Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Hendra virus and Nipah virus animal vaccines

Christopher C. Broder[a,*], Dawn L. Weir[b], Peter A. Reid[c]

[a] Department of Microbiology and Immunology, Uniformed Services University, Bethesda, MD, 20814, United States
[b] Navy Environmental and Preventive Medicine Unit Six, Joint Base Pearl Harbor Hickam, HI, 96860, United States
[c] Equine Veterinary Surgeon, Brisbane, Queensland, 4034, Australia

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Paramyxovirus
Henipavirus
Hendra
Nipah
Animal models
Pathogenesis
Vaccine
Antiviral
Monoclonal antibody

ABSTRACT

Hendra virus (HeV) and Nipah virus (NiV) are zoonotic viruses that emerged in the mid to late 1990s causing disease outbreaks in livestock and people. HeV appeared in Queensland, Australia in 1994 causing a severe respiratory disease in horses along with a human case fatality. NiV emerged a few years later in Malaysia and Singapore in 1998–1999 causing a large outbreak of encephalitis with high mortality in people and also respiratory disease in pigs which served as amplifying hosts. The key pathological elements of HeV and NiV infection in several species of mammals, and also in people, are a severe systemic and often fatal neurologic and/or respiratory disease. In people, both HeV and NiV are also capable of causing relapsed encephalitis following recovery from an acute infection. The known reservoir hosts of HeV and NiV are several species of pteropid fruit bats. Spillovers of HeV into horses continue to occur in Australia and NiV has caused outbreaks in people in Bangladesh and India nearly annually since 2001, making HeV and NiV important transboundary biological threats. NiV in particular possesses several features that underscore its potential as a pandemic threat, including its ability to infect humans directly from natural reservoirs or indirectly from other susceptible animals, along with a capacity of limited human-to-human transmission. Several HeV and NiV animal challenge models have been developed which have facilitated an understanding of pathogenesis and allowed for the successful development of both active and passive immunization countermeasures.

1. Introduction

Hendra virus (HeV) and Nipah virus (NiV) are enveloped, single-stranded negative sense RNA viruses and the prototype members of the genus *Henipavirus* in the family *Paramyxoviridae* [1]. Recently, a third virus isolate Cedar virus (CedPV) has been added to the *Henipavirus* genus [2]. Whereas HeV and NiV are bat-borne disease-causing zoonoses, CedPV is not known to be zoonotic nor has it been shown to be pathogenic in any animal, including those susceptible to HeV and NiV, although it does reside in nature in the same bat species as HeV. To date, bats appear to be predominant natural reservoir hosts for henipaviruses [3]. Although nucleic acid based detection studies have identified related *Henipavirus* species, including complete genomic sequences [4,5], HeV, NiV, and CedPV are the only virus isolates that have been reported.

In several disease-susceptible animal species, and in people, the major pathological observation of HeV and NiV infection is a severe systemic and often fatal neurologic and/or respiratory disease [6–8]. However, HeV and particularly NiV can also cause relapsed encephalitis which follows a recovery from an acute infection and appears to result from a recrudescence of virus replication in the central nervous system (CNS) [9,10]. Outbreaks or spillovers of NiV in Bangladesh and India, since its first emergence in peninsular Malaysia, have continued to occur, as has HeV in Australia, making these henipaviruses important transboundary biological threats [11]. Both HeV and NiV are highly pathogenic in a number of mammalian species and possess several characteristics that distinguish them from all other known paramyxoviruses and are classified as Biosafety Level-4 (BSL-4) agents. Indeed, NiV is considered to have the potential to be a pandemic threat since it can infect humans directly from natural reservoirs (bats) or indirectly following amplification in a susceptible animal species (pig) and has a recognized capacity of, albeit limited, human-to-human transmission [12]. Since their discovery and recognition, a variety of approaches have been taken by multiple research groups to devise countermeasures as a means of addressing the transboundary threat issues brought about by HeV and NiV. Several active and passive immunization approaches have been explored and some have led to successful deployment and human clinical trials. Concurrent with these developments, several animal challenge models

* Corresponding author. Tel.: +1 301 295 3401; fax: +1 301 295 1545.
E-mail address: christopher.broder@usuhs.edu (C.C. Broder).

http://dx.doi.org/10.1016/j.vaccine.2016.03.075
0264-410X/

of HeV and NiV infection and pathogenesis have been established which have provided insight into the nature of HeV and NiV disease [13,14] and afforded the possibility of testing vaccine and therapeutic countermeasures [15–17].

