EMERGING DISEASES ASSOCIATED WITH FLYING FOXES – HOST MANAGEMENT STRATEGIES

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Introduction

Several novel viruses recently described in flying foxes cause disease in animals and humans. These are Hendra virus, Nipah virus (genus *Henipavirus,* family *Paramyxoviridae*) and Australian bat lyssavirus (ABL) (genus *Lyssavirus*, family *Rhabdoviridae*). This paper re-presents previous discussions of management strategies for these viruses [1]Mackenzie, 2003 #449}. Consideration of factors associated with the emergence of these agents from their natural hosts, and an understanding of agent and host ecology, is an integral part of the discussion.

Emergence

Hendra virus (initially called equine morbillivirus) was first described in September 1994, in an outbreak of disease in horses in a training stable in Brisbane. Twenty-one horses and two people were infected, with the resultant deaths of 14 horses and one person [2]. In separate incident in Mackay, two horses and a single human case were fatally infected[3]. A third spillover occurred in Cairns in 1999, with a single horse fatally infected[4]. In late 2004, in separate events in Cairns and Townsville, a further two horses were fatally infected and a human case non-fatally infected [5]. All human cases have been attributed to exposure to infected horses [6, 7]. Extensive wildlife surveillance has identified flying foxes as a natural host of Hendra virus, with infection endemic in the four mainland Australian species (*Pteropus alecto*, *P. poliocephalus*, *P. scapulatus* and *P. conspicillatus*) across their Australian range [8].

Nipah virus was first identified in 1999 as the primary causative agent in a major outbreak of disease in pigs and humans in peninsular Malaysia [9, 10]. Over 1 million pigs were culled to contain the outbreak. Of 265 reported human cases, 105 were fatal. Direct contact with infected pigs was identified as the predominant mode of human infection [11, 12]. Preliminary wildlife surveillance found serological evidence of infection in two species of flying foxes, *Pteropus vampyrus* and *P. hypomelanus* [13]. The subsequent isolation of virus from *P. hypomelanus* strengthens the contention that flying foxes are a natural host of Nipah virus [14]. In Bangladesh, five outbreaks of Nipah virus-associated disease in people between April 2001 and February 2005 have been described [15-18]. In marked contrast to the Malaysian outbreak, human infections were not associated with disease in pigs or other domestic species, and there is evidence of person-to-person transmission.

In October 1996, a rabies-like disease caused the death of a wildlife carer in Australia. The causative agent, Australian bat lyssavirus (ABLV) was first described earlier that same year in a black flying fox [19]. Both flying foxes [20] and humans [21, 22] exhibit a progressive neurological syndrome similar to that associated with rabies. ABLV infection has also been identified in insectivorous bats [8, 23], the first human case being attributed to *Saccolaimus flaviventris*. A second fatal human case, attributed to a flying fox, occurred in December 1998 [22]. While distinct from classical rabies virus, ABLV has serotypic, antigenic and sequence similarities with rabies virus [24]. Australia was previously believed free of viruses of the genus *Lyssavirus*.

Triggers for emergence

It is proposed that emergence of all three agents has been driven by environmental factors that have facilitated movement of the pathogens beyond their ecological niche. Morse [25], Krause [26] and Lederberg *et al* [27] propose that a series of commonly occurring anthropogenic environmental changes drive disease emergence by pushing pathogens outside their normal population parameters. The introduction of pathogens via global air travel and trade, the encroachment of human activities into wilderness regions, urbanization, climatic changes and agricultural intensification are common drivers of emergence. For zoonotic diseases with wildlife reservoirs, anthropogenic factors that alter wildlife population structure, migration patterns and behaviour may also drive emergence of disease in human populations[28]. The introduction of a "new" infection into a human or domestic animal population may follow the incursion of humans (accompanied by their domestic animals) into previously remote natural habitats where unknown disease agents exist in harmony with wild reservoir hosts. Upon contact with new species, an agent may jump species barriers, thereby spilling over into humans or livestock. Unlike the natural host, the new host may have no natural immunity or evolved resistance.

