REPORT

WORKING GROUP ON ZOONOTIC PARAMYXOVIRUSES

Kuala Lumpur, Malaysia
19-21 July 1999

Manila, Philippines
November 1999
REPORT

WORKING GROUP ON ZOONOTIC PARAMYXOVIRUSES

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This report has been prepared by the World Health Organization Regional Office for the Western Pacific for governments of Member States in the Region and for those who participated in the Working Group on Zoonotic Paramyxoviruses, which was held in Kuala Lumpur, Malaysia, from 19 to 21 July 1999.
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Key words

| Paramyxovirus / zoonoses / Malaysia |
SUMMARY

The meeting of Working Group on Zoonotic Paramyxoviruses was held in Kuala Lumpur, Malaysia from 19 to 21 July 1999. Experts from both medical and veterinary fields were invited to discuss recent outbreaks of zoonotic paramyxoviruses: Hendra virus in Australia in 1994 and Nipah virus in Malaysia and Singapore in 1998-1999.

These outbreaks have been characterized by initial observation of diseases in animals (horses in Australia and pigs in Malaysia and Singapore), followed by diseases in humans who have had contacts with infected animals. The Hendra and Nipah viruses belong to the Paramyxovirus family that were previously unknown. Evidence currently available suggests that fruit bats may be the natural hosts and wildlife reservoir of both viruses.

The outbreaks of Hendra virus in horses and humans in Australia were limited and resolved relatively rapidly. The outbreak of Nipah virus in Malaysia was more extensive, affecting a large geographical area, and causing hundreds of cases of clinical disease in humans with a high case fatality rate. The related outbreak in Singapore was restricted to abattoir workers.

In Malaysia and Singapore, once the disease had been recognized as a new entity, control measures were implemented which included restrictions on the importation and movement of pigs, culling of pigs in affected areas, minimizing contact between humans and potentially infected animals, protective clothing and hygiene measures for humans in contact with pigs, and active surveillance for human cases. High level of government commitment was essential in both Malaysia and Singapore in enacting control measures. Coordination between veterinary and human public health services was improved.

Early detection and response are important to minimize the impact of emerging infections. However, identification of newly emerging infections is extremely difficult and requires appropriate surveillance with strong laboratory support to detect cases and identify the new infective agent. Coordination between disease surveillance officers and laboratories, and between human and veterinary public health services, is essential to ensure effective surveillance response.

More research needs to be done to answer some important questions, such as transmission route, geographical distribution of natural reservoir, treatment or prophylaxis, and natural history of infections in humans.

1. Outbreak response and control

The outbreaks of Hendra virus infections in horses and humans in Australia were confined to limited areas and resolved relatively rapidly. The outbreak of Nipah virus infection in Malaysia was much more extensive, spreading to affect a large geographic area, and causing hundreds of cases of clinical disease in humans with a high case fatality rate. The earlier spread of the Nipah virus outbreak was due to illegal movements of infected pigs between farms and the reluctance of farmers to inform proper authorities of the disease. The outbreak in Singapore was restricted to abattoir workers. The social and economic cost of the Nipah outbreak has been very great,
involving the culling of over one million pigs as part of the outbreak response and limiting movement of human populations in the affected areas.

In Malaysia and Singapore, once the disease had been recognized as a new entity, control measures were implemented which included restrictions on the importation and movement of pigs, culling of pigs in affected areas, minimizing contact between humans and potentially infected animals, protective clothing and hygiene measures for humans in contact with pigs, and active surveillance of human cases. High-level government commitment was essential in both Malaysia and Singapore in enacting control measures. Coordination between veterinary and human public health services was improved and cooperation is ongoing.

Although the outbreak has been successfully controlled, various problems were identified, including coordination between human and veterinary public health services and other government departments concerned, coordination of international inputs, and response to mass media. A number of lessons have been learned about outbreak response during the Nipah virus outbreak as reflected in the recommendations below.

Recommendations

• To facilitate dealing with outbreaks of known and emerging communicable diseases including zoonoses, all countries should develop an outbreak response plan at the national level. This plan should cover the following areas at minimum:
  a. the designation of responsible officers for the declaration of an outbreak situation;
  b. a core group should be established for the formation of an outbreak response task force and pooling together of potential members to form different groups that will function at different kinds of outbreak;
  c. the designation of appropriately-trained contact officers for dealing with media and public information; and
  d. a mechanism for regular contact and information sharing between human and the veterinary public health services and laboratory services.

• Appropriate guidelines on dealing with mass media and public information during outbreaks should be developed and widely disseminated.

• The following control measures are recommended in the event of further outbreaks of Nipah virus:
  a. elimination of the infected and in-contact domestic animals,
  b. restrictions on the movement of domestic animals involved,
  c. adoption of protective clothing and procedures for workers in high-risk professions,
d. intensive health education for target groups, and

e. continuous and timely information exchange between human and veterinary public health services and laboratories

- To facilitate the elimination of sources of infection from domestic animals and to prevent further spread through animal movement, appropriate levels of compensation for farmers should be established which would ensure their early and full collaboration.

- Given the current lack of knowledge on the mechanisms of transmission of these viruses, safe animal-handling procedures, including protective clothing and safe injection procedures (a single sterile syringe and needle), should be followed by farmers and veterinarians.

- International collaboration during periods of outbreak response should be coordinated centrally in the country by the Ministry of Health and among external agencies by WHO.

2. Disease and laboratory surveillance

The identification of newly emerging diseases is extremely difficult and requires appropriate surveillance and laboratory systems to detect cases and identify the infective agent. Coordination between disease surveillance officers and laboratories, and between human and veterinary public health services, is essential to ensure effective surveillance and response.

Recommendations

- Simple and effective diagnostic tools for Hendra and Nipah virus infection in animals and humans should be developed as soon as possible and made readily available.

- WHO Guidelines for collection, storage, handling, and transport of specimens which are applicable to investigations for Hendra and Nipah viruses already exist and should be made accessible for collection of clinical specimens during field investigation of outbreaks (WHO/CDS/CSR/ISR/2000.1).

- Hendra and Nipah viruses are extremely dangerous and should be handled at the highest level of biosafety possible. Responsible national authorities should develop appropriate policies and guidelines for laboratory procedures related to these viruses.

- To facilitate the elimination of sources of infection from domestic animals and to prevent further spread through animal movement, enforcement of existing law and regulation to this effect should be ensured, and if there are no such laws and regulations, they should be legislated. Appropriate compensation for farmers should be established to ensure their collaboration.