2. Hendra virus and Nipah virus emergence

In 1994 an outbreak of fatal cases of a severe respiratory disease in horses and humans occurred in the Brisbane suburb of Hendra, Australia. The infectious cause of this event was discovered to be a previously unknown paramyxovirus that was distantly related to certain morbilliviruses [18]. In all, 13 horses and a trainer succumbed to infection together with the non-fatal infection of 7 additional horses and a stable hand. In a separate incident that was retrospectively recognized, this same virus caused a brief aseptic meningitic illness in one person after he had cared for and assisted in the necropsies of two horses near Mackay in central Queensland ~1000 km north of Brisbane, and these animals were later shown to have died from this virus infection [19,20]. Remarkably, 13 months following his recovery, this individual suffered an episode of relapsed fatal encephalitis characterized by uncontrolled focal and generalized epileptic-activity caused by this virus [21]. Provisionally termed equine morbillivirus, this new paramyxovirus was later re-named Hendra virus (HeV), after the location of the first recognized outbreak. To date, HeV has appeared in Eastern Australia on 55 occasions, with the three most recent in 2015, causing the death or euthanasia of 97 horses, 2 HeV antibody positive and euthanized dogs, and 4 fatalities of 7 human cases [11,22–29]. In all recognized HeV spillovers and those cases of confirmed human infections, the horse is the predominant target host acquiring infection from virus-shedding bats and is also the intermediate host from which humans have acquired infection. The epidemiological characteristics and the possible underlying mechanisms behind HeV spillovers have been examined [30,31] and reviewed [32,33]. In 2011, the first confirmed infection of HeV in a dog was reported. The dog was shown to be seropositive for HeV and was euthanized despite showing no clinical signs of disease. A postmortem was not performed and it was thought that transmission of infection had occurred by close contact with an infected horse [34]. A second confirmed HeV infection in a dog was reported in 2013. The dog tested positive to HeV by quantitative reverse transcription PCR (q-RT-PCR) during the apparent early stages of an acute infection and had appeared to have become naturally infected with HeV following close exposure to blood from a euthanized HeV infected horse [35]. This dog was euthanized and extensively analyzed *via* postmortem examination. Although the dog had appeared clinically healthy, histopathologic findings of widespread necrotizing vasculitis was noted, with the most severe lesions recorded in the kidney, brain and lymph nodes, with little involvement of the lungs. Additionally, HeV RNA was detected in multiple tissues [35]. Presently, the extent of HeV transmission from bats to dogs in Australia is an unknown concern and should be the focus of future studies.

A few years following the appearance of HeV there was a large outbreak of encephalitis among pig farmers in Peninsular Malaysia which began in the fall of 1998 and continued into the spring of the next year [36]. A virus was isolated from the cerebrospinal fluid (CSF) of two patients and shown to cross-react with antibodies against HeV [37]. Subsequent molecular genetic studies revealed a new paramyxovirus that was most closely related to HeV [38]. This Hendra-like virus was named Nipah virus (NiV) after the town of Nipah in the state of Perak, Malaysia where it was first isolated from a case of fatal encephalitis [39]. In total there were 265 cases of human infection with 105 fatalities in Malaysia along with an additional 11 cases and one fatality among abattoir workers in Singapore [38,40]. The epidemiological features of this outbreak, its likely causes, and the factors that exacerbated it have been reviewed elsewhere [41,42]. Although NiV has not re-emerged in Malaysia, nearly annual outbreaks of human cases of NiV infection have been recorded since 2001 in Bangladesh and a few in India. The most recent cases of human infections occurred in early 2015 with 9 human fatalities [43]. The outbreaks of NiV in Bangladesh and India have had lower total numbers of human cases but the fatality rates have been notably higher, ranging from 75 to 100%. In these instances, the direct transmission of NiV from bats to humans following the consumption of contaminated fruits or date palm sap has been noted along with several instances of significant human-to-human transmission of NiV infection being documented [44–47]. The epidemiological details of the spillovers of both HeV and NiV into humans have been recently reviewed [48,49]. In all, there have been ~620 cases of human NiV infection with 322 fatalities (reviewed in [43,49,50]).

Pteropus bat species appear to be the major natural reservoir hosts for henipaviruses and all bat isolates of HeV, NiV as well as CedPV have been derived from *Pteropus* bats [2,51–54]. As natural reservoir hosts, overt disease has not been reported in wild bats, nor are there signs of clinical illness in experimentally infected pteropid bats [55–58]. Nevertheless, there continues to be ever expanding evidence of the presence of henipaviruses in a wide variety of other bat species in both Megachiroptera and Microchiroptera suborders [5,59–65], as well as the existence of other henipa-like viruses in rodents [4]. Further, serological and/or nucleic acid evidence of henipaviruses in domestic livestock and in human populations have also been reported, providing evidence of sporadic henipavirus spillover events and also suggesting the existence of related henipaviruses [66–69].

3. The viruses, tropism and entry

HeV and NiV particles are enveloped and pleomorphic with spherical or filamentous forms observed by electron microscopy [70–72]. The viral envelope carries surface projections composed of the viral transmembrane anchored fusion (F) and attachment (G) glycoproteins which have been the major target of antiviral strategies. HeV and NiV are classified into the *Henipavirus* genus, *Paramyxoviridae* family [73] and their genomes are unsegmented, single-stranded, negative-sense RNA [1]. Genomic sequence analysis of many HeV isolates obtained from horses, a human case, and pteropid bats, have shown them to be ~99% identical [51,72,74]. In the initial Malaysian outbreak of NiV, both pig and human isolates were genetically highly similar to those obtained years later from bats [75–78]. However, some diversity among NiV isolates can be noted when comparing Malaysian isolates to NiV isolates from other areas of Southeast Asia, with NiV-Bangladesh sharing ~92% identity with NiV-Malaysia [79], and a third lineage of NiV was isolated from Lyle's flying fox (*Pteropus lylei*) in Cambodia that is more closely related to NiV-Malaysia than to NiV-Bangladesh [53,80].

HeV and NiV are also distinguished by their exceptionally broad species tropism and in addition to pteropid bats, natural or experimental infection has been documented in pigs, horses, cats, dogs, guinea pigs, mice, hamsters, ferrets, squirrel monkeys and African green monkeys and humans (reviewed in [13]). NiV can also productively infect chicken embryos [81] spanning 7 orders (6 mammalian and one avian).

The major determinant of species and cellular tropism of HeV and NiV is derived from the functions of the viral envelope glycoproteins (G and F) which are the mediators of virus attachment and host cell infection. The HeV and NiV G glycoprotein bind to the host cell membrane proteins ephrin-B2 and ephrin-B3 [82–85]. The ephrin-B2 and -B3 molecules are members of a large family of cell surface expressed glycoprotein ligands that bind to Eph receptors

Please cite this article in press as: Broder CC, et al. Hendra virus and Nipah virus animal vaccines. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.03.075