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Review

A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for a soluble glycoprotein vaccine to prevent disease caused by Nipah or Hendra viruses

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ABSTRACT

Auro Vaccines LLC has developed a protein vaccine to prevent disease from Nipah and Hendra virus infection that employs a recombinant soluble Hendra glycoprotein (HeV-sG) adjuvanted with aluminum phosphate. This vaccine is currently under clinical evaluation in a Phase 1 study. The Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) has prepared a standardized template to describe the key considerations for the benefit-risk assessment of protein vaccines. This will help key stakeholders to assess potential safety issues and understand the benefit-risk of such a vaccine platform. The structured and standardized assessment provided by the template may also help contribute to improved public acceptance and communication of licensed protein vaccines.

Contents

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1. Introduction

Protein vaccines generally comprise the viral surface antigen responsible for the stimulation of neutralizing antibodies [1]. They are typically recombinant-derived and highly purified. Peptides are also included in this category of vaccines and most of these are likely to be synthetic in nature. Examples of licensed protein vaccines include an influenza vaccine comprising highly purified recombinant hemagglutinin [2] and a herpes zoster vaccine with highly purified varicella zoster surface glycoprotein E antigen [3]. Many other protein vaccines such as HIV gp120 and gp140 have undergone clinical testing vaccines but are not yet licensed. Recombinant proteins have been used in vector or DNA prime and protein boost regimens, in particular for HIV vaccines [4]. Some recombinant viral antigens spontaneously assemble into virus-like particles (VLPs). These may be single or multi protein structures that are stable and more immunogenic compared to purified protein antigens. Examples of licensed vaccines containing recombinant VLPs include hepatitis B and human papillomavirus vaccines [5]. It should be highlighted that, in contrast to inactivated, live attenuated, and viral vectored vaccines, the manufacture of protein vaccines does not involve the cultivation of any live viruses and they do not contain any viral genomes. Therefore, their production and quality control are simpler, they are generally considered safer in cases where viruses can establish a persistent infection or are oncogenic and are feasible to manufacture even if the virus cannot be cultivated. Commercialized recombinant protein vaccines have been shown to be safe and efficacious, and their manufacture can be scaled-up with relative ease [6,7,8]. However, due to the limited immunogenicity of some protein-based vaccines in humans, their development has also focused on methods to enhance the immune response, through the use of adjuvants, optimizing the route or method of administration, and the use of a heterologous prime-boost strategies (see Table 1).

In particular, protein vaccines are likely to require a potent adjuvant that will direct the immune response to a predominantly Th1-type response. Adjuvants are not usually licensed per se and it is the adjuvanted vaccine that is granted marketing authorization. There are only a few different types of adjuvant used in commercial vaccines although many are under investigation and the availability of particular adjuvants may be limited. Whilst enhancing the immune response, adjuvants impart additional safety considerations to a vaccine that have to be carefully assessed [9]. BRAVATO intends that this template focuses on key questions related to the essential safety and benefit-risk issues relevant for the intrinsic properties of the vaccine components. Although we recognize that other aspects of manufacturing, quality, and implementation can play an important role in the safety of a vaccine and vaccination, we have chosen to keep some of those issues out of scope in order to summarize the most useful information for stakeholders.

2. Background

2.1. Epidemiology

Nipah virus (NiV) and Hendra virus (HeV) are closely related paramyxoviruses in the genus Henipavirus under the family Paramyxoviridae.

Since 1994, when HeV was first isolated in Hendra, Australia, there have been sporadic and minor outbreaks of disease in horses, and in humans with close contact to infected horses in Australia [10].

