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LETTER TO THE EDITOR

Rebuttal to Peel et al. Re: 'The imperative to develop a human vaccine for the Hendra virus in Australia'

This Rebuttal refers to a Letter to the Editor: http://dx.doi.org/10.3402/iee.v6.31658. Which was a reaction to a Commentary: http://dx.doi.org/10.3402/iee.v5.29619.

The respondents, Peel et al., have failed to grasp the key message in our commentary: the recommendation for a Hendra human vaccine **and** *not to censure the current Hendra equine vaccine*. In restating our conclusion, we re-affirm that the development of a Hendra human vaccine should complement *and not replace* current risk management strategies in place (which includes the use of the current Hendra equine vaccine).

Sequencing of Hendra virus (HeV) strains demonstrates different nucleotide sequences associated with each outbreak, and also differ by geography (1, 2). Ecological drivers are presumed to dominate this difference (3). The respondents are valid in their claim that the virus is highly conservative with 'minimal variation accounting $<1\%$'. More recent cases of equine infections have been associated with a greater prevalence of neurological disease as well as differences in viral strains. These variations in disease penetrance are perhaps the result of genetic changes (4). These changes, dismissed by the respondents as insignificant, ought to be viewed with greater caution considering the variation in infection pathogenicity as well as mortality observed amongst outbreaks (5). We concede that the term 'rapidly mutating' was used inadvertently with limited support. However, multiple variants of HeV have been identified, and they have caused infections simultaneously (2). The possibility of the generation of new variants cannot be excluded, and the ongoing identification of variants should be undertaken to maintain confidence in the methods of timely detection of infected hosts.

The Australian Veterinary & Pesticides Management Authority states that the Hendra vaccine does not provide complete protection against the HeV in equines (6, 7). In opposition to respondents' claim, contact prevention and quarantine of infected equines remains the pivotal measure in reducing the risk of infection – even in vaccinated horses (6). This echoes an approach that has repeatedly proven its merit with regard to most infectious diseases.

Much to the chagrin of public health officials, many have abandoned equine vaccination in response to concerning adverse reactions observed post-vaccination (8). These adverse reaction events have caused sufficient concern to result in the Queensland State Parliament initiating a formal inquiry into the Hendra equine vaccine and its related policies (9). A natural consequence of low uptake of equine vaccination is decreased herd immunity. This predisposes humans (and equines) to a greater risk of Hendra infection. As to the efficacy of the Hendra equine vaccine, the vaccine performed as anticipated in controlled clinical trials following its development (10). However, the low uptake of the vaccine coupled with the low prevalence of disease renders accurate assessment and surveillance of the vaccine post-commercialization challenging.

Our knowledge of the clinical syndromes that develop in a human HeV infection is limited, in part, due to the small number of human cases to date. Accordingly, any departure from the observed or expected clinical course permits greater understanding of pathogenesis as well as assists in the identification of potential or future targets for prevention and treatment. In support of changing clinical syndromes observed among human cases, two human cases developed encephalitis soon after infection (11). This clinical course was in contrast to prior cases whereby encephalitis developed significantly later in the patient's prognosis (11). Of relevance, the novel development of acute encephalitis post-infection was associated with equine infections that also demonstrated a predominantly neurological spectrum of clinical symptoms as opposed to respiratory symptoms that had been observed in past equine infections (11). The variation in clinical presentation in both equines and human caes should be taken into consideration when assessing the implications associated with variation between HeV isolates.

Susceptibility of a novel host to Hendra infection does not ordinarily imply an infection risk in that particular host. In a susceptible host, however, the likelihood of exposure directly correlates with the risk of infection. It has been experimentally demonstrated that non-human primates, pigs, cats, and ferrets can be successfully infected with Hendra (10, 12–15). The identification of novel hosts for the HeV has direct implications for the preservation of human life. Hosts, such as cats and dogs, have visibly closer and more frequent contact with the human population (16). This is in contrast to horses, with whom human

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contact is selective and relatively less frequent. The greatest dilemma remains if or when an infected novel host, for example: a pig, should enter the human food supply. It is essential to note direct transmission of the Nipah virus (most closely related to the HeV) from bats to pigs has been documented (17).

The index case of an infected, asymptomatic canine may be attributed to indirect exposure of an infected equine. That being said, it could also be attributed to direct transmission from the bat, as has been observed to occur with the Nipah virus (17). The true route of transmission remains unknown and this salient fact should be thoroughly considered when weighing the lethal ramifications of HeV infection (16).

Continued human–bat interaction is resulting in bats' changing their migratory patterns and locating to new geographical areas. In support of this claim, multiple HeV infections were observed in 2011 in a region totaling 60,000 km^2 southwesterly to known bat habitats (18). Neither HeV nor the bats were known to be present beforehand in these locales that were significantly distant to their native geography (18).

HeV remains a threat to human health. We surmise that the development of a human vaccine for at-risk populations would help mitigate that threat, in conjunction with the existent HeV equine vaccine and other HeV infection control policies in place.

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