The emergence of Nipah virus disease in Malaysia illustrates the two step process described by Morse [29]. The establishment of pig farms within the range of the natural host supported the *initial introduction* into the pig population; the maintenance of high densities of pigs and the transport of pigs led to the *establishment and rapid dissemination of infection* within the pig population in peninsular Malaysia. Amplification of virus within pig populations then facilitated transmission to humans. It is proposed that anthropogenic changes increased the probability of effective contact between flying foxes and pigs, and thus the initial introduction of infection into the pig population. Plausible hypotheses include:

- The unsustainable hunting of *Pteropus* bat species has caused localized niche vacuums ('sinks') with relative resource abundancy, creating regional gradients along which neighbouring bat populations move, resulting in a net movement of virus into human-inhabited areas and so an increased probability of effective contact and spillover.
- Regional deforestation has changed the seasonal foraging movements of *Pteropus* bats and lead to an increased reliance on horticultural crops, resulting in a relative increased density of bats proximate to human and livestock populations. (Climatic changes, forest fires and associated haze events have similarly been hypothesized to influence flying fox movement patterns [30].
- The marked increase in the number, density and distribution of the Malaysian pig population since the early 1990's has led to an increased probability of contact between fruit bats and pigs. This probability has been further increased by the practice of planting fruit orchards immediately adjacent to piggeries.

The increasing urban presence of flying foxes in many Australian cities and towns (thought due to more reliable and abundant food resources) [31] and the associated changes in flying fox population dynamics, represents a similar emergence-promoting scenario (for Hendra virus and ABL) to those described above for Nipah virus.

Host management strategies

Effective disease management requires an understanding of the epidemiology of the disease (knowledge of its cause, maintenance and transmission, host range of the causative agent, and the nature of the host-agent relationship), an ability to detect disease (surveillance and diagnostic capabilities) and political/public/industry support. Current management strategies are directed at minimising direct or indirect contact with the natural host, monitoring intermediate hosts, improving biosecurity on farms, and better disease recognition and diagnosis [32].

Hendra virus

The sporadic nature of spillover events from flying foxes to horses, the low infectivity for horses (and consequently the limited economic impact), and the apparent absence of direct transmission from flying foxes to people has resulted in more emphasis on management strategies for horses than for flying foxes. Quarantine of infected premises, movement controls on stock, and disinfection have proved effective strategies [33]. A Hendra virus vaccine is not currently available and development of one is not foreseen. Australian veterinarians have a high awareness of Hendra virus, and Hendra virus exclusion is routinely undertaken for horses exhibiting an acute respiratory syndrome. Veterinarians involved in these disease investigations wear appropriate protective equipment and use a limited necropsy approach, as horses have been the source of infection for all human cases. Age (>8yo) and housing (paddocked) have been consistent horse-level risk factors for the index case in all five known spillovers. The presence of food trees favoured by flying foxes has also been a consistent observation, and the timing of infection in horses (August, Mackay 1994; September, Brisbane 1994; January, Cairns 1999; October, Cairns 2004; November, Townsville 2004) has overlapped late gestation or the birthing season in flying foxes in those areas. A considerable research focus on the ecology of Hendra virus is yet to establish the route of virus excretion or any temporal pattern of infection in flying foxes. This information, and knowledge of the actual mode of flying fox-to-horse transmission would facilitate a risk management approach to spillover infection in horses.

Nipah virus

In strong contrast to Hendra virus, the Nipah virus outbreak in Peninsular Malaysia in 1999 had an enormous economic and social impact. Nipah virus was highly infectious for pigs. The pattern of on-farm infection was consistent with respiratory transmission; between-farm spread was generally associated with the movement of pigs. The extensive post-outbreak surveillance program in Malaysia showed that farms that did not receive pigs generally remained uninfected even when neighbouring farms were infected. Human infections were predominantly attributed to contact with live pigs; none was attributed to contact with bats. Horizontal transmission was not a feature of infection in humans. Recommended host management strategies primarily target pig-to-pig transmission, secondarily the flying fox-pig interface (that is, the natural host-spillover host interface). The central strategy is the implementation of sound farm management practices, such as monitoring herd health and early recognition of disease syndromes. A second key strategy is the strict application of farm-gate biosecurity [34], with clearly defined protocols for the introduction of new stock. These may include quarantine and/or exclusion testing. A Nipah virus vaccine is not currently available and development of one is unlikely in the near future. Overarching the above is a strategy of advanced planning for emergency management of disease outbreaks.

