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REVIEW

Risk factors, prevention and communication strategy during Nipah virus outbreak in Malaysia

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Abstract

An outbreak of acute febrile encephalitis affecting pig-farm workers and owners was recognized in peninsular Malaysia as early as September 1998. The outbreak was initially thought to be due to Japanese encephalitis (JE) virus and thus very intensive prevention, control and communication strategies directed at JE virus were undertaken by the Ministry of Health and Ministry of Agriculture of Malaysia. There was an immediate change in the prevention, control and communication strategies with focus and strategies on infected pigs as the source of infections for humans and other animals following the discovery of Nipah virus. Information and understanding the risks of Nipah virus infections and modes of transmission strengthened the directions of prevention, control and communication strategies.

A number of epidemiological surveillances and field investigations which were broadly divided into 3 groups covering human health sector, animal health sector and reservoir hosts were carried out as forms of risk assessment to determine and assess the factors and degree of risk of infections by the virus. Data showed that there was significant association between Nipah virus infection and performing activities involving close contact with pigs, such as processing of piglets, administering injection or medication to pigs, assisting in the birth of piglets, assisting in pig breeding, and handling of dead pigs in the affected farms. A complex process of anthropogenic driven deforestation, climatic changes brought on by El Niño-related drought, forest fire and severe haze, and ecological factors of mixed agro-pig farming practices and design of pig-sties led to the spillovers of the virus from its wildlife reservoir into pig population.

Keywords: nipah virus, encephalitis, risk factors, prevention, fruit bats, pigs

INTRODUCTION

Currently, approximately 1400 pathogen species are recognized to infect humans. Fewer than 200 of these are viruses, but on an average, more than two new species of viruses infecting humans are reported worldwide every year.[1] Novel viruses, especially those able to infect humans, are always of a major public health concern, whether causing massive progressive pandemic disease such as human immunodeficiency viruses and the current on-going novel quadruple re-assortant strain of influenza A virus (H1N1), or more transient events such as the Nipah virus in 1998/1999 and SARS coronavirus in 2003.[2-4]

To minimize the health as well as socio-economic impact and extensive spread of emerging infectious diseases, many major challenges reside in the national and international capability and capacity for early recognition, rapid and accurate identification of the causative viruses followed by rapid appropriate response and control. An in-place functional country disease surveillance system is the key to early recognition and detection of any emerging infectious disease outbreak. An established quality public health diagnostic laboratory is central to support public health outbreak investigation for early and accurate identification of the emerging pathogen causing the outbreak. These two components are the cornerstones to determine the correct direction of outbreak response and control. Preparedness and establishment of a robust country infectious disease outbreak response and control system as an integral part of the country crisis management

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system will be more cost-efficient and logical for effective infectious disease outbreak control especially in resource limited countries. An in-place communication strategy is one of the key elements in the crisis management system to ensure a smooth and effective flow of command and operations and at the same time to achieve public co-operation and confidence. In outbreaks of emerging infectious diseases, especially due to novel viruses, effective prevention, control and communication strategy is directly dependent on accurate information of the site, extent and nature of outbreak, particularly, the infectious agent causing the outbreak and its associated mode and risk of transmission and infection. This dependency is exemplified by the prevention, control and communication strategies adopted by relevant governmental and public agencies during the outbreak of Nipah virus in Malaysia.[5]

Prevention and communication strategies in Nipah virus outbreak

In Malaysia, an outbreak of acute febrile encephalitis affecting pig-farm workers and owners was officially recognized as early as in September 1998.[6-8] It was initially thought to be due to Japanese encephalitis (JE) virus because the affected patients were involved in pig farming and also by the fact that JE virus is endemic, especially in the rural areas of Malaysia. Surveillance and chemical fogging of insecticides to destroy mosquitoes, vectors of JE virus, in pig farms and surrounding houses were actively carried out.[5] Vaccination of pig-farm workers and their families were actively performed. Relevant clinical specimens from affected patients were sent to laboratories for confirmation of JE virus as the cause of the outbreak.[5] By end of 1998, despite the findings that only 4 of the initial 28 patients' serum samples tested "positive" for anti-JE virus IgM in the Institute for Medical Research and the outbreak failed to be controlled, the prevention, control and communication strategies directed at JE virus were continued and intensified based on the opinion of the country's senior consultant virologist cum Director of the WHO Arbovirus Research and Reference Centre in Malaysia.[5,9] These strategies and measures included health education of pig farmers on good animal husbandry, larviciding, intensive chemical insecticide fogging of pig farms and dwellings of pig farmers. 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. A total of 644,615 doses of JE vaccines with a value of RM16,575,565.00 was purchased by the Ministry of Health under an emergency fund for mass vaccination of the target groups.[5] JE immunizations were given to all people in Priority Area 1 and children below 15 years old in Priority Area 2. Under the communication strategy, two hundred thousand pamphlets and information booklets on JE were printed and distributed. Electronic media such as national radio and TV channels were actively engaged to disseminate information on the prevention and control of JE outbreak.[5] The communication strategy on messages to the public on prevention of JE virus infection was so "effective" at that period that even residents in the urban areas of the Klang Valley, such as Kuala Lumpur and Petaling Jaya, were requesting for JE vaccination (Newspapers reports).

