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Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: www.tandfonline.com/journals/ierv20

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To cite this article: Sol Kim, Hyolim Kang, Laura Skrip, Sushant Sahastrabuddhe, Ausraful Islam, Sung-Mok Jung, Juan F. Vesga, Akira Endo, W. John Edmunds & Kaja Abbas (2025) Progress and challenges in Nipah vaccine development and licensure for epidemic preparedness and response, Expert Review of Vaccines, 24:1, 183-193, DOI: 10.1080/14760584.2025.2476523

To link to this article: https://doi.org/10.1080/14760584.2025.2476523

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Published online: 11 Mar 2025.

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EXPERT REVIEW OF VACCINES
2025, VOL. 24, NO. 1, 183–193
https://doi.org/10.1080/14760584.2025.2476523

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PERSPECTIVE

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Progress and challenges in Nipah vaccine development and licensure for epidemic preparedness and response

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ABSTRACT

Introduction: Nipah virus is a high-consequence pathogen that causes sporadic outbreaks with high mortality, and there are currently no vaccines or therapeutics available for Nipah. Vaccine development against Nipah faces challenges due to its current epidemiology with limited outbreak sizes, which impedes the feasibility of conducting vaccine efficacy trials focused on disease endpoints.

Areas covered: We review the progress of Nipah vaccine candidates in human clinical trials and highlight the challenges in evaluating the vaccine efficacy due to the sporadic nature of Nipah outbreaks, given the epidemic potential of Nipah virus and its implications for pandemic preparedness. We examine the alternative regulatory pathways, including the US FDA's Animal Rule and EMA's conditional marketing authorization, which permit vaccine approval based on surrogate markers rather than efficacy data from the large-scale Phase-3 efficacy trials. The need for standardized immune surrogate markers is emphasized, alongside calls for international collaboration to develop such endpoints and manage stockpile strategies.

Expert opinion: We recommend alignment among vaccine developers, regulators, and global health stakeholders to incentivize Nipah vaccine development and approval through alternative regulatory pathways, as well as ensuring epidemic preparedness via strategic vaccine stockpiling and response through targeted deployment strategies.

ARTICLE HISTORY
Received 9 November 2024
Accepted 4 March 2025

KEYWORDS
Alternative regulatory pathway; Nipah virus; Henipavirus nipahense; pandemic preparedness; vaccine efficacy trials; vaccine licensure

1. Introduction

Nipah virus (Henipavirus nipahense) (NiV), a zoonotic, single-stranded negative-sense RNA virus belongs to the genus *Henipavirus* in the family *Paramyxoviridae*. It was first identified during outbreaks in Malaysia and Singapore in 1999, primarily affecting pig farmers and abattoir workers [1–3]. Nipah virus infections in humans can cause severe neurological and respiratory illnesses, with symptoms ranging from fever and headache to acute encephalitis [4]. Since 2001, sporadic but recurrent outbreaks have been reported, particularly in Bangladesh and India, where person-to-person transmission has been reported [5–8]. The initial outbreaks in Malaysia and Singapore were attributed to the NiV-Malaysia clade (NiV_M), which predominantly spread through close contact with infected pigs, with no evidence of sustained person-to-person transmission [9,10]. In contrast, outbreaks in Bangladesh and India have been linked to the NiV-Bangladesh clade (NiV_B), which exhibits a higher potential for person-to-person transmission. Studies indicate that 29% of cases in Bangladesh and over 50% in India resulted from person-to-person transmission, contrasting little to none in NiV_M outbreaks in Malaysia and Singapore [4,6,7,11,12]. Specifically, the consumption of date palm or date palm sap contaminated by bat excreta has been identified as a transmission source in the zoonotic cycle of Nipah virus in Bangladesh and India (West Bengal outbreak) [9,13]. In 2014, an outbreak in the Philippines demonstrated additional transmission routes involving the slaughter and consumption of infected horses, as well as person-to-person transmission [14]. In addition to the two primary clades (NiV-Malaysia and NiV-Bangladesh) causing human infections, phylogenetic analyses reveal a distinct Indian clade (NiV-India), though not yet classified as a separate strain from NiV Bangladesh [10,15,16].

