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Status of vaccine research and development of vaccines for Nipah virus☆

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ABSTRACT

Nipah virus (NiV) is a highly pathogenic, recently emerged paramyxovirus that has been responsible for sporadic outbreaks of respiratory and encephalitic disease in Southeast Asia. High case fatality rates have also been associated with recent outbreaks in Malaysia and Bangladesh. Although over two billion people currently live in regions in which NiV is endemic or in which the *Pteropus* fruit bat reservoir is commonly found, there is no approved vaccine to protect against NiV disease. This report examines the feasibility and current efforts to develop a NiV vaccine including potential hurdles for technical and regulatory assessment of candidate vaccines and the likelihood for financing.

1. About the disease and pathogen

Nipah virus (NiV) is a recently emerged highly pathogenic paramyxovirus of the genus *Henipavirus* and is the causative agent of sporadic outbreaks of respiratory and encephalitic disease in Southeast Asia. The World Health Organization (WHO) recently published a concise summary of early knowledge about NiV [1]. NiV was first recognized as an emerging human pathogen in 1998 during an outbreak of encephalitic disease among pig farmers in peninsular Malaysia and Singapore. The Malaysian outbreak was the result of pig-to-human transmission following an outbreak of mild respiratory and encephalitic disease in pigs [2]. Human-to-human transmission was suspected in a few cases (about 1%). The case fatality rate (CFR) for this initial outbreak was 38% in Malaysia and Singapore. *Pteropus* fruit bats were later shown to be the reservoir host for NiV. Spillover from bats to pigs likely occurred via partially eaten fruits or direct exposure to infectious bat secretions. The primary mechanism of exposure to humans in this outbreak was via infectious secretions from pigs resulting in 276 confirmed cases and 105 deaths.

While there are no standardized criteria and methodologies, diagnosis of human infections is based on identification of individuals exhibiting clinical symptoms including altered mental status and/or seizures. Blood drawn from individuals with suspected NiV infection can be tested for NiV-specific IgM by ELISA. PCR-based diagnosis is an alternative method available mainly in higher income countries [1]. The incubation period is between 4 and 30 days, although most cases range between 5 and 18 days [1,3]. Human cases typically present with abrupt onset of fever, headache, dizziness, and vomiting. Neurological signs include reduced levels of consciousness, segmental myoclonus, areflexia, hypotonia, and abnormal doll's eye-reflex which develop in these individuals within a week of fever onset. In the Malaysia outbreak, atypical pneumonia was seen in 14% of patients and neurological symptoms varied among infected individuals. Approximately, 5% of patients developed late-onset encephalitis ten weeks after infection which resolved completely while approximately 9% displayed another round of encephalitis. It is believed that this recurrent encephalitis is a result of recrudescence due to re-immergence of a latent infection rather than as a result of a re-infection. There are currently no known risk factors for relapsed encephalitis [3]. Many survivors of NiV infection have long-term neurological sequelae leading to decreased quality of life and earning potential [4].

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Although no further outbreaks have been reported in Malaysia, two outbreaks have occurred in India and nearly annual outbreaks have occurred in Bangladesh since 2001. Bangladesh outbreaks have been smaller and more isolated than the Malaysia outbreak but resulted in higher CFRs (average 75%) with over 300 confirmed cases from 2001 to 2015. Most outbreaks were clusters of related cases but occasionally cases of individual infections widely separated geographically from other NiV cases have been reported. The clinical presentation is similar to that seen in Malaysia, but results in more frequent severe respiratory disease [5] (70% of cases), and are the result of direct bat-to-human transmission via consumption of contaminated raw date palm sap with subsequent human-to-human spread. The nature of human-to-human transmission is not clear but requires close contact perhaps mediated by droplets, fomites, intimate contact with body secretions or a combination of these elements. Genomic sequencing showed that two distinct NiV strains were responsible for these Malaysia and Bangladesh outbreaks. Whether these observed differences in disease presentation and outcome are due to strain variation, route of exposure, or differences in healthcare remains to be determined [3]. The two outbreaks in Indian regions bordering Bangladesh resulted in similar CFR and were also likely transmitted via consumption of contaminated date palm sap. Recently, a henipavirus, most likely NiV, caused an outbreak in the Philippines with 17 cases and nine fatalities. Human infections occurred following exposure to infected horses, possible human-to-human transmission (likely via close contact), and transmission to domestic cats and a dog was also reported [6]. Due to poor surveillance in rural areas of countries with endemic NiV, the true disease burden is uncertain and many cases likely go undetected. The outbreaks in Malaysia, Bangladesh, India, and the Philippines involved the loss of life and diminished the earning potential of survivors due to long-term disability demonstrating a clear economic impact of the NiV outbreaks. Because NiV is highly infectious to humans by aerosols, and is life-threatening to humans and agricultural animals with a high CFR, NiV is classified internationally as a biosafety level 4 (BSL4 or P4) agent [7].