While strategies directed at the flying fox-pig interface are limited by our incomplete knowledge of the ecology of Nipah virus, several simple on-farm measures can be taken to reduce the likelihood of spillover events occurring. The removal of fruit orchards and other favoured flying fox food trees from the immediate vicinity of pig sheds greatly reduces the probability of flying fox-pig contact. Similarly, the wire screening of open-sided pig sheds is a simple and inexpensive strategy to prevent direct contact between flying foxes and pigs. Indirect contact (with flying fox urine or faeces or partially eaten fruit) can be avoided by ensuring roof run-off does not enter pig pens [30]. In Bangladesh, the pattern of the outbreaks suggests a sporadic and geographically scattered introduction of infection to humans. The mode of transmission (presumed direct from flying foxes to people) needs to be elaborated, and human risk behaviours identified and modified.

Australian bat lyssavirus

Epidemiological evidence suggests that ABLV is endemic in bat populations in Australia. No evidence of infection has been found in any species other than bats and humans. The two known (fatal) human cases of ABL infection have been attributed to direct contact with bats. Thus host management strategies seek to minimize bat-human interactions, and extensive public awareness campaigns have sought to educate members of the general public to avoid any direct contact with bats [32]. This means not picking up sick or injured bats and preventing insectivorous bats from gaining roost access to houses. The former is heavily emphasised, as sick and injured bats have been found to have a significantly higher prevalence of infection than do wild-caught bats [8]. The risk posed by sick and injured bats is highlighted by a study of 'occupations' associated with potential exposure, which found that volunteer animal handlers accounted for 39% of potential exposures, their family members for 12%, professional animal handlers for 14%, community members who intentionally handled bats for 31%, and community members where contact was initiated by the bat for 4% [35].

The strategies of public awareness and contact minimisation are supported by vaccination. Mouse vaccine protection studies showed that rabies vaccine offers protection against infection with ABLV [36, 37]. This provides a management strategy not available for Hendra virus or Nipah virus, and pre-exposure administration of rabies vaccine is recommended for high risk 'occupations', such as those described above. Post-exposure treatment with vaccine and with rabies immune globulin is offered to anyone exposed to bats through bites or scratches, unless ABLV infection can be ruled out in the bat. Bats having at-risk contact with humans or domestic animals are routinely tested for ABLV infection. Vaccination strategies are restricted to humans, although limited research has been undertaken to explore the efficacy of parenteral rabies vaccination in flying foxes [20]. Certainly oral rabies vaccines have dramatically reduced the incidence and spread of rabies in wildlife hosts in Europe and North America. Preliminary research in Australia has also investigated bait or plant-derived vaccination of flying foxes as a future management strategy [32]. Oral sub-unit vaccines appear to offer a less expensive, more stable, more easily administered and safer (incapable of causing infection) alternative to conventional rabies vaccine [32]. Nonetheless, the development of successful management strategies based on vaccination requires careful consideration of the management methods available as well as an understanding of both the agent and target species' behaviour and ecology.

Conclusion

Host management strategies for natural hosts seek to minimize the opportunity for effective contact between the natural host and the spillover host. Incomplete knowledge of the ecology of the agents (the maintenance and transmission of infection, the natural and domestic host range, and the nature of the host-agent relationship) and of the factors associated with emergence (habitat loss, land use change and demographic shifts) precludes a more targeted approach at this time. Strategies for intermediate hosts emphasize surveillance, detection and emergency response capabilities. Strategies for human hosts promote awareness, minimization of contact, use of personal protective equipment and (for ABLV) vaccination.

It is notable that neither the indiscriminate nor targeted killing of bats is contemplated as an effective host management strategy. Certainly such a strategy with nomadic species such as flying foxes is biologically flawed, and as argued earlier, may cause a net influx of bats to the resultant niche vacuum. The forced movement of roosting flying foxes (flying foxes communally roost in trees, frequently in groups of thousands) by sustained noise, smoke, flags has been attempted with mixed success. Permanent removal of flying fox roosts can only be guaranteed by the removal of the roost trees.

The evidence indicates that Hendra, Nipah and ABL are 'old' viruses [2, 24] that have likely evolved with flying foxes, remaining in this niche until ecological changes precipitated their emergence.

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