hospital mortuary facilities and services in the country to handle patients with emerging infectious diseases. In principle, the Cabinet has approved the planning and setting up of BSL 4 in the 8th Malaysia Plan in the country. This future BSL 4 will be the reference centre for the region for research and development in highly contagious micro-organism such as Nipah virus and others. The government has been advised that the existing pig industry has to be improved to the level acceptable to the world standard of internationally accepted pig industry practices.

The Nipah epidemic is believed to have originated in the State of Perak and moved south to the other infected areas. The mode of transmission of the virus among the pig farms within and between the states of peninsular Malaysia was the sale and movement of pigs. Active movement between farm trading of pigs is normal practice in Peninsular Malaysia. Farms that did not receive animals suspected of infection remained free from infection during the testing and surveillance programme, although in some cases such farms were located immediately adjacent to an infected farm. Other routes of transmission between farms in farming communities were considered, for examples, lorries carrying affected pigs, sharing boar's semen and transmission by dogs and cats. However, there is no conclusive evidence to the present time. The disease was observed to have spread rapidly among pigs in infected farms. Transmission between pigs in the same farm was possibly through direct contact with excretory and secretory fluids such as sputum, saliva, pharyngeal and bronchial secretion. The possible role of pig urine has yet to be clarified. Pigs were kept in close confinement, undoubtly a contributing factor.

Mechanical transfer by dogs and cats, the use of unsterilised needles or equipment for health intervention and artificial insemination and sharing of boar semen within the farm were also considered.

Finally by December 1999, a total of 283 viral encephalitis cases with 109 deaths have been reported. Out of this 283 cases, 191 were confirmed to be Nipah, 41 were due to both Nipah and Japanese Encephalitis (JE) and 9 due to JE. Out of the total 109 deaths, 68 have been confirmed due to Nipah, 23 due to both Nipah and JE and 3 due to JE. Since then surveillance of patients infected with JE and Nipah is being monitored. At he same time surveillance of the pig farms is also closely monitored.