The incubation period for Nipah virus infections in humans ranged from 4 days to 2 months in Malaysia, with 92% of patients experiencing an incubation period of two weeks or less, while it was shorter at 6 to 11 days in

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Article highlights

- Nipah vaccine candidates can leverage existing regulatory pathways such as the US FDA's Accelerated Approval Program, Animal Rule, and EMA's conditional marketing authorization or marketing authorization under exceptional circumstances. This requires early engagement between regulators, developers, and funders, as well as collaboration among regulatory authorities for successful licensure.
- Recommend a common master platform where regulators such as the US FDA, EMA, DGDA (Bangladesh), and CDSCO (India) can convene and align licensure requirements and conditions. This will help harmonize regulatory frameworks, streamline the licensure process among regulatory authorities, and enhance transparency for vaccine developers.
- Recommend alignment between vaccine developers and regulatory authorities to establish surrogate immune markers, such as neutralizing antibody titers based on animal models, as primary endpoints for vaccine efficacy. This will expedite the licensure process, especially when Phase-3 trials focused on disease endpoints are not feasible.
- Governments and stakeholders of pandemic preparedness should incentivize vaccine development through public-private partnerships, grants, tax incentives, and funding for research on low-incidence but high-consequence pathogens like Nipah virus.
- Developing global and national (especially for Bangladesh and India) strategies for vaccine stockpiling and identifying use cases for future Nipah vaccines will help expedite vaccine development and inform efficient vaccine deployment strategies.

Bangladesh [1,4,17]. The duration from symptom onset to death is rapid, with a mean of 8 days (range, 3–31 days) in Bangladesh and India [7]. The case fatality rate is high at 78% in Bangladesh and 93% in India [4,7]. The spectrum of clinical manifestations among severe cases includes broad cellular tropism affecting endothelial, neuronal, and respiratory epithelial cells [18–21]. Nipah virus has two surface glycoproteins critical for viral entry, making them key target platforms for vaccine development [22,23]. The attachment (G) glycoprotein facilitates binding to host cell receptors ephrin-B2 and ephrin-B3, while the fusion (F) glycoprotein mediates membrane fusion, allowing the virus to enter host cells [24–26].

2. Nipah vaccine candidates in human clinical trials

No Nipah vaccine has obtained licensure (as of November 2024), and four Nipah vaccine candidates are in Phase-1 clinical trials in healthy adults (Figure 1 and Table 1).

2.1. Viral vectored vaccines

The rVSVΔG-EBOV GP/NiV G is a live-attenuated, recombinant vesicular stomatitis virus (rVSV) vector vaccine [32,36]. This was developed via collaboration between Crozet Biopharma LLC, Public Health Vaccines Inc., the National Institute of Allergy and Infectious Diseases (NIAID), and the Coalition for Epidemic Preparedness Innovations (CEPI). rVSVΔG-EBOV GP/NiV G leverages the rVSV platform to express glycoproteins from both the Zaire strain of Ebola virus (EBOV glycoprotein) and NiV_B (NiV attachment (G) glycoprotein) viruses. The EBOV GP assists in fusion and cell entry, while the NiV G glycoprotein enables attachment to cell receptors, potentially blocking the attachment and infection of wild-type NiV. In a lethal challenge study with African green monkeys, rVSVΔG-EBOV GP/NiV G demonstrated robust protective efficacy by generating neutralizing antibodies. Specifically, a neutralizing antibody titer of ≥ 1:5 correlated with 100% survival, while a titer of ≥ 1:40 resulted in sterile immunity, effectively preventing both clinical illness and viral replication [32]. Although the precise level of protection has not been fully established, these immune correlates of protection represent a promising step with its progress through clinical trial phases. rVSVΔG-EBOV GP/NiV G is being tested in the US (NCT05178901, NCT06221813) for a single dose schedule with various dose levels [27,31]. The first Phase-1 clinical trial that evaluated safety and immunogenicity in 60 healthy adults was completed in 2023 (NCT05178901) [27]. The second Phase-1 clinical trial (Phase-1b) is ongoing, with the primary outcome measures of adverse events and immunogenicity [31].

The ChAdOx1 NipahB vaccine is a recombinant adenoviral vector vaccine [33,37]. This was developed by the University of Oxford in collaboration with CEPI. Utilizing