- Communicable disease surveillance mechanisms should be developed in all countries to improve the capacity to detect, investigate and respond to outbreaks of emerging diseases. These systems should include:
a. designated surveillance staff at national and subnational levels
b. designated national laboratories
c. mechanisms for coordination between human and veterinary public health and surveillance staff and laboratory staff

- Surveillance for Nipah virus should continue to be conducted in Malaysia:
  a. surveillance of pigs to identify infected herds/farms (testing of tagged pigs sampled at farms and final testing at abattoirs)
  b. active surveillance for human encephalitis in each state

3. Research requirements

There is as yet no evidence of transmission of these viruses from fruit bats directly to humans. The mechanism of the infection of horses and pigs from the wildlife reservoir of the virus is unknown. There is as yet no evidence to indicate that Hendra virus can spread from horse to horse. However, Nipah virus once introduced into the pig population was able to spread. The mode of transmission from animal to animal in this secondary host species is unknown. The humans involved in these outbreaks in general had close contact with infected horses or pigs, but the mechanism of infection of humans is still not clearly defined. While there is clear evidence of Nipah virus spreading among pigs, there is as yet no conclusive evidence of transmission from human to human.

Recommendations

- The natural history of the virus in the wildlife reservoir must be described, including the mode of transmission and the effect of the virus in these populations. This will enable the postulation of mechanisms for transmission of the virus to domestic animal species and some appreciation of the risks of introduction to animal and human populations in the future.

- As this is an entirely new disease entity, all epidemiological and clinical information should be carefully documented and analysed. This analysis should produce the following:
  a. a clear epidemiological description of the disease,
  b. identification of risk factors for animal and human infection,
  c. establish the illness to infection ratio,
  d. a working case definition suitable for surveillance in both humans and animals,
  e. guidelines on case management.

- As little is known about the natural history of the disease in humans, all known cases should be carefully followed up with regular clinical and laboratory examination.
• The mechanisms and other factors associated with transmission of Nipah virus from pig to pig, pigs to other animals such as dogs and cats, and pigs to humans must be identified. The potential role of other domestic animal species in transmission to humans, and potential routes of human to human spread need to be assessed. This can be done through appropriate animal experiments.

• Further research needs to be done on the potential efficacy to antiviral agents and other treatment and prophylactic agents (including animal vaccines) in Hendra and Nipah virus infection of humans and animals.

• The economic impact of the Nipah virus outbreak in Malaysia should be properly assessed to detail the full effects of a significant outbreak of an emerging disease.
1. INTRODUCTION

1.1 Objectives

(1) to review the recent outbreaks of Hendra and Nipah virus infections in humans and animals and assess the potential public threat of these viruses;

(2) to assess national and regional capacities for the surveillance, prevention and control of these and other zoonotic diseases;

(3) to make recommendations on regional and global research and control needs in the area of zoonotic diseases; and

(4) to establish networks for the dissemination of information on these and other zoonotic diseases.

1.2 Participants

Eighteen temporary advisers attended the meeting. There were also eighteen observers/representative, one consultant, and five secretariat members.

The members of the meeting elected Ybhg Tan Sri Dato (Dr) Abu Baker bin Suleiman of Malaysia as Chairperson, Dr Mohamad Taha Bin Arif from Malaysia and Dr Nobuhiko Okabe from Japan as Vice-Chairpersons, and Dr John Mackenzie of Australia and Dr Tom Ksiazek from the United States of America as rapporteurs.

1.3 Opening Ceremony

Dr Julian Bilous, Director, Combating Communicable Diseases, WHO Regional Office, opened the meeting on behalf of Dr Shigeru Omi, Regional Director of WHO Regional Office for the Western Pacific. Dr Bilous stated that many participants at the meeting had unique roles in the recent outbreak of Nipah virus in Malaysia and Singapore. Lessons learnt in these outbreaks should be fully utilized to plan future strategies. He also stressed that local and international collaborations are crucial to respond to outbreaks of emerging diseases such as Hendra and Nipah viruses. He emphasized the importance of holding working group discussions to examine various issues and activities related to zoonotic paramyxoviruses in order to formulate further strategies based on the technical consensus reached at the meeting.
2. PROCEEDINGS

2.1 Background

2.1.1 Emerging/re-emerging infections

After World War II, new and improved vaccines as well as numerous antibiotics and other antimicrobial drugs were developed. With these developments, incidence of communicable diseases decreased, and eradication of smallpox was achieved. There was an optimistic view that communicable diseases would no longer pose a major threat to general public health. However, this has not proved to be the case. The world has been and probably will continue to face the problem of emerging and re-emerging diseases well into the future.

Emerging diseases are due to newly identified or previously unknown communicable diseases that cause public health problems. Re-emerging infections are due to the reappearance of diseases that are already known, but had fallen to low levels and were no longer considered to be public health problems.

In the Western Pacific Region, the number of emerging and re-emerging communicable disease outbreaks that have been reported has been steadily increasing over the past decade. These outbreaks have included cholera, dengue/dengue haemorrhagic fever, E. Coli O157, hantavirus, enterovirus 71, new type of influenza A (H5N1, H9N2), and more recently, the newly identified Nipah virus.

2.1.2 Overview of Paramyxovirus

The family Paramyxoviridae comprises of a large number of viruses that cause both human and animal diseases. Paramyxoviruses are negative-stranded, pleomorphic enveloped RNA viruses that generally exhibit specificity over a single or limited host range. There are two major groupings within the family, the subfamily containing the pneumoviruses and the subfamily containing the other paramyxoviruses. Within the subfamily Paramyxovirinae, four main subgroups are parainfluenza viruses, rubulaviruses, morbilliviruses, and an unnamed group containing the newer Nipah and Hendra viruses. Phylogenetic analysis of the nucleoprotein (N) gene further supports this division into four genera that make up the subfamily Paramyxovirinae: parainfluenza viruses (e.g., human parainfluenza viruses), rubulaviruses (e.g., mumps, New Castle Disease virus), morbilliviruses (e.g., measles virus, canine distemper virus), and a proposed new genus containing Nipah and Hendra viruses. Respiratory syncytial viruses (RSV) make up the other subfamily.