NiV and HeV are classified as biological safety level-4 (BSL4) viruses and possess several characteristics, such as the ability to be transmitted via aerosol, which make them adaptable for misuse as bioterror agents. They are listed as Category C biothreat agents by the NIH and CDC. Hendra virus (HeV), a paramyxovirus distantly related to measles virus, was isolated from fatal cases of respiratory disease in horses and humans in 1994 [10]. This first HeV outbreak, in the Brisbane suburb of Hendra Australia, resulted in the death of 13 horses and their trainer, and the non-fatal infection of a stable hand and seven other horses. At about the same time, in an unrelated incident 100 km north of Hendra, a man experienced a brief aseptic meningitis illness after caring for two horses and assisting at their necropsies; it was later shown the horses died from HeV. Thirteen months later, this individual suffered a recurrence of severe encephalitis characterized by uncontrolled focal and generalized epileptic-activity and died from the HeV acquired from the infected horses [11]. Genetic analysis of HeV confirmed that it was a member of the Paramyxoviridae [12,13,14]. Since 1994, 18 outbreaks of Hendra virus in horses have been recorded in Australia's Queensland and New South Wales [15]. Approximately 80% of the outbreaks occur in winter during the foaling season when veterinarians and horse owners have frequent contact with horses and their bodily fluids, increasing the chance of zoonotic disease transmission [16]. To date, there have only been seven documented human infections and four deaths from Hendra virus, although the concern of contracting the disease from infected horses remains high amongst veterinarians and others who work with the animals, due to the high mortality rate of the disease [16].

In 1998, an outbreak of encephalitis in people with close contact exposure to pigs began in Malaysia and Singapore. By mid-June 1999, more than 265 cases of encephalitis, including 105 deaths, had been reported in Malaysia and 11 cases of disease with one death in Singapore [17]. Electron microscopic, serologic, and genetic studies indicated that this virus was a paramyxovirus closely related to HeV. It was named Nipah virus (NiV) after the village in Malaysia from which one of the first isolates were obtained, from the cerebrospinal fluid of a fatal human case [18–22]. Due to their close relatedness, NiV and HeV were classified into a new genus, Henipavirus [23,24,25].

Following this large outbreak and the culling of over one million pigs, which were the amplifying hosts, there have been no further cases reported in these countries [13]. In 2001, NiV was identified as the cause of a human disease outbreak in Bangladesh. Since then, there have been repeated human disease outbreaks in Bangladesh [14,17], and a few outbreaks in India [18,19,20], although the isolated virus has been of a different genotype (NiVB) than the Malaysian isolate (NiVM) [21,22]. There was also a reported outbreak of human disease in the Philippines in 2014 caused by Nipah or a closely related virus [25]. In 2018, a Nipah disease outbreak occurred in northern Kerala, India, resulting in 17 deaths. In the investigation of this outbreak, the incubation period was an average of 9.5 days (6-14d) with a 91% fatality rate [26].

Fruit bats of the genus Pteropus have been identified as natural reservoirs of NiV and HeV. Considering the distribution of the fruit bats and epidemiologic evidence of more widespread infection in fruit bats, outbreaks of NiV are likely to continue in South and South-East Asian countries, including those without any outbreaks to date. Indirect transmission of NiV to humans may result from the ingestion of raw date palm sap contaminated by infectious bat excretions and there has also been evidence of direct human-to-human transmission of NiV [24,25,26].

2.2. The disease

The primary clinical manifestations of infections with both HeV and NiV are respiratory or neurologic leading to significant morbidity and mortality, with human case fatality of 38% (Malaysia and Singapore) and ≥75% (Bangladesh and India). In humans,

Table 1
Brighton Collaboration: Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines.