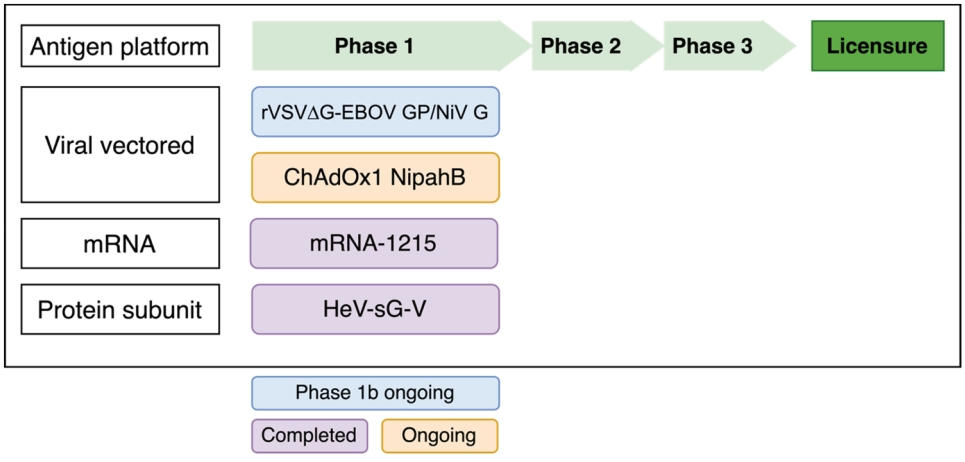

Figure 1. Nipah vaccine candidates in clinical trials. As of November 2024, there are Nipah vaccine candidates in Phase-1 clinical trials in humans. This figure uses investigational names.

Table 1. Nipah vaccine candidates in clinical trials.

Vaccine candidates	Platform	rVSV		Adenoviral vector	HeV-sG-V adjuvanted with Aluminum hydroxide	mRNA
	Developer	Public Health Vaccines Inc.		University of Oxford	Auro Vaccines	Vaccine Research Center, NIAID, ModernaTX
	Technology	Replicating viral vector		Non-replicating viral vector	Protein subunit	mRNA-LNPs
	Antigen	NiV_B glycoprotein G		NiV_B glycoprotein G	HeV-sG-V	Prefusion F/G* of NiV_M
Clinical trial	Status	Phase 1a	completed	Phase 1 ongoing	Phase 1 completed	Phase 1 completed
		Phase 1b	ongoing			
	Trial ID	Phase 1a	NCT05178901 [27]	ISRCTN87634044 [28]	NCT04199169 [29]	NCT05398796 [30]
		Phase 1b	NCT06221813 [31]			
	Number of participants	Phase 1a	60†	51†	192†	40†
		Phase 1b	120‡			
	Dose schedule	Single dose or two doses (dosing interval: 28 days)		Single dose or two doses (dosing interval: 84 days)	Two doses (dosing interval: 7 days or 28 days)	Single dose or two doses (dosing interval: 28 days)
	Outcome measures	Safety, immunogenicity		Safety, tolerability, immunogenicity	Safety, tolerability, immunogenicity	Safety, tolerability, immunogenicity
Preclinical study	NHP study	Complete protection in AGMs against NiV_B and NiV_M [32]		Complete protection in AGMs against NiV_B and NiV_M [33]	Complete protection in AGMs against NiV_B and NiV_M [34,35]	Not yet published
	Other animal study	Immunogenicity in Golden hamsters against NiV_B and NiV_M [36]		Immunogenicity in Syrian golden hamsters against NiV_B and NiV_M [37]	Immunogenicity in cats, ferrets, and horses against either NiV_B, NiV_M, or HeV [38–40]	Immunogenicity in mice [41,42]

rVSV, recombinant vesicular stomatitis virus vector. HeV-sG-V, Hendra virus soluble G glycoprotein vaccine. mRNA, Messenger ribonucleic acid. NIAID, National Institute of Allergy and Infectious Disease. LNPs, Lipid nanoparticles. NiV_B, Nipah virus Bangladesh clade. NiV_M, Nipah virus Malaysia clade. * Prefusion stabilized F component linked to G monomer. † Actual number of enrolled participants. ‡ Target number of enrolled participants. NHP, Non-human primate. AGMs, African Green Monkeys. HeV, Hendra virus.

the same chimpanzee adenovirus vector platform as the Oxford/AstraZeneca SARS-CoV-2 vaccine, this candidate incorporates the NiV glycoprotein gene to stimulate an immune response [33,37]. The ongoing Phase-1 clinical trial aims to evaluate the safety and immunogenicity of the ChAdOx1 NipahB vaccine in healthy adults in the UK, investigating single-dose and two-dose schedules (ISRCTN87634044) [28]. The ChAdOx1 NipahB vaccine was also tested in an African green monkey lethal challenge model, demonstrating NiV-G glycoprotein-specific IgG and neutralizing antibody responses after both single-dose and two-dose administration [33]. The NipahB G glycoprotein-specific serological response identified in the non-human primate (NHP) study is expected to play a key immunologic protective role and thus will be evaluated in the Phase-1 clinical trial as the secondary outcome measure.