Paramyxoviruses are responsible for a range of human diseases, from acute pharyngitis and laryngotracheobronchitis (croup) due to human parainfluenza viruses 1, 2, and 3, and acute reactive airway disease and pneumonia due to RSV, to the vaccine-preventable measles and mumps. Other paramyxoviruses cause a variety of animal diseases, such as New Castle Disease, Rinderpest, and respiratory diseases due to animal parainfluenza and RSV viruses. Hendra and
Nipah viruses are unique in that they have a very wide species range and yet may cause different clinical disease patterns among the susceptible species.

Recent identification and description of other viruses causing animal disease include Menangle virus from swine in Australia and Tupaia virus from tree shrews in Thailand. Although other paramyxoviruses have been isolated from assorted species and described in varying detail in epidemiological literature, many are not known to be associated with diseases. However, only minimal investigation of most of these viruses has been undertaken.

2.2 The Hendra and Menangle virus outbreaks in Australia

2.2.1 Hendra virus outbreaks in Australia

Two incidents of a previously unknown disease in horses and humans occurred in Queensland in 1994. In the first outbreak in Brisbane in September 1994, 21 thoroughbred racehorses and two humans were infected with an acute respiratory disease, from which 14 horses and a human died. The two human cases were a 49-year-old horse trainer, whose stables housed most of the infected horses, and his 40-year-old stable-hand. The latter developed an influenza-like illness. His lethargy persisted for six weeks and he gradually recovered. The trainer also became ill six days after the death of the index mare. He was admitted to hospital on the fifth day, and transferred to the intensive care ward on the sixth day for ventilation. Chest radiographs showed diffuse alveolar shadowing. On the seventh day he developed cardiac irritability that led to prolonged periods of asystole and finally death. Findings at autopsy showed both lungs were congested, haemorrhagic and filled with serous fluid. Lung histology revealed focal necrotising alveolitis with many giant cells, some syncytial formation and viral inclusions. A virus was isolated from various equine tissues and from the kidney of the fatal human case. Based on distant nucleotide and amino acid homologies and on its morphology and ultrastructure, the virus was named equine morbillivirus (EMV).

The second incident occurred in Mackay, approximately 1000 km north of Brisbane, in which two horses and a 35-year-old sugar cane farmer died. The farmer ran a horse stud on his property with his wife, a veterinarian. He became unwell in August 1994; with brief aseptic meningitis illness after caring for two horses that died and then assisting at their necropsies. The patient made a full recovery after the initial episode. The patient was admitted to hospital twelve months later after two weeks of irritable mood and low back pain, with a generalised tonic-clonic seizure. Two days before he had three focal motor seizures involving the right arm. By the seventh day of the hospital stay, dense right hemiplegia, signs of brainstem involvement, and depressed consciousness had developed and the patient required intubation. Although his clinical seizures were controlled, electroencephalography revealed persistent periodic epileptiform discharges. He remained deeply unconscious with persisting fever, and died 25 days after admission. A diagnosis of EMV infection was made from a rising anamnestic antibody titre and a demonstration of virus in his CSF by PCR amplification. Subsequent investigation revealed that both horses that had died in August 1994 had died of EMV, and that the patient had a low titre of neutralising antibody in serum taken during his first illness. Thus this second incident actually preceded the Brisbane outbreak, but the virus entered a latent phase for just over a year before reactivating as fatal encephalitis. A third but minor incident occurred in January 1999, when a
single case of EMV infection was discovered in a horse that died near Cairns in far north Queensland.

The epidemiology of the outbreaks is still not well understood. The index case of the first outbreak, a pregnant mare, had been brought back to the stable at Hendra from a paddock about 8 km distant where it had been pastured. The horse was very sick and died within a day of arrival at Hendra, with symptoms identical to those seen in later cases. This index case gave rise to 20 further infections, of which 13 died and 7 were subclinical infections but were later destroyed. No further cases occurred subsequently, and thus the mechanism by which the virus was spread from the index case to the other horses remains unknown. The trainer and the stable-hand had very close contact with the index case, and the trainer was reported to have had abrasions on his arms that had been inflicted by the mare while it was being force-fed. In addition, 157 humans who had some association with the sick horses or human cases, including people who have been involved in carrying out autopsies of the horses at the stables without any precautions, were all sero-negative.

The other interesting epidemiological finding is an apparent association with pregnancy. The index horses in both Brisbane and Mackay were pregnant; the initial isolation from fruit bats was from a pregnant bat; and both outbreaks occurred during the birthing season of fruit bats. The relevance of this is not yet clear.

As further information on the virus became available, it quickly became clear that the name 'equine morbillivirus' was a misnomer; it was neither an equine virus nor a morbillivirus. The name Hendra virus has been proposed. Studies of the structure, biology and genome of the virus have shown that it is very different from other members of the family Paramyxoviridae. The major differences are the large host range in vitro and, to a lesser extent, in vivo, compared to other members of the family; the cleavage site of the F protein; the orientation of the cell surface from which the virus is released; the double fringed morphology of the virions; the size of the genome which is 15% larger than other members of the family due largely to the 3' untranslated regions at the end of each transcription unit; and the presence of an additional open reading frame located between those of the C and V proteins and which potentially encodes a small basic protein. The actual gene order of Hendra virus is similar to members of the Paramyxovirus and Morbillivirus genera, and on the basis of the sequencing data, it is a member of the subfamily Paramyxovirinae and probably a member of a new genus, tentatively called Megamyxovirus. Some aspects of its genomic structure and coding potential, however, are closer to Filoviridae, such as the long 3' untranslated regions and potential small open reading frame for a small basic protein.

2.2.2 Menangle virus outbreak in Australia

An apparently new virus in the family Paramyxoviridae was isolated from stillborn piglets with deformities in New South Wales. In 1997, the farrowing rate declined from an expected 82% to 60%; the number of live piglets declined; the proportion of mummified and stillborn piglets, some with deformities, increased; and occasional abortions occurred. Virus was isolated from lung, brain and heart tissues of infected piglets. No disease was seen in postnatal animals, but the incidence of neutralising antibodies was very high in all ages.
The role of this new paramyxovirus in human infection and human disease is still unconfirmed. Sera from two workers - one at the affected piggery and the other at an associated piggery - had high titre convalescent-phase neutralising antibodies to the new virus. Both workers had an influenza-like illness with rash during the outbreak, but extensive serological testing could find no evidence of an alternative cause for the symptoms, and the disease is, therefore, believed to have been due to the new virus. Menangle virus is a member of the Paramyxoviridae, and in the genus Paramyxovirinae.