Following the discovery of the Nipah virus, a novel paramyxovirus, as the cause of the outbreak of the acute febrile encephalitis, there was an immediate change in the prevention, control and communication strategies. The focus and strategies were no more directed at prevention and control of the vectors of JE virus but rather on infected pigs as the source of infections for humans and other animals.[5] Understanding the risks and modes of transmission and infections strengthened the directions of prevention, control and communication strategies. The Cabinet Task Force Committee was set up during a Parliamentary Cabinet meeting as soon as the novel virus was confirmed on 17 March 1999. The Cabinet Task Force Committee was chaired by the Deputy Prime Minister with direct involvement of Ministers of 7 Ministries and Deputy Ministers of 3 Ministries.[5] The Secretariat for the Cabinet Task Force Committee was chaired by the Director-General of Health. Corresponding State Outbreak Committees and District Outbreak Committees were also set-up in respective states and districts affected by the outbreak.[5] Policies, terms of reference, roles and responsibilities of each respective ministry was drafted for smooth and co-ordinate operation. A 24-hour disease control operating room (National Operation Room) was established at the Ministry of Health which included representation from other ministries to co-ordinate all the outbreak control and prevention operations and provide communication and hotline services to any public enquiry.[5] Similar patterns of operation

rooms were established at state and district levels where outbreaks occurred. The Department of Veterinary Services under the Ministry of Agriculture was empowered under the Animal Ordinance 1953 to remove all diseased and in-contact pigs and potentially Nipah virus infected pigs through the following respective procedures; Legislation, Logistics, Enforcement and Movement Control of pigs, Financial Assistance/Compensation, and Mass Culling and Depopulation of diseased farms.[5]

In subsequent prevention and communication strategies, farmers were evacuated from the infected areas and infected farms were quarantined. A public announcement about the outbreak being due to a novel virus was made and extensive health education was carried out to advise high-risk groups on self-protection and hygiene when dealing with pigs. Special protocols and guidelines were produced which included those for management of acute encephalitis cases, carrying out autopsy examinations, handling and disposal of dead bodies with Nipah virus infection, occupational exposure to Nipah virus and the use of chemoprophylaxis. Intensive health education especially for the target population groups was started through mass media, television, radio, schools and others. Posters, pamphlets, booklets, health education materials in various languages were produced and distributed. The health education materials for the special groups included 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. Since Nipah virus is an envelope virus and envelope viruses were known to be easily disrupted and destroyed by soap and detergent, those involved in the handling of pigs were advised to wash thoroughly with water and soap or normal detergent as these were also easily available and cheap.[5] Similar advice was given for items used for cutting meat, vehicles involved in transportation of pigs, premises and abattoirs housing pigs. The Ministry of Health also set up its web-site and hotlines to provide information to the general public. Following laboratory confirmation of the presence of Nipah virus in respiratory secretions and urine of patients, all health-care providers and in-contact patients' relatives were advised to take extra precaution by wearing appropriate personal protective clothing and equipments to prevent possible human to human transmission of the Nipah virus.[10]

Risk factors and relative risk in Nipah virus infections

During the Nipah virus outbreak, a number of epidemiological surveillances and field investigations were carried out as forms of risk assessment to determine and assess the factors and degree of risk of infection by the virus. The types, purpose and nature of surveillances were covered under the topic "Epidemiology, Surveillance and Control of Nipah virus infections in Malaysia". It was broadly divided into 3 groups covering human health sector, animal health sector and reservoir hosts of Nipah virus.[5]

In the human health sector, surveillance of high risk populations was carried by three study main teams, namely the veterinary epidemiology teams, case-control study teams, and clinical study teams. The high risk populations included in the study were pig-farm workers (inclusive of owners) and their families, lorry drivers, the general population in nearby villages, veterinary workers in abattoirs and field workers, civil servants including health staff involved in the outbreak (913), army personnel (1413), and laboratory staff (16) in both private and public sectors. Other groups of people under surveillance were pig cullers (120), abattoir workers (713), volunteers (112), pork sellers (48), and horse stable workers (144). Surveillance of high risk populations was carried out through home visits, field investigation teams and contact tracing by health staff. A total of 4,662 blood samples were collected and screened for Nipah antibodies by 3rd July 1999 during the outbreak period.[5] Those who tested positive but were asymptomatic, were also registered at the national registry and a second blood sample was collected for confirmatory testing by a serum neutralization antibody test performed in the Center for Disease Control and Prevention, Atlanta, USA.