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines	
1. Authorship	**Information**
1.1 Author(s) and affiliation(s)	Susan Sciotto-Brown, John Eldridge, Michael Egan, Stefan Hamm, Demetrius Matassov, Tracy Chen, Alan Gordon et al
1.2 Date completed/updated	04 June 2021
2. Basic Vaccine information	**Information**
2.1 Vaccine name	HeV-sG-V
2.2 Protein type (e.g., molecular clamp, virus-like particle, peptide) and any special characteristics	The protein subunit HeV-sG is a soluble form of the Hendra virus attachment glycoprotein
2.3 Type of heterologous expression system used for antigen production (e.g., bacteria, yeast, plants, mammalian or insect cells, chemical synthesis)	The HeV-sG antigen is expressed in Human Embryonic Kidney (HEK293) cells
2.4 Adjuvant (if applicable)	Aluminum hydroxide
2.5 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g., preservatives (e.g., thimerosal, phenol, benzethonium chloride, 2-phenoxyethanol), complexing with polymers, encapsulation within microparticles, liposomes, depot formulations)	HeV-sG is absorbed to Aluminum hydroxide. It contains no preservative.
2.6 Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal)	HeV-sG-V is administered by intramuscular injection using needle and syringe.
3. Target Pathogen and Population	**Information**
3.1 What is the target pathogen?	Nipah Virus
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:	
• In healthy people	Infection with Nipah virus may be asymptomatic or can cause fever, chills, headache, and myalgia and can progress to severe respiratory distress and/or acute encephalitis. Nipah virus can also cause relapsing encephalitis in infected individuals for months to years following recovery from acute infection.
• In immunocompromised people	Similar to healthy people, with greater likelihood of severe disease
• In neonates, infants, children	There is little data regarding Nipah virus infection in children, however Nipah disease is found more in adults than in children (possibly because adults are more likely to work with infected animals or care for infected patients).
• During pregnancy and in the fetus	Unknown
• In elderly	Unknown, but expect that the elderly may be more susceptible to severe disease.
• In any other special populations	Unknown
3.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g., incubation period, communicable period, route/s of transmission, case fatality rate, transmissibility characteristics such as basic reproductive ratio (R_0), and spontaneous mutation)?	Onset of disease is typically 5-14 days after exposure[1] although it may incubate for up to 2 months[2]. Communicable period is expected to be during the incubation period thru resolution of symptoms.[3,4] Nipah virus infection can occur through contact with the droppings of infected animals, e.g., bats, pigs (directly, or from contaminated food) and from the body fluids of infected people. The case fatality rate has been between 40 and 100%. The R_0 is approx. 0.48, suggesting that Nipah virus is unlikely to cause a sustained human pandemic from person-to-person transmission.[5]
3.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast feeding), adult, elderly)	People who work with infected animals have the highest risk[3]. Adults are more susceptible to disease than children.[1]
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?	Neutralizing antibody protects against disease as shown in our preclinical challenge studies and by the successful use of the monoclonal antibody m102.4 in infected patients[6].
3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk	None
4. Characteristics of Antigen	**Information**
4.1 Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence ?	Yes. It also expected to be protective against Hendra virus.
4.2 What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	Studies in mice, ferrets, cats, dogs, horses, and monkeys have shown the ability of HeV-sG to elicit a protective immune response characterized by functional and neutralizing antibody responses. Preclinical studies using strongly neutralizing antibodies further emphasize the role of the humoral immune response in protecting from Nipah virus infections. There are currently no immunogenicity data available in humans.
4.3 Is there homology in the sequence of the vaccine antigen and human proteins?	No, HeV G is a viral attachment protein.
5. Adjuvant (if applicable)	**Information**