2.2.3 The search for a natural reservoir of Hendra virus

Epidemiological characteristics and serological surveys in domestic animals suggested that Hendra virus existed in a wildlife reservoir. To evaluate this theory, a serological survey of wildlife species was initiated in 1995. In April 1996, antibodies to Hendra virus were found in flying foxes in Australia. Antibodies were first identified in a black flying fox (*Pteropus alecto*) in central Queensland. Within weeks, antibodies were found in all four *Pteropus* flying fox species in Australia. Initial serology indicated a seroprevalence around 10%. In September 1996, a Hendra-like virus was isolated from the uterine fluid of an apparently healthy grey-headed flying fox which committed euthanasia after injuring herself on a wire fence and aborting twin fetuses. Comparison of this new bat isolate with the isolate from horses showed it to be indistinguishable from Hendra virus by a range of tests, including a comparison of genome sequences.

The distribution of flying foxes worldwide includes parts of Australia, the Pacific Islands to the east of Australia, South East Asia, India, Madagascar, and much of Africa. The genus *Pteropus* extends across this entire range except for Africa, and it is flying foxes of this genus that are the most numerous in Australia.

Neutralizing antibodies were found in all four *Pteropus* species in Australia, and over a geographic area extending from Millstream in Western Australia to the Northern Territory, and on down the east coast of Queensland and New South Wales to Melbourne in the South. Preliminary analysis of serological data from Queensland indicates a crude seroprevalence in flying fox of 40%.

There appears to be an endemic pattern of subclinical infection with Hendra virus in flying fox populations throughout Australia. No gross pathology or history of attributable illness has been detected in infected flying foxes, and there are no historical reports of major unexplained illness or death in flying-fox populations in Australia.

The epidemiological evidence suggests that flying foxes are the probable natural host of Hendra virus. Experimental infections of flying foxes, which produced seroconversion and subclinical diseases, but not clinical disease, support this proposition.

2.2.4 Transmission studies of Hendra virus in animals

Eight grey-headed fruit bats (*Pteropus poliocephalus*) were inoculated and housed in contact with three uninfected bats and two uninfected horses. In a second experiment, four horses were inoculated by subcutaneous injection and intranasal inoculation and housed in contact with three uninfected horses and six uninfected cats. In a third experiment, 12 cats were inoculated...
and housed in contact with three uninfected horses. Two surviving horses were inoculated at the conclusion of the third experiment: the first orally and the second by nasal swabbing. All animals were necropsied and examined by gross and microscopic pathological methods, immunoperoxidase to detect viral antigen in formalin-fixed tissues, virus isolation was attempted on tissues and SNT and ELISA methods were used to detect Hendra virus-specific antibody. Grey-headed fruit bats seroconvert and develop subclinical disease when inoculated with Hendra virus. Horses can be infected by oronasal routes and can excrete Hendra virus in urine and saliva. It is possible to transmit Hendra virus from cats to horses. Transmission from P poliocephalus to horses could not be proven and neither could transmission from horses to horses or horses to cats. Under the experimental conditions of the study, the virus is not highly contagious.

2.3 The Nipah virus outbreak in Malaysia and Singapore

2.3.1 Outbreak in Malaysia

For the period from 29 September 1998 to 31 May 1999, 265 cases of viral encephalitis were reported to the Ministry of Health of Malaysia. A cluster of viral encephalitis cases first started(384,419),(872,493) in the Kinta District of Perak from the 29 September 1998 to 30 March 1999. A total of 27 cases were reported with 15 deaths. In December 1998 the outbreak spread southward to Sikamat in Negeri Sembilan. From 20 December 1998 to 1 January 1999, there were 7 cases with 5 deaths. The outbreak spread to Bukit Pelandok area in the same state from 12 December 1998. Till 30 April 1999 there were 224 cases in this area with 81 fatalities. The last cluster appeared in Sungai Buloh, Selangor State from 7 to 27 May 1999. There were 7 cases with 4 deaths.

The cases associated with this outbreak typically presented with fever headache altered sensorium and other signs and symptoms. Out of a total of 265 encephalitis cases, 155 were confirmed to be Nipah virus infections, 37 were due to both Nipah virus and Japanese encephalitis (JE) and 11 due to JE alone. Out of a total of 105 deaths, 55 have been confirmed due to Nipah virus, 21 to both Nipah virus and JE, and 4 to JE.

The majority of cases (192 cases) were confirmed to be Nipah virus infection. Forty-eight (48) cases including 37 Nipah positives were also positive for Japanese encephalitis (JE). The majority of cases (93%) have been reported among those involved directly in the pig farming industries. Therefore, majority of cases involved adult (20-49 years old) male. Only 6.4 % of cases occurred among the age group 10-19 years and 1.2% among children below 10 years old. Ethnic 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 involve the Chinese.

2.3.2 Outbreak response in Malaysia

The seriousness, nature of the disease, and the national impact of the disease required tremendous amount of collaboration and cooperation (both within and from other countries). Various committees were established, which included National Task Force Technical Committee, International Technical Collaboration, and State Level Committee. A 24-hour Disease Control Operations Room was set up at the Ministry of Health with representation from other Ministries.
and Agencies. Similar control centres were in operation at the state and district levels. Various public health interventions were instituted as follows:

a. With the help of the Veterinary Services Department, police and local authorities the movement of pigs except to the abattoirs was banned to prevent the further spread of the disease to other farms.

b. Culling of pigs was being carried out in two phases. Phase I involved areas where there were outbreak of cases. A total of 1,000,000 pigs were culled. The culling of pigs was started from 20 March 1999 and was done in a systematic way in areas that included the affected farms and the farms within the 10 km radius (buffer zone). Phase II involved surveillance in all pig farms throughout the country.

c. All patients were isolated, and barrier nursing was practised to minimize exposure within the ward as well to optimize nursing and medical observation. All patients suspected of Nipah virus was placed in special wards with close monitoring (24 hours) by special teams consisting of medical specialists, medical officers, physiotherapists, occupational therapist, counsellors and others. Special protocols and guidelines were produced which included: (a) management of suspected viral encephalitis cases; (b) autopsy for Nipah infection; (c) transport and disposal of dead bodies due to Nipah infection; (d) occupational exposure to Hendra-like virus; and (e) chemoprophylaxis for people exposed to Nipah virus.

d. Intensive health education, especially for the target groups was also started through the mass media, television, radio, schools and other means. Posters, pamphlets, health education material in 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 soap and detergents easily destroy the virus, those involved in the handling of pigs were advised to wash themselves thoroughly with water and soap or normal detergent. Similar advice was given for items used for cutting meat, vehicle involved in transportation and slaughterhouses.

e. Active human case detection in infected farms was carried out.

f. Farmers and workers were moved away from infected farms to prevent transmission. Enforcement of existing Infectious Disease Act was done to facilitate evacuation and culling of pigs in the affected farms.