Several risk factors have led to the proposal that NiV poses a pandemic threat including: a broad host range, widespread distribution of the predominant *Pteropus* bat reservoir as well as less dominant *Eonycteris*, *Cynopterus*, *Scotophilus*, and *Hipposideros* bat reservoirs across Southern Asia, Australia, and Madagascar, and high seroprevalence rates in reservoirs. Antibodies against henipa-like viruses have also been discovered in *Eidolon helvum* bats [8] and domestic pigs [9] in Ghana as well as in humans reporting contact with bats in Cameroon [10]. In addition, over half of cases in Bangladesh are due to human-to-human transmission [11]. As demonstrated by the recent West African Ebola outbreak, there is potential for highly pathogenic emerging infections that normally cause only small, isolated and containable outbreaks to occasionally result in large epidemics that inflict a significant mortality and morbidity burden. In this regard, the number of people at risk of acquiring NiV in Bangladesh and the neighboring West Bengal state of India (regions that experience more frequent outbreaks) exceeds 250 million. The total number of people at risk, including all countries that experience NiV outbreaks and in which the *Pteropus* bats occur naturally, exceeds two billion.

Despite the potential importance of NiV as an emerging disease pathogen, no specific therapeutics or vaccines are currently approved for use in humans. Current prevention of disease in endemic countries relies on behavior modifications to prevent spillover, including farming practices which decrease livestock exposure to bats, the use of bamboo skirts to prevent date palm sap contamination, and pasteurizing date palm sap. Though these approaches appear to be effective strategies of prevention, their implementation is often problematic due to cultural factors [12].

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

Although no licensed human vaccines for NiV exist, there is strong evidence that an effective vaccine is feasible. Other related paramyxoviruses, such as measles virus (MV) and mumps virus, yield long-term immunity after natural infection, and safe, efficacious live attenuated vaccines with defined correlates of protection have been developed that have been used safely against these pathogens for decades. Recent evidence also suggests that almost all successful viral vaccines target viruses with average incubation periods of at least 5–7 days whereas efforts have proved largely unsuccessful to produce vaccines for viruses with shorter incubation periods [13]. The evidence suggests that the average incubation period for NiV is above the 5–7 day threshold and therefore has strong potential for the development of a successful vaccine. Additionally, various candidate vaccine platforms have demonstrated the feasibility of using one or both of the NiV outer-membrane proteins, the glycoprotein (G) and fusion (F) protein, as the antigen(s) to stimulate a protective immune response in various preclincal challenge models including hamsters [14,15], cats [16], ferrets [17], African green monkeys (AGMs) [18,19], and pigs [20]. Neutralizing antibody titers typically ranging from about 160 to 16,000 were induced in several animal models by these vaccines. Little or no clinical signs of disease were observed in vaccinated animals after NiV challenge and protection against mortality was typically 100% depending on the vaccination route and dose. Immune responses are also produced in mice, although mice are not susceptible to NiV infection and therefore protection could not be assessed [21]. The nature of the protective immunity provided by immunization with these vaccine antigens is not completely defined but likely due to inhibitory/neutralizing antibodies that prevent binding and/or fusion of NiV with host cells. This mechanism would be consistent with the ability of various polyclonal or monoclonal antibodies against the NiV or HeV F and/or G proteins to protect in animal models when administered either pre- or post-exposure [22,23].