5.1 Describe the type of adjuvant, if it has been tested in humans, whether novel or commercialized, and if applicable, what other vaccines (preventive and therapeutic) are formulated with this adjuvant	This vaccine uses an aluminum hydroxide adjuvant Al(OH_3) which has a long history of safety in prophylactic vaccines including Hepatitis A and B, Diphtheria, Tetanus and Pneumococcal vaccines.
5.2 What is the evidence that an adjuvant improves/boosts/enhances the immune response?	The aluminum increases immunogenicity of this vaccine by up to 12-fold. It also helps stabilize the Drug Product tetramer: dimer: monomer ratio.
5.3 What is the mechanism of action of the adjuvant (if known)?	The mechanism is complex, including a depot effect of HeV-sG adsorbed to the aluminum hydroxide which allows for slower antigen release. It also causes a local inflammatory reaction which activates dendritic cells and activates complement[9]. Some studies indicate that aluminum hydroxide adjuvants activate caspase-1 and induce IL-1beta and IL-18 release[7].
5.4 How is the adjuvant formulated with the antigen?	The high dose of HeV-sG-V contains 100 mcg HeV-sG and 1 mg Al^{3+}, a 1:10 antigen /adjuvant ratio. The adjuvant is combined with the antigen during final formulation.
5.5 How might the adjuvant impact the safety profile of the vaccine?	The aluminum concentration of the highest dose considered for the clinic is near the upper limit allowed within FDA guidelines[8]. No safety issues are anticipated based on pre-clinical studies with this vaccine, and historical data of aluminum as an adjuvant.
5.6 Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen	The safety and potency of aluminum adjuvants has been established in man, in combination with many vaccines, over decades, involving billions of doses, and the accumulated experience represents an important and substantive "body of evidence". [9]
6. Delivery and Administration	**Information**
6.1 How might the vaccine formulation (antigen and adjuvant already formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?	Coformulation of the HeV-sG antigen and the aluminum adjuvant improves the immunogenicity of the vaccine. Coformulation minimizes the inconvenience and risk of contamination if the two were mixed immediately prior to administration.
6.2 If the vaccine is part of a heterologous prime-boost regimen, describe the regimen that this vaccine is a part of and the possible impact on safety	N/A; The Nipah vaccine is expected to be a single dose vaccine, with a possible homologous booster dose administered at 6-12M to enhance long-term protection (unpublished data).
6.3 Describe how components of the vaccine formulation that facilitate stability and delivery into cells (Section 2.5) may impact the safety profile of the vaccine	Aluminum hydroxide formulated vaccines have a long and positive safety record in vaccinology.[10]
6.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)	The 0.5mL dose is administered by intramuscular injection with needle and syringe. Safety risks can include local reactions at the injection site such as pain or tenderness, swelling or induration, and erythema.
* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purpose.	
7. Toxicology and Nonclinical	**Information**
7.1 What is known about biodistribution of the antigen in its final formulation and mode of administration in animal models?	Biodistribution studies were not conducted with this candidate and are not typically required for protein subunit vaccines.
7.2 How long does the vaccine antigen persist in vivo (may specify in tissue/serum; proximal/distal to site of administration)?	Unknown
7.3 What is the possible risk of autoimmunity or a harmful immune response?	Since HeV soluble glycoprotein is a viral attachment glycoprotein and shows no close homology to with any human protein, there is no foreseeable risk of autoimmunity or harmful immune response.
7.4 Summarize the preclinical safety data that support the use of this product in humans including any related information from similar products	Toxicology has been tested in New Zealand White rabbits. The vaccine was well-tolerated and transient changes were consistent with an expected mild inflammatory reaction.
7.5 Summarize the preclinical immunogenicity and efficacy data that support the use of this product in humans including any related information from similar products	See section 4.2
7.6 What is the evidence of disease enhancement or absence thereof *in vitro* or in animal models?[8]	None
7.7 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?	No
7.8 What is the evidence that the vaccine has generated a beneficial immune response in:	
• Small animal models?	Dose dependent IgG titers were generated in mice, rabbits, and ferrets. Two doses of 10mcg were shown to be protective against lethal challenge with both Nipah and Hendra viruses.
• Nonhuman primates (NHP)?	Two doses of 10 mcg were protective against lethal Nipah virus challenge in Ferrets and African Green Monkeys. A single 100 mcg dose was protective as rapidly as 7 days after inoculation.
8. Human Efficacy and Other Important Information	**Information**
8.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?	Challenge studies in African Green Monkeys indicate that two doses of 10 mcg or a single dose of 100 mcg can be protective against lethal challenge with wildtype Nipah

(*continued on next page*)

