WHO Target Product Profiles for Nipah virus Vaccines

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Purpose of the document

Selected disease areas are identified as WHO priorities for product development. In the case of Nipah virus (NiV), target product profile development follows the selection of NiV as part of the WHO R&D Blueprint for Action to Prevent Epidemics.¹ The target audience includes vaccine scientists, product developers, manufacturers and funding agencies.

All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply. The criteria below lay out some of the considerations that will be relevant in WHO’s case-by-case assessments of NiV vaccines in the future.

None of the characteristics in the tables below dominates over any other. Therefore should a vaccine’s profile be sufficiently superior to the critical characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Vaccines which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO’s processes.

A generic description of WHO’s Vaccine Prequalification process can be found at the end of this document.

Acknowledgement

WHO gratefully acknowledges the many individuals and institutions that provided comments to the draft at the public consultation stage.

I. Background

Nipah virus (NiV) is an emerging pathogen first identified in 1999 in Malaysia, with cases also seen in Singapore, in an outbreak of acute encephalitis in pigs and humans. Since then, human NiV outbreaks have been reported in India and Bangladesh. While no new outbreaks have been reported in Malaysia and Singapore, repeated outbreaks have been noted in Bangladesh almost every year since 2001 in select districts with occasional outbreaks in neighbouring India.[1,2]

From 1998 to 2015, there have been at least 600 cases of NiV human infections, with case fatalities in later outbreaks in India and Bangladesh ranging between 43 and 100%. [3,4] Human to human transmission is particularly notable in the outbreaks in India and Bangladesh, accounting for 75% and 51% of cases respectively.[5,6] NiV infection has both a neurological and respiratory disease presentation. Respiratory involvement differs in prevalence between the outbreak in Malaysia (29%) and Bangladesh (75%). [7–9] Relapsing NiV encephalitis distinct from acute NiV encephalitis has been described and is estimated to occur in <10% of survivors. [10]

NiV is related to Hendra virus (HeV), another paramyxovirus which has been classified as a member of the genus Henipavirus. Pigs and horses have been implicated as potential multiplier hosts for NiV and HeV, respectively. The primary reservoir of NiV is fruit bats of the genus Pteropus. Pigs were the intermediate hosts in the outbreaks in Malaysia and Singapore, while in Bangladesh humans were infected as a result of consuming date palm sap that had been contaminated by infected fruit bats. [11] While not the focus of this document, there are approaches investigating veterinary vaccines and diagnostics for both NiV and HeV. [12–17]

This document describes the preferred and minimally acceptable profiles for a human vaccine for reactive/emergency use intended to prevent NiV disease in vaccinated individuals as well as interrupt chains of transmission to terminate an outbreak. Its use may be in populations experiencing an outbreak, in populations geographically close to an outbreak and at high risk for importation of NiV cases from areas experiencing an outbreak.

During the development of this TPP, a vaccine strategy intended for preventive use for health care workers was also considered. Health care workers have been affected by NiV infection in several outbreaks. [5,18–21] However, as most cases of secondary transmission have involved family and friends of infected individuals, priority was given to the development of a TPP for reactive use. There is a need for more information to better define the population for which a preventive use vaccine will be beneficial. Should data become available which identifies high risk groups for a preventive use vaccine, this TPP may be revised to include a second profile for preventive use. Some vaccine products may address both scenarios.

This TPP is the result of an ongoing consultation process with key stakeholders in the public and animal health, scientific, funding and manufacturer communities. It is hoped that the final versions will guide and prioritize the development of vaccines. As new scientific evidence is generated, these TPPs may require further review and revision.
Considerations:

Need for improved diagnostics. Timely implementation of a reactive vaccination strategy relies on effective diagnostic tests in addition to acute encephalitis syndromic surveillance in affected areas. Previous NiV outbreaks have mainly relied on IgM serology testing for detection of acute infection. Studies have shown that some patients confirmed by RT-PCR or viral isolation of NiV may not have detectable IgM. [5,22] Viral isolation is only performed in BSL-4 facilities. Detection of NiV RNA by PCR testing has been used in urine and cerebrospinal fluid (CSF) samples in acute infection. [5,22,23] NiV RNA has also been detected by PCR testing in saliva. (Hassan, MZ et al. Manuscript under review) In animal studies, NiV RNA was detected by RT-PCR in respiratory tract secretions earlier than in whole blood (day 3 vs day 5 post inoculation), particularly to ferrets infected with the NiV Bangladesh strain. Detection of NiV RNA in urine was not significant. Anti-NiV IgM response was noted from day 4 post inoculation. [24] There is a need for more information on kinetics of NiV detection in CSF, blood and non-blood samples to correctly identify all infected patients in different stages of the disease. This information will be important in the development of better diagnostic tests for NiV detection in various intended use settings.