2.3.3 Outbreak and response in Singapore

After receiving a report of encephalitis cases in Malaysia in October 1998, several control measures against Japanese encephalitis were taken. During 10 March through 19 March 1999, 11 cases of encephalitis or pneumonia that resulted in 1 death occurred among workers in 1 of 2 abattoirs in Singapore. Virological tests confirmed Nipah virus infections in all 11 patients.
Among 11 confirmed cases, 8 had encephalitis and 3 had pneumonia. One fatality case had encephalitis. On 19 March 1999, import of live pigs from Malaysia was banned and abattoirs were closed. After these measures, no new cases occurred.

Laboratory tests were carried out at the Centers for Communicable Disease Prevention and Control (CDC), Atlanta, United States of America. The confirmation of Nipah virus infections was released to the press on 30 March 1999. Joint epidemiological investigations were conducted with CDC epidemiologists in April 1999.

2.3.4 Human Epidemiological Studies in Malaysia

To assess factors associated with Nipah virus infection, a case-control study was conducted among residents of a well-defined region from where three-fourths of outbreak cases were reported. Cases were individuals hospitalized for encephalitis that showed evidence of antibody to Nipah virus. Serological assays used Hendra virus antigens, which cross-react with antibodies against Nipah virus. Two groups of controls were selected; community controls were individuals from farms without encephalitis cases while case-farm controls were individuals from the same farm as the case. Controls with antibody to Nipah virus were reclassified as cases. A total of 92% of cases reported contact with pigs. Cases were more likely than community controls to report an increase in sick or dying pigs on the farm. Cases were also more likely than case-farm controls to work with pigs, report contact with sick pigs, and perform activities involving contact with secretions and body fluids. It was concluded that contact with secretions and bodily fluids of pigs presumably infected with Nipah virus was the most important source of infection for humans in this outbreak. Absence of disease in pigs cannot be definitively used to identify farms where humans are not at risk for Nipah virus infection.

To determine whether person to person transmission of Nipah virus occurred, a cohort study of health care workers from three hospitals that reported >80% of outbreak cases was conducted. Exposure was defined as providing care for, or performing an autopsy on, a patient with presumed Nipah virus encephalitis. The unexposed group consisted of health care workers from wards that do not admit encephalitis cases such as orthopaedics, obstetrics, and ophthalmology. Pathologists and pathology assistants who had not performed autopsies on suspected Nipah virus patients were recruited as a comparison group for exposed pathology workers. Infection was confirmed using a serological assay based on Hendra virus antigens. A total of 363 exposed and 288 unexposed health care workers, pathologists, and pathology assistants were recruited. The two groups were similar in terms of job description, age, sex and ethnicity. The rate of any illness reported between the two groups was not significantly different nor was the rate of any febrile illness. None of the unexposed individuals had a positive test for Nipah virus antibody but three exposed nurses were positive for IgG antibody to Nipah virus. However, none of these nurses developed a corresponding IgM response as would be expected in an acute infection. Analysis of the clinical data demonstrates no evidence for transmission of the Nipah virus from patients to health care workers or pathologists. The laboratory results, however, are inconclusive. Further investigations to confirm the laboratory findings are in progress.
2.3.5 Laboratory investigations for Nipah virus

   a. Discovery of Nipah virus

     The outbreak in Negri Sembilan started in late February 1999, about five months after the outbreak in Perak Seremban Hospital, the closest referral hospital to the site of the outbreak, requested Department of Medical Microbiology, University of Malaya, for help. Clinically, the cases were viral encephalitis mainly in male adults and with history of contact with pigs.

     The epidemiological evidence suggested that the outbreak might not be due to Japanese encephalitis (JE) because adult pig farmers were mainly affected and some of the patients had received the full course of JE vaccination. In addition, there were reports of pigs dying in the farms, which is unusual for JE.

     When the first few samples of blood and cerebrospinal fluid were sent to the laboratory in University of Malaya on 1 March, attempts for virus isolation were started using a number of cell lines, including insect cell lines to isolate JE virus. By 5 March, post-inoculation syncytial formations were noted in Vero cells, which rapidly spread to form large multinucleated giant cells. The isolate was passaged the next day (6 March) and slides of the infected cells made and stained for immunofluorescence using antibodies against flavivirus, JE, Herpes simplex and cytomegalovirus, respiratory viruses including paramyxoviruses, measles and panenterovirus. All were negative. However, IgM and IgG antibodies to the isolate were found in one CSF and three serum samples of patients.

     Infected cells harvested on 8 March were also fixed for electron microscopy and examined on 11 March. Pleomorphic viral-like particles measuring between 160 to 300 nm were observed. Isolates were then sent to Centers for Disease Control and Prevention (CDC), Fort Collins, the Unites States, arriving on 13 March. The earlier EM observation was confirmed and the virus was morphologically similar to paramyxovirus. All tests for arboviruses were negative. By 18 March 1999, further analysis was carried out at CDC, Atlanta. The isolates reacted to Hendra antibodies and limited sequencing data on the P gene showed 10% divergence to Hendra virus. This confirmed the discovery of new virus, which is related Hendra virus.

   b. Molecular Biology

     Sequence analysis of nucleoprotein (N), phosphoprotein (P) and matrix (M) genes of Nipah virus showed 70%-78% nucleotide homology with Hendra virus. This similarity confirmed the initial observation that Hendra and Nipah virus are closely related but distinct viruses within the family of Paramyxoviridae. The N gene of Nipah virus was identical among several isolates from human and animal samples collected in Malaysia and Singapore. This provided genetic evidence for close link between these events. Phylogenetic analysis on N genes of different viruses in the family of Paramyxoviridae also shows that Hendra and Nipah viruses form a distinct cluster of within the family of Paramyxoviridae and probably represent a new genus in this family.
c. Diagnostic assays

Several different diagnostic methods, which include virus isolation, reverse transcription polymerase chain reaction (RT-PCR), antibody detection and immunohistochemistry were used. Virus isolation was carried out using Vero cells. Syncytial-cell formation on Vero cell culture several days after inoculation indicated the presence of the virus. RT-PCR was performed with primers designed to amplify a region of the N gene of Nipah virus. Serum and cerebrospinal fluid were tested for antibodies with an IgM capture enzyme linked immunosorbent assay (ELISA) and indirect IgG ELISA using Hendra virus antigens. These tests were effective during the outbreak, pending the development of antibody tests that used Nipah virus antigens. Immunostaining for tissue samples was also performed with an anti-Hendra virus hyperimmune serum and later with an anti-Nipah virus hyperimmune serum. Eosinophilic, mainly intracytoplasmic, viral inclusions were seen in affected neurons and other parenchymal cells.

