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PERSPECTIVE



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.

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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 $\geq 1:5$ correlated with 100% survival, while a titer of $\geq 1:40$ 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

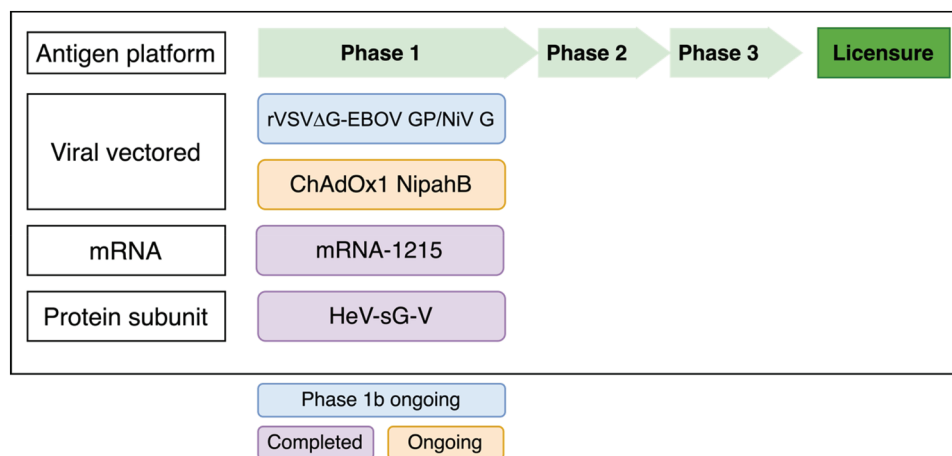


Figure 1. Nipah vaccine candidates in clinical trials. As of November 2024, there are Nipah vaccine candidates in Phase-1 clinical trials in humans. This figure uses investigational names.

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
Clinical trial	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
	Status	Phase 1a completed Phase 1b ongoing	Phase 1 ongoing	Phase 1 completed	Phase 1 completed
	Trial ID	Phase 1a NCT05178901 [27] Phase 1b NCT06221813 [31]	ISRCTN87634044 [28]	NCT04199169 [29]	NCT05398796 [30]
Preclinical study	Number of participants	Phase 1a 60 [†] Phase 1b 120 [†]	51 [†]	192 [†]	40 [†]
	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
	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	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 ($\mu\text{PRNT}_{50} \geq 150$), 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 $\mu\text{PRNT}_{50} \geq 150$ threshold conferred protection upon challenge [82]. Additionally, a seroprevalence study conducted in the Philippines demonstrated that a threshold of $\text{PRNT}_{80} \geq 10$, approximately equivalent to a $\mu\text{PRNT}_{50} \geq 50$, 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 $\mu\text{PRNT}_{50} \geq 150$ 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.

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Declaration of interest

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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.

References

Papers of special note have been highlighted as: • of interest •• of considerable interest

