



WHO Target Product Profile for Nipah virus Vaccine

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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

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¹ http://www.who.int/csr/research-and-development/priority_disease_list_review_short_summary_25Jan2017.pdf

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 NiV. There is currently a licensed horse vaccine for 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, and in populations geographically close to an outbreak and at high risk for importation of NiV cases.

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. A reactive use strategy may include vaccination of health care workers in the vicinity of an outbreak. There is a need for more information to better define the population for which a prophylactic 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 use cases.

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. The TPP also includes considerations which highlight technical challenges to vaccine development and limits to scientific and epidemiological understanding which are important for subsequent vaccine implementation.

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 either IgM serology or RT-PCR 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] and 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 in 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 models covering both respiratory and CNS involvement will be needed. Early animal data indicate that neutralizing antibodies may be protective. [25–27]

Mathematical modelling. Estimating 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. The current estimate of reproductive number is based on analysis of outbreaks in Bangladesh from 2001 to 2007.[6] A more current analysis of all outbreak data is needed to evaluate any change in the estimated reproductive number. A separate assessment for the development of a NiV vaccine stockpile will be needed, as with existing vaccine stockpiles. Factors in this assessment will include vaccine related factors such as effectiveness, time to onset of partial and full protection, formulation and administration, safety, dosing schedule and shelf life. [28] NiV vaccines for reactive use should be suitable for stockpiling. The size of the NiV vaccine stockpile can be estimated based on previous outbreak epidemiology and estimated reproductive number. Possible changes in the virus [2] and independent non-virus 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. Vaccine platforms with a surge capacity for rapid scalability of vaccine production would be ideal. Mathematical modelling may be useful in simulating these scenarios.

1 **II. Target Product Profile**2 For reactive use in outbreak settings with rapid onset of immunity

Vaccine characteristic	Preferred	Critical or Minimal
Indication for use	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	
Target population	All age groups ² and populations at high risk of NiV disease	All healthy adults excluding pregnant women and lactating women at high risk of NiV disease
Safety/Reactogenicity	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	Safety and reactogenicity whereby vaccine benefits clearly outweigh safety risks
Measures of Efficacy	<p>At least 90% efficacy in preventing NiV infection or disease in healthy adults</p> <p>Rapid onset of immune response likely to confer protection (less than 2 weeks after first dose)</p> <p>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</p>	<p>At least 70% efficacy in preventing NiV infection or disease in healthy adults, including some protection after first dose</p> <p>Rapid onset of immune response likely to confer protection (2 weeks after last dose)</p> <p>If demonstration of clinical efficacy is not feasible, pre-clinical immunogenicity and efficacy in a standardized and relevant animal model together with clinical immunogenicity may be considered^{3,4}</p> <p>If regulatory authorization is provided without clinical efficacy data, effectiveness data are to be</p>

² Median age of NiV cases between 2004-2012 in Bangladesh was 25 years (range from 6 months to 75 years).

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.

		generated during use in a future outbreak, to the extent possible
Dose regimen	Single-dose primary series	Primary series: No more than 2 doses, preference for short interval between doses and with some protection after first dose Homologous schedules preferred over heterologous prime-boost
Durability of protection	Confers long lasting protection of at least 1 year Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases	Confers protection of at least 6 months ⁵ Duration of protection may be inferred from immune kinetics, as well as documentation of breakthrough cases
Route of Administration	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for WHO PQ or needle-free delivery Oral or non-parenteral route desirable	Injectable (IM, ID or SC) using standard volumes for injection as specified in programmatic suitability for WHO PQ
Coverage	Monovalent against Nipah virus with documentation of neutralization of NiV Bangladesh and NiV Malaysia	
Product Stability and Storage	Shelf life of 5 years at 2-8°C Additional data on thermostability at higher temperatures The need for a preservative is determined and any issues are addressed Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary	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 issues are addressed Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container

⁵ The season during which yearly outbreaks occurs in Bangladesh covers a three month period. Several sporadic outbreaks are reported during this period.

	container	
Co-administration with other vaccines	The vaccine will be given as a stand-alone product not co-administered with other vaccines	
Presentation	<p>Vaccine is provided as a liquid product in mono-dose or multi-dose presentations with a maximal dosage volume of 0.5 mL</p> <p>For injectable vaccine product, multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy⁶</p>	<p>Vaccine is provided as a liquid or lyophilized product in mono-dose or multi-dose presentations with a maximal dose volume of 0.5 mL</p> <p>For injectable vaccine product, multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy</p> <p>Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent</p>
Registration and Prequalification	<p>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)</p> <p>Please refer to the considerations for Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the event that NiV is declared a public health emergency of international concern⁷</p>	

⁶ http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf

⁷ http://www.who.int/medicines/news/EUAL-vaccines_7July2015_MS.pdf?ua=1

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 (WHO TRS 978) available here: <http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf>.

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.

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