2.2. mRNA vaccine

The mRNA-1215 vaccine is a lipid nanoparticle-formulated messenger RNA vaccine that targets the NiV_M strain [41,42]. This was developed by Moderna in collaboration with the Vaccine Research Center at NIAID. It encodes viral glycoproteins, specifically the fusion (F) and attachment (G) proteins of NiV, to induce an immune response. A Phase-1 clinical trial with a dose-escalation design, which measured the safety, tolerability, and antibody responses in healthy adults in the US (NCT05398796), was completed in September 2024 [30]. Preclinical studies demonstrated immunogenicity and neutralizing antibody responses against NiV_M, NiV_B, and cross-reactivity with Hendra virus (HeV) in mice models [41,42].

2.3. Protein subunit vaccine

The HeV-sG-V vaccine is designed to elicit protection against both NiV (Bangladesh and Malaysia strains) and Hendra virus (HeV) by utilizing the soluble G glycoprotein of HeV (HeV-sG), formulated with aluminum hydroxide adjuvant [34,35]. This was developed by Auro Vaccines LLC in collaboration with the Program for Appropriate Technology in Health (PATH) and CEPI. In preclinical studies, including NHP models, a single-dose regimen provided complete protection against lethal challenges from both Nipah and Hendra viruses by inducing neutralizing antibody responses and eliminating detectable viral RNA in vaccinated animals [34]. A Phase-1 clinical trial in 192 healthy adults in the US used a dose-escalation approach, evaluating both single-dose and two-dose regimens to evaluate the safety, tolerability, and immunogenicity of HeV-sG-V vaccine (NCT04199169) [29]. The findings from the Phase-1 clinical trial (available in preprints) suggest that a single administration of HeV-sG-V produced limited immunogenicity, while two doses induced strong neutralizing antibody responses [43]. The highest response rates were observed in participants who received two doses of 100 micrograms administered 28 days apart [43].

3. Feasibility of Phase-3 Nipah vaccine efficacy trials

Nipah outbreaks have been sporadic and limited in size, which does not allow sufficient sample size for conducting traditional Phase-3 efficacy trials with a randomized controlled design focused on disease end-points. A modeling study assessing the feasibility of conducting a Phase-3 vaccine trial in Bangladesh under current conditions inferred that it would take 516 years for a cluster-randomized ring vaccination trial, 43 years for a cluster-randomized mass vaccination trial, and seven years for an observational case-control study to complete at current levels of incidence [44]. Given these challenges, the need for alternative trial designs for efficacy evaluation, such as controlled animal studies for vaccine licensure, has been highlighted [11,32,44]. The low incidence of Nipah infections also indicates weak incentives for stakeholders such as vaccine developers, manufacturers, and governments of affected countries to invest in the research and development of medical countermeasures against Nipah, especially in resource-limited settings with competing priorities.

Given the high case fatality rate and the potential for Nipah virus to become more transmissible in the future, the World Health Organization (WHO) has listed Nipah as a priority pathogen, and CEPI and NIAID have also supported the research and development of Nipah vaccines from the epidemic and pandemic preparedness perspective [45,46]. For Nipah vaccine candidates to make progress for licensure and use, alternative approaches in testing the safety and efficacy are required. Key considerations include: (1) Identification and qualification of animal models that closely represent human disease endpoints, including harmonization of challenge doses and routes of administration; (2) Validation of immunological assays to establish reproducible surrogate endpoints; and (3) Dose selection and extrapolation from animal models to humans supported by pharmacokinetic and pharmacodynamic data [11,47]. Additionally, international stakeholders and WHO-listed (regulatory) authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as the national regulatory agencies of Bangladesh (Directorate General of Drug Administration) and India (Central Drugs Standard Control Organization) should explore the approval of Nipah vaccine through alternative regulatory approval pathways [48,49].

4. Regulatory challenges

Ebola virus was first identified in 1976 and emerged through zoonotic transmission, likely from fruit bats, and caused sporadic outbreaks in Africa until 2013 [50]. However, it was not until 2014–2016 that the Ebola virus triggered a major epidemic. During the 40 years leading up to this outbreak, the affected countries remained vulnerable, allowing the pathogen to evolve and eventually cause significant public health impact. The experience of the 2014–2016 Ebola epidemic led to improved global epidemic preparedness and response capabilities and spurred the establishment of CEPI in 2016 [51]. This aimed to change the pattern of short-term emergency response to a long-term view of epidemic preparedness and

innovations, including vaccine development against high-consequence pathogens like Nipah virus.