Due to the extreme lethal nature of NiV, producing a safe, live attenuated vaccine with no potential of reversion is generally considered a difficult approach, although recombinant-derived NiV mutants have been produced that are attenuated in hamster and ferret models and generate a strong neutralizing antibody response [24,25]. Most candidate vaccine platforms have either focused on the subunit vaccine or live-vectored vaccine approaches. It is notable that there are no current vaccine candidates using formalin-inactivated NiV, likely due to the safety issues that have arisen in the past with formalin-inactivated paramyxovirus vaccines including early attempts with MV [26,27] and respiratory syncytial virus vaccine development [28,29]. The most studied vaccine candidate is a subunit vaccine consisting of a soluble glycoprotein (sG) from the related henipavirus Hendra virus (HeV), which causes human and equine disease. HeV and the NiV Malaysia strain share amino acid homology between all viral proteins of between 68 and 92%. For the F protein, the homology is 88% whereas there is a homology of 83% for the G protein [30]. This HeV sG vaccine also protects ferrets and AGMs from experimental challenge with NiV as well as HeV. One formulation of this HeV sG vaccine called Equivac® HeV, has recently been licensed to vaccinate horses in Australia against HeV, thus demonstrating the feasibility of henipavirus vaccine development [23]. The characteristics and formulation of this vaccine will be described in Section 3.

Various vectored vaccine candidates have been described in the literature including vesicular stomatitis virus (VSV), rabies virus (RABV), canarypox virus (CNPV ALVAC strain), adeno-associated virus (AAV), MV, Newcastle disease virus (NDV), and Venezuelan equine encephalitis virus (VEEV) [22]. The RABV and MV vectors are

based on current vaccine strains of these viruses with known safety profiles. Ebola vaccine candidates utilizing a VSV vector similar to the strategy for NiV are currently in advanced clinical evaluation [31–33]; their safety and efficacy data will help determine the feasibility of utilizing the VSV vaccine platform for NiV vaccines. Research to date has focused on two strains of NiV: the Malaysia (NiV_M) and Bangladesh (NiV_B) strains. These strains share 95% amino acid homology in the G protein and 98% homology in the F protein. Although they share even less homology with the G and F proteins of HeV, several studies have shown significant or complete cross-protection with vaccines for NiV_M, NiV_B, and HeV. The durability of protection for the various vaccine candidates has not yet been assessed with the exception of a single study showing the HeV sG vaccine conferring protection against NiV at least 12 months after two vaccinations administered 20 days apart in ferrets [34].

Monoclonal antibodies targeting the surface glycoproteins of HeV have shown efficacy against both HeV and NiV as pre- and post-exposure prophylaxis in animal models [35] but since these antibodies must be administered before the onset of clinical signs, they are unlikely to be useful for treating symptomatic patients in an outbreak scenario, but may prove beneficial in prophylactically treating potentially exposed individuals. In this regard, a humanized monoclonal antibody specific for the Hendra G protein and cross-reactive with the related G protein of NiV has been used as a therapeutic treatment in ten humans with significant exposure risk to HeV or NiV [36].

2.2. General approaches to vaccine development for this disease for low and middle income country markets

Age does not appear to be a factor in NiV disease as documented infections have occurred in individuals from all age groups and no difference in disease severity has been observed among different age groups. The only country with regular, recurring outbreaks at the present time is Bangladesh, thus that population is likely in greatest need of a NiV vaccine. However, seropositive *Pteropus* bats have been detected throughout much of Southeast Asia and pose potential for risk of NiV outbreaks to further human populations.

NiV outbreaks have been associated with infection of pigs or horses with subsequent spread to human populations, although the annual outbreaks in Bangladesh are not associated with domestic livestock, but direct contamination from infected fruit bats and human-to-human transmission. Some vaccination strategies include vaccinating swine herds or horses to prevent spread to human populations; however, this strategy would not pertain to Bangladesh, and potentially other countries where human vaccination is needed to prevent disease.

Several vaccination strategies for direct protection of humans are possible but are highly influenced by the unpredictable occurrence of NiV outbreaks and the limited number of cases typically found in an average NiV outbreak. One strategy would deploy a stockpiled vaccine for ring vaccination around a village or area where NiV cases are discovered similar to that examined in the current Ebola outbreak [32]. Other possible approaches involve creating vectored vaccines capable of protecting against both NiV and other pathogens such as MV or RABV in order to reduce the costs and ease the logistics of delivering this vaccine.