2.3.6 Pathology

Autopsies of 32 fatal cases of serologically and immunohistochemically confirmed Nipah infection were studied. Nipah virus infection caused multi-systemic involvement, primarily affecting the blood vessels in various organs with predilection of the central nervous system.

In general, the macroscopical gross appearance of the brain showed generalised congestion and oedema. The cut section of the brain also showed petechial haemorrhage and small foci of haemorrhagic areas.

Microscopical appearances included vasculitis, syncytial cells formation and eosinophilic inclusions. Vasculitis mainly affected the small vessels including capillaries and venules and the medium sizes vessels. The vasculitis was characterised by the endothelial cells destruction, mural necrosis, karyohexis, infiltration by neutrophils and the mononuclear cells sometimes associated with thrombosis. Areas of micro-infarction and necrosis were normally found adjacent to the vasculitis. Syncytial cells formation is multinucleated giant cells that were occasionally found in the endothelium of vessels, alveolar cells lining, glomerular capillaries, Bowman's capsule and splenic parenchyma. Eosinophilic inclusions were the intranuclear and intracytoplasmic bodies found mainly in the neurons, glial cells and the syncytial cells. They were usually small, discrete, single or multiple and may fill up the entire cytoplasm and nuclei or seen at the periphery of the cell membrane.

In the central nervous system, there was extensive vasculitis with adjacent necrotic plaques that were discrete and well-circumscribed, round to oval in shape. Their sizes were generally small but the confluent plaques were more than 10 mm. Other pathological changes included parenchymal inflammation, perivascular cuffing, neuronophagia, microglial nodules and gliosis. Meningitis was seen in some cases. However, there was no predilection for specific region in the central nervous system. In lung, extensive patchy areas of fibrinoid necrosis associated with small vessel vasculitis and segmental or circumferential vasculitis of muscular arteries were noted. Occasional multinucleated giant cells were also seen in the alveolar spaces. Rarely, the bronchial lining epithelium appeared inflamed. Major findings in kidney included fibrinoid necrosis of the glomeruli, with syncytial cells in the glomeruli, Bowman's capsule or the tubular epithelium. In heart, vasculitis of muscular arteries associated with myocardial infarction was seen in some of
the cases. In spleen, necrosis of the periarteriolar regions and lymphoid depletion were found. Vasculitis was also noted in pancreas, adrenal, mesenteric artery. There was no apparent pathological finding in liver, thyroid, stomach, skeletal muscle and bone marrow.

**Immunohistochemistry:** Immunohistochemistry using Hendra or Nipah antibodies were used to confirm the diagnosis and localised the viral antigens. These viral antigens were seen in the endothelial cells, eosinophilic inclusion bodies, cytoplasmic and nucleus of the syncytial cells, neurons, glial cells, neutrophils, ependymal cells, smooth muscle, myocytes, alveolar wall, bronchial epithelium, glomerular capillaries, and macrophages. (The microscopic features of vasculitis, syncytial cell formation, eosinophilic inclusions along with microinfarction and necrosis primarily involving the central nervous system are characteristic of Nipah virus infection. Immunohistochemistry to detect the viral antigen should be done to confirm the diagnosis.)

**2.3.7 Clinical Overview**

Government agencies were brought together and manpower and resources were pooled to control and manage the Nipah virus outbreak. At the hospital, guidelines of management of viral encephalitis, infection control and follow-up were developed and circulated. The implementations of these protocols were monitored and modifications made from time to time based on the information available.

A protocol to gather information on the clinical characteristics of the Hendra-like (Nipah) encephalitis was developed and distributed to all physicians managing the cases. Completed protocols were later analysed by a central team. The demographic and clinical features, complications, bad prognostic features, response to treatment and outcome of the cases studied were analysed. Several unique clinical and imaging features of this encephalitis were identified.

From the earliest stage of the epidemic, it was emphasized that the core component of the treatment of viral encephalitis was general management, which included good nursing care, fluid balance, nutrition, treatment of fever and hyperpyrexia, postural care and care of the unconscious patient. Complications of the acute illness such as seizures, raised intracranial pressure, additional infection, and haematological and metabolic derangement were treated appropriately. The very ill and the unconscious patients were treated in the Intensive Care Units (ICU) and many of them required ventilatory support. At the peak of the epidemic the need for infection control, ICU care and ventilators were beyond the ordinary capacity of the hospitals. Thus new wards and ICU had to be created, requiring quite major mobilization of staff and equipment as well purchase of new equipment.

Prior to the identification of the virus, general measures for infection control were observed to minimize risk to staff and visitors. These include universal precautions, proper handling of specimens and disposal of clinical wastes. Subsequently, these measures were reinforced and greater care was exercised in patient handling, management of specimens and clinical wastes. Following viral identification, a ten-day course of ribavirin was used as a specific treatment. This was based on its in-vitro effect on the virus and its efficacy in some new viral haemorrhagic diseases. The definitive value of this treatment is still being evaluated.
Discharged patients would be followed-up for at least a year to monitor general well being, organ system function, cognitive function, psychosocial adjustment and antibody response using a prepared protocol. This period of follow-up would allow for monitoring of recovery and also possible relapse of the illness.

2.3.8 Veterinary

Generally, mortality in infected animals was low but morbidity may have been high. The mode of transmission of the disease between and within pig farms was not established. However, it was postulated that movement of pigs or the use or sharing of boars for breeding might aid in the spread of the disease. On farms with active disease, pigs, especially sows, showed higher seroprevalence (>30%) than other age groups (<5%). Retrospectively, the disease was present in pigs as early as 1995 as evident from histological materials received for disease diagnosis.