However, the sporadic nature of Nipah outbreaks limits the feasibility of traditional Phase-3 vaccine efficacy trials and necessitates alternative regulatory pathways that are suited for high-consequence pathogens with infrequent outbreaks. As an alternative to the traditional large-scale Phase-3 efficacy trial, CEPI considers the use of investigational stockpiles for priority pathogens to evaluate the vaccine efficacy in outbreak situations [52]. In the example of the 2014–2016 Ebola epidemic in West Africa, the emergency deployment of the Ebola virus vaccine (recombinant vesicular stomatitis virus-Zaire Ebola virus) during outbreaks allowed for efficacy assessments using the ring vaccination trial model [53,54]. While the ring vaccination trial design in Guinea showed high efficacy, providing a proof of concept for deploying investigational vaccines effectively during an outbreak, logistical and infrastructure issues hampered the trial implementation in other settings, such as Liberia [54,55].

Historically, vaccines against influenza, pneumococcal and meningococcal disease, smallpox, rabies, yellow fever, Japanese encephalitis, and COVID-19 have been approved using immune surrogates, not the conventional disease endpoints [32,56–58]. These approvals often involve comparing immune responses to those seen with preceding established vaccines to demonstrate similar or superior efficacy through non-inferiority clinical trials. However, this is not applicable for Nipah, where no preexisting licensed vaccine or defined immune correlates of protection with human clinical data exist to compare in non-inferiority clinical trials. Consequently, alternative regulatory pathways need to be explored, such as demonstrating efficacy through immune responses in animal models [35]. Immune protection is measured through experimental endpoints such as survival, disease progression, or viral load reduction and can be used as surrogates for human efficacy. A relevant example is the MVA-BN-Filo boost vaccine against Ebola virus disease, showing a strong correlation between protection in a non-human primate (NHP) model and human IgG-binding antibody levels using a combined approach of NHP studies and human clinical trials [59,60]. Nipah vaccines may be considered for a similar evaluation process, in which case a protective immunity level, such as neutralizing or binding antibody titers, needs to be defined to determine the surrogate of immune protection quantitatively. This alternative regulatory pathway offers a way forward for Nipah vaccines, but it is highly dependent on the regulatory willingness in the endemic countries to accept these alternative measures of efficacy. At the Nipah@20 meeting in 2019, the importance of early engagement and dialogue among national regulatory agencies was emphasized, leading to the formation of a multinational Nipah-focused regulatory group [47]. However, progress on this initiative was significantly delayed by the onset of the COVID-19 pandemic, which occurred shortly after the meeting. The following sections describe the alternative regulatory pathways that could potentially be used for the approval of Nipah vaccines in the development pipeline.

4.1. Food and drug administration (FDA) – United States

The US FDA's 'Accelerated Approval' pathway allows the use of surrogate endpoints to approve therapeutics and vaccines for fatal diseases in a shortened timeline compared to the traditional pathways [61,62]. Accelerated approvals may be subject to conducting post-licensure Phase-4 Nipah vaccine effectiveness studies to estimate vaccine effectiveness [61]. Additionally, the human challenge model could be considered to demonstrate vaccine efficacy in unique situations [61,63]. However, for highly lethal pathogens like Nipah, conducting human challenge trials poses safety and ethical concerns that make the approach highly unlikely [64].

Another possibility is the FDA's 'Animal Rule,' which offers a pathway for vaccine licensure where human efficacy studies are infeasible or unethical [65,66]. Under this rule, Phase I/II safety and immunogenicity trials are conducted in healthy humans, while efficacy is demonstrated in well-established animal models. These models must meet specific criteria – understanding the pathogen's mechanism of toxicity and prevention, demonstrating effects in predictive animal species, linking animal study endpoints to human benefits, and using pharmacokinetic and pharmacodynamic data to select effective human doses [65]. As of November 2024, two vaccines (Anthrax Vaccine Adsorbed Emergent BioSolutions and Anthrax Vaccine Adsorbed, Adjuvanted) for anthrax pre- and post-exposure prophylaxis have been approved through the Animal Rule [65–68]. For Nipah, key animal models include Syrian golden hamsters, ferrets, and African green monkeys, which reflect various aspects of human disease progression [11,20,69,70]. However, standardizing and validating immunoassays remains a significant hurdle, given the technical challenges of biosafety level 4 (BSL-4) containment for live virus experiments [11]. The development and acceptance of surrogate assays using pseudoviruses are potential solutions, requiring extensive validation and stakeholder support.