A community-based case control study of risk factors of Nipah virus infections for humans identified one hundred and ten (79 + 11 + 20) persons with serological evidence of Nipah virus infection, including 79/101 (78%) encephalitis patients, 11/171 (6%) community-farm controls and 20/175 (11%) case-farm controls.[5,11] Most cases (92%) reported contact with pigs. Cases were more likely than community-farm controls to report increased sick/dying pigs (62% versus 25%, relative risk [RR] = 5.04, 95% CI = 2.88 – 8.82), dogs (25% versus 9%, RR = 3.33, 95% CI = 1.58 – 7.03) and chickens (11% versus 2%, RR = 5.16, 95% CI = 1.52 – 17.5) on the farm.[5,11] In multivariate analysis, infection was

significantly associated with increased sick/dying pigs (4.50, 2.44 – 8.33) but not dogs or chickens. Cases were more likely than case-farm controls to perform activities involving direct contact with pigs (88% versus 52%, RR = 5.44, CI = 2.00 – 14.8).[5,11] Breeding of pigs, birthing of pigs, injecting pigs and handling of dead pigs were significant risk factors for Nipah virus infection. Direct, close contact with pigs, especially sick pigs, was the primary source of human infections. Other animals may be the source of some infections but the fact that the outbreak ceased after culling of pigs suggest that ultimately infected pigs are required to sustain transmission.[5,11,12]

Three hundred thirty eight exposed health care workers and two hundred eighty eight unexposed controls were enrolled in a cohort study of health-care workers who attended to Nipah patients in hospitals. No significant differences were noted in the occurrence of clinical illness. Three (<1%) exposed health-care workers and none of the unexposed worker developed an anti-Nipah IgG response without an IgM response. The risk of transmission of Nipah virus from patients to health-care workers is unknown but likely to be very low, especially in a situation with adequate use of personal protection equipment.[5,13-15]

Among 713 abattoir workers from 11 states in Peninsular Malaysia; 435 (61%) worked with pigs, 241 (34%) worked in ruminant sections and the remainder worked in other sections. None of the workers who worked in ruminant sections had antibodies against Nipah virus. Seven (1.6%) workers who worked with pigs were found to have anti-Nipah antibodies. Two of them 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 urinary bladders, one bathed live pigs and sometimes helped in slaughtering, one was an administrative worker helping in stamping, gambrelling and herding of pigs, and one was 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 bladders (12.5%), and gambrelling (11.1%).[5,16] A higher risk of Nipah virus infection among abattoir workers was also noted in Singapore.[17]

Six hundred and forty veterinary personnel participated in the investigation of risk of Nipah virus infection. Thirteen (2%) of the 640 veterinary personnel were found to be positive for anti-Nipah antibodies. Administering oral medication to sick pigs recorded the highest risk of getting infected (O.R. = 17.7, 95% CI = 3.27 – 96.3), followed by castrating pigs (O.R. = 14.2, 95% CI = 1.46 -137.4), giving oral medication to non-sick pigs (O.R.= 12.36, 95% CI = 2.39 – 63.8) and conducting autopsies on sick pigs (O.R. = 11.8, 95% CI = 3.68 – 38). The risk of infection was highest among workers who did not use coveralls and respiratory masks.[5]

A total of 1,412 army personnel involved in the pig culling operation were investigated for risk of Nipah virus infection. The mean duration of exposure was nine days. The culling activities were shooting pigs (63%), herding, hitting or carrying live pigs (61%) and carrying dead pigs (26%). Seven (0.5%) had reactive IgM antibodies to Hendra virus antigen, six of whom had borderline values and none had IgG response. The transmissibility of Nipah virus from pigs to army personnel involved in the culling operation was considered to be very low.[5,18] Of the 28 pork sellers obtaining their meat from outbreak areas investigated, one tested positive for anti-Nipah antibodies. The one who tested positive also had a second job in an abattoir where he was required to remove urinary bladders from carcasses.[5,19] None of the 144 persons who worked in horse stables was noted to have anti-Nipah antibodies.[5] Although the majority of encephalitis cases gave a history of contact with pigs, there were a few cases who had no history of pig exposure. Nipah encephalitis was diagnosed in four patients who did not have a history of exposure to live pigs though one had the history of exposure to two sick dogs that had visited a pig farm.[5,20] One of the 28 family contacts of confirmed Nipah case tested positive for anti-Nipah IgG antibodies. These results suggest that humans can acquire Nipah infection from sources other than infected pigs during the outbreak. However, in a sero-survey, serum samples were collected from 169 villagers residing in Tioman Island where Nipah virus was isolated from the *P. hypomelanus* found on the same island. None was found to have anti-Nipah antibodies though 5 (3%) were found to have antibodies against Tioman virus, another novel paramyxovirus isolated from the urine of the same colonies of *P. hypomelanus* found on the island.[21,22] The finding suggests the risk of direct transmission of Nipah virus from its natural reservoir hosts to human is probably very low.