	virus after 7 days (unpublished data). In addition, a monoclonal antibody to HeV-sG (m102.4) has been shown to be protective against Nipah disease.[6]	
8.2 Describe other key information that may impact benefit-risk	None	
9. Adverse Event (AE) Assessment of the Vaccine Platform:	**Information**	
9.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately. _____	As of 28 May 2021 (NCT04199169), 11 humans have received two 10 mcg doses, 71 have received two 30 mcg doses, and 27 have received their first dose 100 mcg of the vaccine.	
9.2 Method(s) used for safety monitoring:	The safety monitoring in this first clinical study include: 1. local and systemic AEs for 6d following vax administration 2. abnormalities in clinical safety laboratories following initial vax administration 3. unsolicited AEs w/in 28d of vax admin 4. medically attended AEs and serious AEs thru last study visit.	
• Spontaneous reports/passive surveillance	Yes, see section 9.2	
• Diary	Yes	
• Other active surveillance	No	
9.3 What criteria were used for grading the AEs?		
• 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	Our AE grading scale was adapted from this 2007 FDA Guidance	
• If no criteria were used for grading, or if other metrics were employed, please describe:	N/A	
9.4 List and provide frequency of any or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):	No SAEs have been observed.	
9.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:	None to date.	
• Describe the control group: _____.	Saline placebo	
9.6. List and provide frequency of Adverse Events of Special Interest	None to date	
9.7 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes	
• Did it identify any safety issue of concern?	No (not related to the vaccine, however the study was paused due to COVID-19)	
• If so describe:		
10. Overall Risk Assessment	**Information**	
10.1 Please summarize key safety issues of concern identified to date, if any:	No safety concerns have been identified to date.	
• how should they be addressed going forward	Follow through careful monitoring in the clinic.	
10.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as: none, minimal, low, moderate, high, or unknown**
• healthy humans?	Expected to be minimal based on preclinical studies	Minimal
• immunocompromised humans?	Expected to be minimal based on preclinical studies	Minimal
• human neonates, infants, children?	Expected to be minimal but will assess in later pediatric dose escalation studies. Note that a lower dosage and/or improvements in formulation may allow for a lower quantity of aluminum to be administered	Minimal
• pregnancy and in the fetus in humans?	Expected to be minimal but will know better once a developmental and reproductive toxicology study has been conducted.	Minimal
• elderly?	Expected to be minimal	Minimal
• in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?	Expected to be minimal.	Minimal

infection with Hendra virus can cause mild clinical signs including fever, headache, drowsiness, and influenza-like symptoms. Severe infections are often fatal with respiratory and/or neurological signs (e.g., confusion, motor deficits and seizures). Relapsing encephalitis is possible after recovery from an acute infection and appears to be due to recrudescence of viral replication in the central nervous system [16]. NiV infection in humans may be complicated by encephalitis leading to disorientation and coma, either acutely, as a relapse, or even as a late onset manifestation of the infection. Animal infection studies in African green monkeys (AGM) have shown NiVB to be more pathogenic than NiVM, and ferret studies showed that NiVB infection resulted in increased oral shedding, a more rapid onset of productive infection, and higher levels of virus replication in the respiratory tract compared to NiVM. These observations may explain why more cases in Bangladesh and India had shorter incubation periods, more respiratory symptoms, greater human-to-human transmission, and higher case fatality risks [27].

2.3. The vaccine

There are currently no approved products that prevent or treat NiV or HeV infections in humans. An effective prophylactic NiV and HeV vaccine would find application with medical personnel and close contacts of cases during outbreaks in endemic areas, with laboratory workers engaged in NiV or HeV research, and with military and civilian personnel threatened by weaponized versions of the viruses. A Hendra vaccine is also needed for veterinarians and those who care for sick horses in areas where Hendra is endemic. Zoetis Australia Pty Ltd currently has a licensed veterinary vaccine, Equivac® HeV, which effectively prevents Hendra infection in

horses. Equivac HeV is based on the same HeV-sG immunogen as the proposed human Nipah vaccine, however the vaccine is made by a different manufacturing process, and has a different formulation, administration schedule, and adjuvant than proposed for the human vaccine.

Auro Vaccines has developed a vaccine to protect humans against Nipah and Hendra virus infection based on the soluble glycoprotein of the Hendra virus ectodomain (HeV-sG) developed by Christopher Broder's laboratory at Uniformed Services University, Bethesda, MD. Preclinical studies show that the administration of Auro Vaccines' adjuvanted HeV-sG elicits potent immune responses against both Nipah and Hendra virus infection.

Auro Vaccines' HeV-sG vaccine is currently under investigation in a Phase 1 clinical trial.

3. Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the Working Group. They do not necessarily represent the official positions of any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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