4.2. European medicines agency (EMA) – European union

The EMA guideline on clinical evaluation of vaccines stipulates non-traditional measures for estimating vaccine efficacy when conducting vaccine efficacy trials is infeasible [71]. As with the US FDA, consideration of a human challenge trial is specified under the EMA guideline, but poses safety and ethical concerns for Nipah vaccines [64]. Alternatively, the EMA guideline specifies the use of animal models in the form of either challenge studies or passive transfer studies using sera or T-cells from vaccinated animals or humans. When vaccines are authorized based on such data, approvals are granted through 'conditional marketing authorization' with conditions to conduct post-approval vaccine efficacy or effectiveness studies [71,72]. Conditional marketing authorizations are usually valid for one year and renewed annually. Additionally, the EMA's 'PRIME: priority medicines' scheme provides a platform for vaccine developers to receive enhanced support from the EMA from the early phases of vaccine development [73,74]. For Nipah vaccine candidates, entry into PRIME is a potential pathway toward vaccine

approval and aligns the manufacturer to generate the requisite data needed by the regulatory authority for vaccine approval in the absence of vaccine efficacy data measured through disease endpoints.

Marketing authorizations under 'exceptional circumstances' are distinct from conditional marketing authorizations in that they are granted when comprehensive data on a vaccine's efficacy and safety cannot be reasonably obtained [72,75]. This regulatory pathway is also relevant for Nipah vaccines, given the limited applicability of traditional efficacy trials for Nipah vaccines. Under exceptional circumstances, authorization is granted based on incomplete data due to the rarity of the disease, limitations in scientific knowledge, or ethical concerns regarding data collection. Unlike conditional marketing authorizations, where full data is expected to be eventually gathered, marketing authorizations under exceptional circumstances are not intended to lead to the completion of a full dossier. These authorizations are initially valid for five years, with the benefit-risk balance reassessed annually based on the evolving data.

4.3. Directorate general of drug administration (DGDA) – Bangladesh

DGDA is the national regulatory authority that evaluates vaccines' safety, efficacy, and quality for licensure approval in Bangladesh. Preclinical and clinical trials are specifically guided to be conducted as per the WHO Technical Report Series (TRS 927, 987, 924, 1004) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guidelines [76]. DGDA regulates 'special consideration for vaccine development' based on limited data when traditional efficacy trials are not feasible due to the rarity of the infection or lack of established immunological correlates of protection using animal studies, similar antigens, and functional immune response measurements [76].

4.4. Central drugs standard control organization (CDSCO) – India

CDSCO is the national regulatory authority that evaluates and approves vaccines in India under the Drugs & Cosmetics Act of 1940 and the Drugs & Cosmetics Rules of 1945. In 2022, the 'Conditional Market Authorization' category was created, which allows fast-track, conditional approval for drugs or vaccines with incomplete clinical trial data [77]. CDSCO requires specific dossiers for imported and locally manufactured vaccines. There is a need for an aligned registration procedure for domestic and foreign manufacturers, which will enhance access to vaccines, including future Nipah vaccines.

4.5. Chikungunya vaccine approval through an alternative regulatory pathway

The example of the first chikungunya vaccine approved by the US FDA (in November 2023), EMA (in May 2024), and Health Canada (in June 2024) represents a novel approach to approval using the surrogate threshold of protection established by the NHP passive transfer studies [78–81]. This serves as an option to consider for the potential alternative regulatory pathway for licensure of Nipah vaccine. Although chikungunya and Nipah viruses differ in their epidemiology, viral structure, and pathogenesis, the approval pathway for the chikungunya vaccine without a large-scale randomized controlled trial could be similar for a Nipah virus vaccine.

In a Phase-1 clinical trial involving 120 healthy adults, three dose levels of the chikungunya vaccine were tested, and the final dose was identified. This led to the establishment of a conservative surrogate threshold of a 50% micro-plaque reduction neutralization test titer of ≥ 150 (μPRNT50 ≥ 150), based on animal [82] and sero-epidemiological data [79,83]. An NHP passive transfer study, using the human sera from the Phase-1 clinical trial to 46 cynomolgus macaques, showed that this μPRNT50 ≥ 150 threshold conferred protection upon challenge [82]. Additionally, a seroprevalence study conducted in the Philippines demonstrated that a threshold of PRNT80 ≥ 10, approximately equivalent to a μPRNT50 ≥ 50, correlated with protection against symptomatic chikungunya infection in humans [83].