Correlate of protection. Studies of vaccine immunogenicity and efficacy in non-human primate model covering both respiratory and CNS involvement will be needed. Early animal data indicate that neutralizing antibodies may be protective. [25,26]

Mathematical modelling of the potential impact of NiV vaccines with different efficacy profiles and administered in the different vaccination strategies is a priority to help refine desired characteristics. Current estimate of reproductive number is based on analysis of outbreaks in Bangladesh in 2001 to 2007. [6] A more current analysis of all outbreak data is needed to evaluate any change in the estimated reproductive number. NiV vaccine stockpile to respond to annual local outbreaks can be estimated based on previous outbreak epidemiology and estimated reproductive number. Possible changes in the virus[2] and non-virus independent factors (i.e., community density and interconnectivity, movement and spread to a major city, etc.) which would result in a larger outbreak should be considered and vaccine platforms with a surge capacity for rapid scalability of vaccine production would be ideal. Mathematical modelling may be useful in simulating these scenarios.
## II. Target Product Profile

For **reactive use in outbreak settings with rapid onset of immunity**

<table>
<thead>
<tr>
<th>Vaccine characteristic</th>
<th>Preferred</th>
<th>Critical or Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for use</td>
<td>For active immunization of at-risk persons in the area of an on-going outbreak for the prevention of NiV disease; to be used in conjunction with other control measures to curtail or end an outbreak</td>
<td>All healthy adults excluding pregnant women and lactating women at high risk of NiV disease</td>
</tr>
<tr>
<td>Target population</td>
<td>All age groups(^2) and populations at high risk of NiV disease</td>
<td>All healthy adults excluding pregnant women and lactating women at high risk of NiV disease</td>
</tr>
<tr>
<td>Safety/Reactogenicity</td>
<td>Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; ideally with only mild, transient adverse events related to vaccination and no serious AEs related to vaccination</td>
<td>Safety and reactogenicity whereby vaccine benefits clearly outweigh safety risks.</td>
</tr>
<tr>
<td>Measures of Efficacy</td>
<td>At least 70% efficacy in preventing NiV disease in healthy adults</td>
<td>Mathematical modelling is needed to inform the percentage of vaccine efficacy that could have a substantial impact if deployed appropriately during an ongoing outbreak.</td>
</tr>
<tr>
<td></td>
<td>Rapid onset of immunity (less than 2 weeks)</td>
<td>Rapid onset of immunity (preferably less than 4 weeks)</td>
</tr>
<tr>
<td></td>
<td>If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak, to the extent possible.</td>
<td>If demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a</td>
</tr>
</tbody>
</table>

\(^2\) Median age of NiV cases between 2004-2012 in Bangladesh was 25 years (range from 6 months to 75 years)
A standardized and relevant animal model together with clinical immunogenicity may be considered.\(^3\)\(^4\)

If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be generated during use in a future outbreak, to the extent possible.

<table>
<thead>
<tr>
<th>Dose regimen</th>
<th>Single-dose primary series</th>
<th>Primary series: No more than 2 doses, preference for short interval between doses and with some protection after first dose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durability of protection</td>
<td>Confers long lasting protection of at least 1 year</td>
<td>Confers protection of at least 3 months(^5)</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. Oral or non-parenteral route desirable</td>
<td>Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for PQ.</td>
</tr>
<tr>
<td>Coverage</td>
<td>Monovalent against Nipah virus with documentation of neutralization of NiV Bangladesh and NiV Malaysia</td>
<td></td>
</tr>
<tr>
<td>Product Stability and Storage</td>
<td>Shelf life of 5 years at 2-8°C. Additional data on thermostability at higher temperatures</td>
<td>Shelf life of at least 12 months at -20°C, and demonstration of at least 1-month stability at 2-8°C. The need for a preservative is determined and any</td>
</tr>
</tbody>
</table>

\(^3\) These considerations should be discussed between manufacturers and regulators early in the development process.

\(^4\) An attempt should be made to identify correlates of protection in an appropriate preclinical model.

\(^5\) The season during which yearly outbreaks occurs in Bangladesh covers a three month period. Several sporadic outbreaks are reported during this period.
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>The need for a preservative is determined and any issues are addressed.</td>
<td>Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container</td>
</tr>
<tr>
<td>Co-administration with other vaccines</td>
<td>The vaccine will be given as a stand-alone product not co-administered with other vaccines</td>
</tr>
<tr>
<td>Presentation</td>
<td>Vaccine is provided as a liquid product in mono-dose or multi-dose (10-20) presentations with a maximal dosage volume of 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy</td>
</tr>
<tr>
<td></td>
<td>Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose (10-20) presentations with a maximal dose volume of 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Multi-dose presentations should be formulated, managed and discarded in compliance with WHO’s multi-dose vial policy</td>
</tr>
<tr>
<td></td>
<td>Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent</td>
</tr>
<tr>
<td>Registration and Prequalification</td>
<td>Should be WHO pre-qualified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/BS/10.2155).</td>
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</tbody>
</table>

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6 http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf
II. Considerations on Programmatic suitability

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, the vaccine alliance, require WHO Prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Licensure by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The prequalification procedure is described in detail in the document Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies 

The WHO PQ process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification. (http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf

Considerations of Programmatic Suitability for Prequalification

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO’s preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. In addition, introduction of new vaccines that have higher volume, cold chain capacity or disposal demands have had a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.
References:

1. World Health Organization (WHO) Regional Office for South-East Asia. Nipah virus outbreaks in the WHO South-East Asia Region.