Clinical signs in pigs varied among different age groups. In suckling pigs, the disease developed as respiratory problem typified by open mouth breathing and dyspnea. In weaners (>4 weeks) and growers, the disease developed as an acute febrile (>39.9°C) illness with development of respiratory signs accompanied by one or more of the neurological signs. Respiratory signs ranged from increased or forced respiration to harsh loud non-productive cough or open mouth breathing, epistaxis. Neurological signs included tremble, neuralgic twitches, muscle fasciculation, tetanic spasms, incoordination, rear leg weakness and varying degrees of paresis. In sows and boars, the disease was more pronounced developing initially as an acute febrile (>39.9°C) illness with labored breathing (open mouth), increased salivation, nasal discharge (possibly bloody) and possible abortion (1st trimester). Sows and boars may die very rapidly (24 hours) with no signs of clinical disease. Some or all of the following neurological signs may be present: head pressing, agitation/biting at bars, tetanic spasms, and general convulsion. Sows may abort.

Dogs sampled from the outbreak area showed more than 50% positive to Nipah virus antibodies by ELISA. Other animals such as cats, horses and goats found in the infected areas were also positive. Captured dogs at the periphery of infected farms showed signs resembling distemper with more pronounced nasal and ocular discharge. There was no clinical disease observed in horses during the outbreak. Seroprevalence in horses was low in one premise (5/47) and zero in other categories of horse (0/3197). There were no reports of clinical diseases seen in cats and other peri-domestic animal species in the outbreak area.

2.3.9 Experimental studies in animals

Pigs and cats were experimentally infected with Nipah virus to identify the ability to reproduce disease in pigs, epidemiologically important information, and susceptibility in cats. Work was conducted under bio-safety Level 4 conditions.

Animals were infected with 50 000 TCID50 of an isolate of Nipah virus that was supplied by the University of Malaya, Department of Medical Microbiology. In the pig experiment, a total of eight six-week-old pigs were divided into two groups. In each group, three were infected, and one was in contact with infected animals. One group was infected parentally, and another group
orally. All animals were observed daily, and sampled every two days and also at post-mortem. In the cat experiment, the oro-nasal route infected two adult female cats.

All three pigs inoculated parentally had clinical symptoms; two pigs with fever and neurological syndrome and one with fever and respiratory symptoms (cough and nasal discharge). The two orally inoculated pigs developed fever only. Both in-contact pigs showed no clinical signs over the 21-day observation period. One of two inoculates cats had febrile disease with severe dyspnea, and another one also had fever and recovered.

All pigs including in-contacts were sero-converted by serum neutralization test by day 14. Virus was also isolated from seven out of eight pigs and both of two cats. Samples from which virus were isolated included nasal swabs, throat swabs, tonsils, eye swabs, rectal swabs, and urine (only in cats). Post-mortem histopathological examinations in pigs showed that vasculitis and fibrinoid were noted in a wide variety of tissues. Other finding included alveolitis, meningitis, necrosis of lymphoid tissue, and syncytium formation. Viral antigen was demonstrated to varying degrees in meninges, vascular walls, lymphoid tissue, bronchial epithelium, alveolar endothelium, tonsillar crypts and glomeruli.

2.3.10 Natural reservoir

The apparent close relationship between Nipah virus and Hendra virus focused the initial wildlife surveillance efforts on bats, and specifically on flying foxes (suborder Megachiroptera) which were recognized as the probable natural host of Hendra virus in Australia. Surveillance of flying foxes in Papua New Guinea to the immediate north of Australia also found neutralising antibodies to Hendra virus in five of the six species tested. Malaysia has a diversity of bat fauna, with two species of flying fox, at least 11 species of smaller fruit bats, and more than 60 species of insectivorous bats. With the notable exception of Tioman Island (off the east coast), sampling of bats was largely confined to the west coast of Peninsular Malaysia, in the states of Perak, Negeri Sembilan and Johor. Sampling locations included, but were not restricted to, the outbreak areas of the pig disease. A total of 325 bats from 15 species (including fruit bats and insectivorous bats) were sampled, and blood and tissue specimens were collected for laboratory testing.

While serological investigations at the Australian Animal Health Laboratory are yet to be completed, interim laboratory reports confirmed the presence of neutralising antibodies to Nipah virus in both species of flying fox, Pteropus vampyrus and Pteropus hypomelanus. Fresh tissue samples from these species are being forwarded to the Centres for Disease Control and Prevention in Atlanta, USA, for virus isolation attempts. Until virus is isolated, it is premature to suggest that these results identify flying foxes as the reservoir hosts of Nipah virus. It needs to be asserted that these antibodies are not simply cross-neutralising antibodies to a related virus.

Nevertheless, the serological indications of our preliminary wildlife investigations are encouraging. Further fieldwork is needed to fully describe the occurrence and frequency of these antibodies in flying fox populations in the region. Likewise, an understanding of the biology and the ecology of flying foxes in this region are essential before we can unravel the natural history of any virus they may harbour.
2.4 OIE Code

The OIE (Office International Des Epizootie/World Animal Health Organization) publishes every five to six years a new edition of the "International Animal Health Code", which is commonly known as the "OIE Code". This code contains international regulations that ensure the health security of international trade in animal and animal products through the detailed definition of health guarantees to be met by trading partners so as to avoid the spread of disease agents that are pathogenic for animals or humans. Transmissible diseases are classified into two groups: List A and List B diseases.

List A diseases are selected diseases which have the potential for very serious and rapid spread, which are of serious socio-economic or public health consequence and are of major importance in the international trade of animal and animal products. Diseases listed in List A should be reported immediately to the OIE Headquarters in Paris.

List B diseases are also important diseases, but not usually so highly transmissible as List A diseases. List B diseases are grouped by the susceptible host. Reports are normally submitted to OIE Headquarters once a year.