In the Phase-3 pivotal clinical study, which enrolled 362 healthy adults, the immunogenicity endpoint of μPRNT50 ≥ 150 was successfully met [79,84]. The chikungunya vaccine was approved for adults by the US FDA through the Accelerated Approval pathway and subsequently by the EMA under the PRIME scheme with conditional marketing authorization. The approvals are subject to conditions for conducting post-marketing Phase-4 real-world effectiveness studies and long-term evaluation of safety and immunogenicity in endemic countries within five years [78,79]. This case study highlights the importance of collaboration between vaccine developers and regulatory authorities in exploring alternative regulatory pathways for vaccine licensure.

The US FDA's Accelerated Approval pathway and Animal Rule and EMA's conditional marketing authorization pathways are adaptable to vaccines against high-consequence pathogens with sporadic outbreaks, such as Nipah virus. Similarly, Bangladesh's DGDA and India's CDSCO have provisions for considering limited clinical data and surrogate endpoints for vaccine approval [44,47]. Current Nipah vaccine candidates in Phase-1 clinical trials could pursue US or EU approvals based on robust animal model data and immunological markers and then seek parallel recognition by DGDA and CDSCO. Harmonization and alignment of regulatory expectations through international platforms would streamline vaccine approval processes, allowing the Nipah vaccine candidates to meet country-specific requirements by providing validated immunoassays, NHP challenge data, and post-approval commitments for effectiveness studies, ultimately facilitating timely licensure across multiple jurisdictions.

5. Nipah vaccine use case

A draft Target Product Profile (TPP) for Nipah vaccines by WHO specifies the use of vaccines as a reactive immunization strategy that is initiated to control ongoing outbreaks [85]. The TPP suggests the vaccine elicit immunity rapidly, preferably within

two weeks after a single dose, with high efficacy (i.e. >90%). While the TPP states reactive immunization of at-risk individuals during an outbreak and target population as all age groups, use cases are unclear. Defining target populations across different outbreak scenarios is critical to ensuring the efficient and strategic use of limited vaccine supplies and prioritizing those at the highest risk of infection.

Based on the observed spillover events and transmission patterns for Nipah, potential high-risk groups include individuals in close contact with bats, those who consume contaminated fruits and fruit products, and healthcare workers [7,17]. Additionally, evidence from Bangladesh suggests that the risk of Nipah infection through person-to-person transmission is associated with older age, exposure to body fluids, and prolonged contact with case-patients [17]. While these findings provide insights to help guide the identification of target populations for Nipah vaccination, further research is needed to develop Nipah vaccine use cases tailored to the evolving understanding of Nipah transmission dynamics and outbreak scenarios.

6. Nipah vaccine development and rollout strategies supported by modeling

Modeling can inform decision-making in pre- and post-licensure stages of Nipah vaccine development. In the pre-licensure stage, model-based simulations can explore and optimize clinical trial designs by factoring in varied epidemiological settings like transmission rates and outbreak scales, thereby enhancing the potential for trials to measure vaccine efficacy under unpredictable outbreak patterns [86,87]. In the post-licensure stage, modeling approaches can be applied to simulate outbreak scenarios under varied vaccination strategies, such as deploying investigational stockpiles, ring vaccination, or mass immunization campaigns, to predict their epidemiological impact and evaluate cost-effectiveness. Geospatial modeling can project the optimal vaccine stockpiling needs for outbreaks of emerging viruses based on spillover geography and human mobility networks [88]. These approaches have proven effective in guiding Ebola vaccine deployment and preparedness for cholera and influenza [89,90].

Modeling also serves as a valuable tool for broader epidemic and pandemic preparedness through extensions to project the potential impact of vaccination under the emergence of a novel pathogen with characteristics similar to Nipah (NiV-like Disease X), thereby providing strategic insights for vaccine development and strengthening pandemic preparedness and response against future outbreaks of NiV-like Disease X. For example, a mathematical modeling study, which investigated the potential health and economic impact of Lassa virus vaccine, projected the impact of achieving 100 Days Mission vaccination targets for a hypothetical Lassa-X pandemic scenario [91,92].

7. Conclusion

While the licensure of Nipah vaccines faces regulatory challenges due to the sporadic and low-incidence nature of outbreaks, we highlight recommendations to overcome these challenges. Alternative regulatory pathways, including the use of immune surrogate markers and animal models, present viable pathways toward approval of Nipah vaccines in the development pipeline. Harmonization of Nipah vaccine licensure requirements among national regulatory authorities (US FDA, EMA, DGDA (Bangladesh), and CDSCO (India)) will lower the regulatory burden of vaccine developers and expedite approval. In the context of epidemic preparedness, strategic stockpiling of Nipah vaccines and response through targeted deployment strategies will enhance the public health impact through prevention and control of Nipah outbreaks.