3. Technical and regulatory assessment

No clinical trials have yet begun for NiV vaccine candidates. The epidemiology and sporadic nature of NiV outbreaks makes large scale, Phase III clinical trials difficult to plan to assure achieving meaningful efficacy results that would support licensure. A pathway for approval might be possible in the United States via the Food and Drug Administration's (FDA) Animal Rule or through the identification of surrogate markers of immune protection. The FDA's Animal Rule is intended to enable approval of drugs against highly lethal infections in situations where definitive human efficacy studies cannot be conducted because it would be unethical, and/or field trials have not been feasible. In this instance, efficacy via protection in one or two experimental animal models that replicate key characteristics of the human disease and are predictive of the mechanism of protection in humans may offer an alternative licensure pathway. The AGM, ferret, and hamster models are well established and accurately model human disease. Furthermore, the sG and VSV vaccines have protected AGMs and ferrets from lethal intranasal and intratracheal NiV challenge. However, although this mechanism may represent a potential pathway for NiV vaccine approval in the United States, no vaccines have been approved through this mechanism to date. Even with the Animal Rule, human Phase I/II trials will still be required for safety trials, and having these conducted before the beginning of a large-scale outbreak is important in allowing for a rapid response. The lack of these trials prior to the current Ebola outbreak has been a hindrance in the rapidity of deploying a vaccine in a timely manner [31–33].

Identification of an accurate correlate or surrogate of protection might serve as a satisfactory vaccination outcome to facilitate regulatory approval, although true correlates of protection against NiV are not completely defined and standardized methods for measuring immune correlates are currently lacking. The correlate of protection against NiV infection of humans will likely involve neutralizing antibody levels [37]. Neutralizing antibodies appear to be a main mediator of protection as evidenced by the ability of the several vaccine candidates to induce neutralizing antibodies, and by the protective role of passive antibody transfer in experimental animal models. The sG vaccine animal efficacy data suggests that neutralizing antibody titers as low as 16 or 32 offer full protection against NiV and HeV [37] but we do not know how this level of neutralizing activity translates to protection in humans. The necessity of performing neutralization assays with virulent NiV under conditions of high biocontainment complicates development of neutralization assays using standardized reagents, NiV strains, and assay conditions. More importantly, this issue precludes common use of these assays in most basic and clinical laboratories. The use of pseudotype viruses in neutralization assays may overcome assay development and standardization gaps by allowing assays to be performed under biosafety levels attained in most basic and clinical laboratories [38]. As an alternative approach, identification and quantification of potential non-neutralizing, serological surrogate markers of vaccine protection may involve the use of multiplexed microsphere assays or ELISA assays for quantification of NiV-specific IgG, IgA, and IgM responses. However, further work is needed to standardize reagents and assay conditions and to define any relationship between specific antibody levels and immune protection [18].

Most candidate NiV vaccines are in early stages of development. Experimental vaccines in which NiV proteins are expressed by various virus vectors represent an attractive approach in NiV vaccine development. VSV-vectored Ebola vaccines are currently in Phase III efficacy trials [32], suggesting that a similar safety and efficacy testing pathway might be implemented for VSV vectored NiV vaccines. However, as mentioned previously, a subunit vaccine called Equivac HeV® incorporating sG is already in production as an approved veterinary vaccine for HeV in Australia [37]. This vaccine is formulated using 100 μg of sG prepared from either 293F human embryonic kidney or CHO cells with a proprietary immunostimulatory complex adjuvant. Currently, the vaccine is administered to horses by the intramuscular route as two immunizations, three to six weeks apart followed by boosting at six month intervals.

Table 1
Development status of current vaccine candidates.

Candidate name/ identifier: institution	Preclinical	Developers	Ref
Subunit vaccine			
HeV sG	X	Zoetis, Inc./USU	[16,18,34,39]
Vectored vaccines			
VSV-NiV_B F and/or G	X	UTMB	[17]
VSV-NiV_M G	X	CDC	[15]
VSV-NiV_M G	X	RML	[14,19]
VSV-NiV_M F and/or G	X	Yale University	[40]
VSV-HeV G:	X	TJU/RML	[41]
RABV-HeV G:	X	TJU/RML	[41]
ALVAC-F/G	X	CFIA-NCFAD	[20,42]
AAV-NiV_M G	X	INSERM	[43]
rMV-Ed-G	X	UoT	[44]
V-NiVG	X	USU	[45]
rLa-NiVG and/or rLa-NiVF	X	CAAS-SKLVB	[21]
Passive antibody transfer			
Polyclonal serum NiV F or G	X	INSERM	[46]
Mouse mAbs NiV F or G	X	INSERM	[47]
Human mAb m102.4 Henipah G	X	USU	[35,48]