OIE will not include all new diseases in List A or B. If a new disease is recognized and continue to spread to other countries, a meeting of the experts may be held by the OIE in order to characterize and define the disease. It would be necessary to decide the most appropriate name that is acceptable by the experts and international committees concerned. The report of the meeting will be reviewed by OIE Standards Commission and Animal Health Code Commission for possible follow-up actions to be taken. If these commissions recommend including the disease in the OIE List A or B, the OIE International Committee will discuss this.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Outbreak response and control

The outbreaks of Hendra virus infections in horses and humans in Australia were localized and resolved relatively rapidly. The outbreak of Nipah virus infection in Malaysia was much more extensive, spreading to affect a large geographic area, and causing hundreds of cases of clinical disease in humans with a high case fatality rate. The Malaysian outbreak was complicated because the authorities had to contain two outbreaks of Japanese encephalitis and of the Nipah virus outbreaks at the same time. The Nipah virus outbreak was further spread earlier because of the illegal movements of infected pigs between farms and the reluctance of farmers to inform relevant authorities of diseases among their pigs. The related outbreak in Singapore was restricted to abattoir workers. The social and economic cost of the Nipah outbreak has been very great, involving as it did the culling of over one million pigs as part of the outbreak response, and significant movement of human populations in the affected areas.
In Malaysia and Singapore, once the disease had been recognized as a new entity, control measures were implemented which included restrictions on the importation and movement of pigs, culling of pigs in affected areas, minimizing contact between humans and potentially infected animals, protective clothing and hygiene measures for humans in contact with pigs, and active surveillance of human cases. High-level government commitment was essential in both Malaysia and Singapore in enacting control measures. Coordination between veterinary and human public health services was improved and cooperation is ongoing.

Although the outbreak has been successfully controlled, various problems were identified including coordination between human and veterinary public health services and other involved government departments, coordination of international inputs, and response to the mass media. A number of lessons have been learned about outbreak response during the Nipah virus outbreak and these are reflected in the recommendations below.

Recommendations:

• To facilitate dealing with outbreaks of known and emerging communicable diseases including zoonoses, all countries should develop an outbreak response plan at the national level. This plan should cover the following areas at minimum:
  
a. the designation of responsible officers for the declaration of an outbreak situation;

b. a core group of members for the formation of an outbreak response task force and a pool of potential members depending on the nature of the outbreak;

c. the designation of appropriately trained contact officers for dealing with the media and public information; and

  d. a mechanism for regular contact and information sharing between human and veterinary public health services and laboratory services.

• Appropriate guidelines on dealing with mass media and public information during outbreaks should be developed and widely disseminated.

• The following control measures should be adopted in the event of further outbreaks of Nipah virus:
  
a. elimination of the infected and in-contact domestic animals;

b. restrictions on the movement of domestic animals involved;

c. adoption of protective clothing and procedures for workers in high-risk professions;

d. intensive health education for target groups; and

c. continuous and timely information exchange between human and veterinary public health services and laboratories.
• To facilitate the elimination of sources of infection from domestic animals and to prevent further spread through animal movement, appropriate levels of compensation for farmers should be established which would ensure their early and full collaboration.

• Given the current lack of knowledge on the mechanisms of transmission of these viruses, safe animal-handling procedures, including protective clothing and safe injection procedures (a single sterile syringe and needle), should be followed by farmers and veterinarians.

• International collaboration during periods of outbreak response should be coordinated centrally, in country by the Ministry of Health and among external agencies by WHO.

3.2 Disease and laboratory surveillance

The identification of newly emerging diseases is extremely difficult and requires appropriate surveillance and laboratory systems to detect cases and identify the infective agent. Coordination between disease surveillance officers and laboratories, and between human and veterinary public health services, is essential to ensure effective surveillance and response.

Recommendations:

• Simple and effective diagnostic tools for Hendra and Nipah virus infection in animals and humans should be developed as soon as possible and made readily available.

• Guidelines for collection, storage, handling, and transport of specimens which are applicable to investigations for Hendra and Nipah viruses should be made accessible through WHO (specific references).

• Hendra and Nipah viruses are extremely dangerous and should be handled at the highest level of biosafety possible. Responsible national authorities should develop appropriate policies and guidelines for laboratory procedures related to these viruses.

• To facilitate the elimination of sources of infection from domestic animals and to prevent further spread through animal movement, enforcement of existing law and regulation to this effect should be appropriately taken and if there is none, enactment of such law and regulation should be made. Appropriate levels of compensation for farmers should be established which would ensure their early and full collaboration.

• Communicable disease surveillance mechanisms should be developed in all countries to improve the capacity to detect, investigate and respond to outbreaks of emerging diseases. These systems should include:

  a. designated surveillance staff at national and sub-national levels;
  b. designated national laboratories; and
  c. mechanisms for coordination between human and veterinary public health and surveillance staff and laboratory staff.
• Surveillance for Nipah virus should continue to be conducted in Malaysia:
  a. surveillance of pigs to identify infected herds/farms (testing of tagged pigs sampled at farms and final testing at abattoirs); and
  b. active surveillance for human encephalitis in each state.

3.3 Research requirements

There is as yet no evidence of transmission of these viruses from fruit bats directly to humans. The mechanism of the infection of horses and pigs from the wildlife reservoir of the virus is unknown. There is as yet no evidence to indicate that Hendra virus can spread from horse to horse. However, Nipah virus once introduced into the pig population was able to spread. The mode of transmission from animal to animal in this secondary host species is unknown. The humans involved in these outbreaks in general had close contact with infected horses or pigs, but the mechanism of infection of humans is still not clearly defined. While there is clear evidence of Nipah virus spread among pigs, there is as yet no conclusive evidence of transmission from human to human.

Recommendations:

The natural history of the virus in the wildlife reservoir must be described, including the mode of transmission and the effect of the virus in these populations. This will enable the postulation of mechanisms for transmission of the virus to domestic animal species and some appreciation of the risks of introduction to animal and human populations in the future.

As this is an entirely new disease entity, all epidemiological and clinical information should be carefully documented and analysed. This analysis should produce the following:

a. a clear epidemiological description of the disease;
b. identification of risk factors for animal and human infection;
c. establishment of the illness to infection ratio;
d. a working case definition suitable for surveillance in both humans and animals; and
e. guidelines on case management.

As little is known about the natural history of the disease in humans, all known cases should be carefully followed up with regular clinical and laboratory examination.

The mechanisms and other factors associated with transmission of Nipah virus from pig to pig, pigs to other animals such as dogs and cats, and pigs to humans must be identified. The potential role of other domestic animal species in transmission to humans, and potential routes of human to human spread, need to be assessed. This can be done through appropriate animal experiments.
Further research needs to be done on the potential efficacy to antiviral agents and other treatment and prophylactic agents (including animal vaccines) in Hendra and Nipah virus infection of humans and animals.

The economic impact of the Nipah virus outbreak in Malaysia should be properly assessed to detail the full effects of a significant outbreak of an emerging disease.