In the animal health sector, studies showed that the disease spread rapidly among pigs in the infected farm. Transmission between pigs in

the same farm is attributed to direct contact with excretions and secretions such as urine, saliva, pharyngeal and respiratory secretions of infected pigs. The possible mechanical transmission by repetitive 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 were also implicated. The possible role of transmission by infected dogs and cats found in the affected farm could not be excluded. The spread of the virus among pig farms within and between states of peninsular Malaysia was due to movement of pigs.[23] Field investigations showed 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.[23]

In tracking for the reservoir hosts of Nipah virus, previous field works by Mohd Yob *et al*. and Chua *et al*. have confirmed that flying foxes found in Malaysia, *P. vampyrus* and *P. hypomelanus*, are the natural reservoir hosts of Nipah virus.[24,25] Subsequent field investigations by Chua *et al*. suggests 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 partially-eaten fruits and/or urine from fruitbats, most probably *P. vampyrus*, to pigs in the index farms of the epicenter of the outbreak (Ampang village, suburb of Ipoh) in 1997 and 1998.[26]

Lessons learnt

The Nipah virus outbreak serves as an excellent example of an emerging infectious disease outbreak due to a novel zoonotic pathogen. Many lessons were learned and can still be learned from the outbreak of Nipah virus in Malaysia, ranging from the pre-outbreak phase (anthropogenic, climatic and ecologic factors contributing to its emergence), outbreak phase (detection, confirmation, response and control, patient management, risk communication and assessment), and post-outbreak phase (follow-up care, evaluation, research and development). The Nipah virus outbreak emphasizes the importance of information sharing on any unusual illnesses or epidemiological events in animals and humans, an **open-minded approach**, close collaboration and co-operation of the medical professionals (clinician, epidemiologist, and laboratory personnel), veterinarians and wildlife specialists, in the investigation of such occurrences. Environment mismanagement (deforestation and land-use) can have far-reaching effects, leading to increase in wildlife-domestic animal-human inter-phase and potential encroachment of wildlife into human habitats and the introduction of novel zoonotic infections into domestic animals and humans.

The interplay of anthropogenic driven deforestation, forest fire and severe haze, climatic changes brought on by El Niño-related drought and ecological factors of mixed agro-pig farming practices and design of pig-sties led to Nipah virus spillovers from its wildlife reservoir into the pig population.[26] Based on the findings of these contributing factors and complex process of spillovers, an important lesson to be learned is to develop strategies for prevention of future spillovers of any fruitbats' viruses, not just Nipah virus from their reservoir hosts to pigs. Experiences gained from past field investigations into the emergence of a couple of novel viruses (Nipah virus, Tioman virus, Pulau virus, Melaka virus, Kampar virus) discovered in Malaysia, the preventive strategy to be adopted is not as simple as advocated previously by either chopping down fruit trees or avoiding planting fruit trees in the vicinity of pig-sties. Field investigations, especially into the emergence of Kampar virus in the northern part of Peninsular Malaysia, show that fruitbats were capable and often carried ripen fruits and fed on the fruits while hanging on the supporting roof beams of buildings or branches of trees that were picked from other fruiting trees.[27] Bat proofing of pig-sties using appropriate sized metal wire-maze, especially for commercial pig-farming, is probably a more logical solution in the prevention of spillover of not only Nipah virus but other potential fruitbats' viruses (Ebola virus, Marburg virus, SARS coronavirus, Tioman virus, Menangle virus, Kampar virus, etc.) to the pig population. The size of the wire-maze used to enclose the pig-sties needs to be carefully selected so that the air-flow and ventilation of the enclosure is not too compromised. Properly constructed pig-sties with adequate bat proofing have also the potential of preventing the spillover of avian viruses, such as influenza A virus, from birds to the swine population.

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