Abbreviations: USU (Uniformed Services University of the Health Sciences); UTMB (University of Texas Medical Branch); CDC (Centers for Disease Control and Prevention); RML (Rocky Mountain Laboratories); TJU (Thomas Jefferson University); CFIA-NCFAD (Canadian Food Inspection Agency – Centre for Foreign Animal Diseases); Institut national de la santé et de la recherché médicale (INSERM); UoT (University of Tokyo); CAAS-SKLVB (Chinese Academy of Agricultural Sciences (CAAS) – State Key Laboratory of Veterinary Biotechnology (SKLVB)).

The success of experimental sG vaccines in experimental animal models and the use of Equivac HeV® as an effective vaccine in horses suggest this approach may also be efficacious in humans. Formulation of sG with an approved adjuvant represents a platform that should likely be investigated through human clinical studies.

4. Status of vaccine R&D activities

All R&D activities for NiV vaccines are in the pre-clinical stage having been tested in the hamster, ferret, and/or AGM preclinical challenge models. Table 1 provides a summarized list of current preclinical vaccine candidates. Various experimental subunit vaccines utilizing sG protein and adjuvants such as Alhydrogel® and CpG oligodeoxynucleotide have been shown to be protective against NiV in multiple animal models. The most advanced vaccine of this category is Equivac HeV® that is formulated with a proprietary immunostimulatory complex adjuvant. The sG vaccine has been shown to be cross-protective between NiV_M and HeV. There are other various vectored vaccine candidates that have been tested in animal models. Of these, the most studied by multiple groups is the VSV vector using a similar strategy to that being employed in Ebola virus vaccine candidates in current clinical trials, however the VSV vector used is not identical among studies. Additional vaccine vectors include RABV, CNPV ALVAC, AAV, MV, VEE, and NDV. All of these candidate vaccines utilize the NiV outer-membrane G and/or F proteins as target antigens to elicit neutralizing antibodies and give full protection in hamster [15], ferret [17], or AGM [19] models after a single injection without the use of adjuvants. A VSV-vectored vaccine has been shown to be cross-protective between NiV_B and NiV_M [17]. The remaining cross-protection studies have not been performed or published. Passive antibodies to NiV or HeV G and/or F have also been demonstrated to give protection against NiV [22].

Almost all published results have occurred within the last five years and are preliminary studies with small numbers of animals, and all of these candidates are from academic laboratories (Uniformed Services University of the Health Sciences [USU], University of Texas Medical Branch [UTMB], Yale University, Thomas Jefferson University [TJU], and University of Tokyo [UoT]) or government (United States [US] Centers for Disease Control and Prevention [CDC], Rocky Mountain Laboratories [RML], Canadian Food Inspection Agency [CFIA] National Center for Foreign Animal Diseases [NCFAD], Institut national de la santé et de la recherche médicale [INSERM], and Chinese Academy of Agricultural Sciences [CAAS] State Key Laboratory of Veterinary Biotechnology [SKLVB]), with the HeV sG vaccine also having vaccine pharma partners (e.g. Pfizer Animal Health, and Zoetis, Inc.).

5. Likelihood for financing

An effective NiV vaccine would likely find use primarily in the low and middle income countries where the virus is currently endemic. Vaccine financing could potentially be made available through mechanisms such as The Gates Foundation or Gavi, although there are potential impediments to this approach. Bangladesh and India are currently Gavi-eligible but other NiV-endemic countries such as Malaysia and the Philippines are not. Due to the current low incidence of disease and relatively early development status of vaccine candidates, it is unlikely that NiV vaccines would be selected for funding from these types of programs as a general childhood vaccine unless the vaccine was coupled with another, more common vaccine such as for MV. A non-coupled NiV vaccine for use primarily as a traveler's vaccine or for immunization of military recruits would likely have to be developed and funded by universities with government and eventual pharmaceutical partnering, in a similar fashion to the current Ebola virus vaccine candidates.

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