8. Expert opinion

Developing a Nipah vaccine poses unique challenges due to the sporadic nature of outbreaks, the high mortality rate, and the significant regulatory and logistical hurdles in developing a vaccine for a low-incidence but high-consequence (high case fatality rate) pathogen. Successfully overcoming these challenges could transform global epidemic preparedness and response approach, not only for Nipah virus but also as a model for other emerging infectious diseases of low incidence and high case fatality rate.

Advances in regulatory frameworks from major regulatory agencies, such as the US FDA's Animal Rule and EMA's conditional marketing authorization, provide mechanisms for approving vaccines based on limited efficacy data from surrogate markers rather than large-scale human efficacy trials focused on disease endpoints. In the context of Nipah virus, these pathways could expedite vaccine availability in the event of an outbreak, allowing public health responses to be more agile and effective. However, these advances also require significant preemptive engagement and coordination among national regulatory authorities in Bangladesh and India, as well as vaccine developers to use validated surrogate markers and conduct clinical trials during outbreaks to generate vaccine efficacy data. Establishing a common regulatory platform would facilitate the global alignment needed for such approvals. Without such frameworks in place, adoption into clinical practice would be delayed as developers face disparate requirements and lengthy review processes across different jurisdictions, thereby hindering the rapid use of vaccines.

Establishing an investigational stockpile for efficacy trials during outbreaks would play a pivotal role in gathering essential data on vaccine effectiveness. Such a stockpile could also act as a rapid-response tool through the WHO Emergency Use Listing (EUL) measure, allowing for immediate deployment in high-risk regions, even before definitive efficacy data is available. This approach has proven effective for diseases like Ebola and polio, where investigational vaccines have been deployed to mitigate outbreaks [93].

A critical area that requires advancement is the standardization of surrogate immune markers for efficacy. Currently, the lack of universally accepted endpoints for Nipah and similar pathogens hampers rapid vaccine licensure and limits the ability to compare results across trials. Solutions include establishing well-coordinated international research collaborations,

funding animal model studies, and supporting shared databases to accelerate the generation and validation of surrogate markers of protection. Furthermore, projecting the optimal stockpile size and preparing for stockpile management strategies should also be part of proactive epidemic preparedness. Addressing these limitations would pave the way for faster vaccine evaluation and deployment when outbreaks occur and prevent vaccine shortages.

From a pandemic preparedness perspective, harmonizing regulatory frameworks, optimizing stockpiling strategies, and incentivization models for Nipah vaccine development would serve as a blueprint for developing vaccines against other reemerging and newly emerging pathogens. Further, vaccine platforms that target viral families rather than individual pathogens would enhance efficiency in preparing for novel threats. In the next five to ten years, the global landscape of Nipah vaccine development is likely to evolve significantly with the support from WHO and CEPI as well as the CEPI 2.0 strategy with a shifted focus on the rapid vaccine development and licensure, rather than deploying pre-licensed vaccine stockpiles during outbreaks to estimate efficacy.

Acknowledgments

We thank Timothy Endy (CEPI) and Richard Jarman (CEPI) for the helpful discussions. This work was presented at the 2024 Symposium on Vaccinology: Science and Public Health, organized by the Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA) of the Japan Agency for Medical Research and Development (AMED), in collaboration with the Nagasaki University WISE Program, the London School of Hygiene & Tropical Medicine, and the Vaccine Research and Development Center Nagasaki University (VRDC).

Funding

This manuscript was funded by the Japan Agency for Medical Research and Development under Grant [JP223fa627004]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. S Kim, H Kang, L Skrip, A Endo, WJ Edmunds, and K Abbas are supported by the Japan Agency for Medical Research and Development under Grant [JP223fa627004]. S Kim is supported by the [Nagasaki University Doctoral Program for World-leading Innovative and Smart Education for Global Health, KENKYU SHIDO KEIHI]. H Kang and K Abbas are supported by the [Vaccine Impact Modelling Consortium] under Grant [INV-034281]. A Endo is supported by the [Japan Science and Technology Agency] under Grant [JPMJPR22R3]; the [Japan Society for the Promotion of Science] under Grant [JP22K17329]; and the [National University of Singapore Start-Up Grant]. S-m Jung is supported by the [Centers for Disease Control and Prevention Safety and Healthcare Epidemiology Prevention Research Development program] under Grant [200-2016-91781].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

S Kim and K Abbas conceptualized and designed the study. S Kim wrote the original draft of the manuscript. All authors contributed to the interpretation of the work, critical review of important intellectual content, and manuscript editing. All authors had final responsibility for the decision to submit for publication.

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