- Goh KJ, Tan CT, Chew NK, et al. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *N Engl J Med*. 2000;342(17):1229–1235. doi: [10.1056/NEJM200004273421701](#)
- Paton NI, Leo YS, Zaki SR, et al. Outbreak of Nipah-virus infection among abattoir workers in Singapore. *Lancet*. 1999;354(9186):1253–1256. doi: [10.1016/S0140-6736\(99\)04379-2](#)
- Gurley ES, Montgomery JM, Hossain MJ, et al. Person-to-person transmission of Nipah virus in a Bangladeshi community. *Emerg Infect Dis*. 2007;13(7):1031–1037. doi: [10.3201/eid1307.061128](#)
- Ang BS, Lim TC, Wang L, et al. Nipah virus infection. *J Clin Microbiol*. 2018;56(6):10.1128/jcm.01875–17. doi: [10.1128/JCM.01875-17](#)
- Chadha M, Comer J, Lowe L, et al. Nipah virus-associated encephalitis outbreak, Siliguri, India. *Emerg Infect Dis*. 2006;12(2):235. doi: [10.3201/eid1202.051247](#)
- Arun Kumar G, Chandni R, Mourya DT, et al. Outbreak investigation of nipah virus disease in Kerala, India, 2018. *J Infect Dis*. 2019;219(12):1867–1878. doi: [10.1093/infdis/jiy612](#)
- Hegde ST, Lee KH, Styczynski A, et al. Potential for person-to-person transmission of henipaviruses: a systematic review of the literature. *J Infect Dis*. 2024;229(3):733–742. doi: [10.1093/infdis/jiad467](#)
- Montgomery JM, Hossain MJ, Gurley E, et al. Risk factors for nipah virus Encephalitis in Bangladesh. *Emerg Infect Dis*. 2008;14(10):1526. doi: [10.3201/eid1410.060507](#)
- Luby SP, Gurley ES, Hossain MJ. Transmission of human infection with Nipah virus. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2009;49(11):1743–1748. doi: [10.1086/647951](#)
- AbuBakar S, Chang L-Y, Ali ARM, et al. Isolation and molecular identification of Nipah virus from pigs. *Emerg Infect Dis*. 2004;10(12):2228–2230. doi: [10.3201/eid1012.040452](#)
- Moore KA, Mehr AJ, Ostrowsky JT, et al. Measures to prevent and treat Nipah virus disease: research priorities for 2024–29. *Lancet Infect Dis [Internet]*. 2024 [cited 2024 Jul 9];24(11):e707–e717. doi: [10.1016/S1473-3099\(24\)00262-7](#)
- Satter SM, Aquib WR, Sultana S, et al. Tackling a global epidemic threat: Nipah surveillance in Bangladesh, 2006–2021. *PLoS Negl Trop Dis*. 2023;17(9):e0011617. doi: [10.1371/journal.pntd.0011617](#)
- Islam MS, Sazzad HMS, Satter SM, et al. Nipah virus transmission from bats to humans associated with drinking traditional liquor made from date palm sap, Bangladesh, 2011–2014. *Emerg Infect Dis*. 2016;22(4):664. doi: [10.3201/eid2204.151747](#)
- Ching PK, de Los Reyes VC, Sucaldito MN, et al. Outbreak of henipavirus infection, Philippines, 2014. *Emerg Infect Dis*. 2015;21(2):328. doi: [10.3201/eid2102.141433](#)
- De Campos GM, Cella E, Kashima S, et al. Updated insights into the phylogenetics, phylodynamics, and genetic diversity of Nipah virus (NiV). *Viruses*. 2024;16(2):171. doi: [10.3390/v16020171](#)
- Yadav PD, Sahay RR, Balakrishnan A, et al. Nipah virus outbreak in Kerala State, India amidst of COVID-19 pandemic. *Front Public Health*. 2022;10:818545. doi: [10.3389/fpubh.2022.818545](#)
- Nikolay B, Salje H, Hossain MJ, et al. Transmission of nipah virus — 14 years of investigations in Bangladesh. *N Engl J Med*. 2019;380(19):1804–1814. doi: [10.1056/NEJMoa1805376](#)
- Chua KB, Bellini WJ, Rota PA, et al. Nipah virus: a recently emergent deadly paramyxovirus. *Science*. 2000;288(5470):1432–1435. doi: [10.1126/science.288.5470.1432](#)

19. Wong KT, Shieh W-J, Kumar S, et al. Nipah virus infection: pathology and pathogenesis of an emerging paramyxoviral zoonosis. *Am J Pathol.* 2002;161(6):2153–2167. doi: [10.1016/S0002-9440\(10\)64493-8](https://doi.org/10.1016/S0002-9440(10)64493-8)
20. Geisbert TW, Daddario-DiCaprio KM, Hickey AC, et al. Development of an acute and highly pathogenic nonhuman primate model of nipah virus infection. *PLOS ONE.* 2010;5(5):e10690. doi: [10.1371/journal.pone.0010690](https://doi.org/10.1371/journal.pone.0010690)
21. Dawes BE, Freiberg AN. Henipavirus infection of the central nervous system. *Pathog Dis.* 2019;77(2):ftz023. doi: [10.1093/femspd/ftz023](https://doi.org/10.1093/femspd/ftz023)
22. Erbar S, Diederich S, Maisner A. Selective receptor expression restricts Nipah virus infection of endothelial cells. *Viol J.* 2008;5(1):142. doi: [10.1186/1743-422X-5-142](https://doi.org/10.1186/1743-422X-5-142)
23. Maisner ANJ, Weingartl H, Weingartl H. Organ- and endotheliotropism of Nipah virus infections in vivo and in vitro. *Thromb Haemost.* 2017;102(12):1014–1023. doi: [10.1160/TH09-05-0310](https://doi.org/10.1160/TH09-05-0310)
24. Harcourt BH, Tamin A, Halpin K, et al. Molecular characterization of the polymerase gene and genomic termini of Nipah virus. *Virology.* 2001;287(1):192–201. doi: [10.1006/viro.2001.1026](https://doi.org/10.1006/viro.2001.1026)
25. Eaton BT, Broder CC, Middleton D, et al. Hendra and Nipah viruses: different and dangerous. *Nat Rev Microbiol.* 2006;4(1):23–35. doi: [10.1038/nrmicro1323](https://doi.org/10.1038/nrmicro1323)
26. Negrete OA, Levroney EL, Aguilar HC, et al. EphrinB2 is the entry receptor for Nipah virus, an emergent deadly paramyxovirus. *Nature.* 2005;436(7049):401–405. doi: [10.1038/nature03838](https://doi.org/10.1038/nature03838)
27. Study details | a phase 1 study to evaluate safety & immunogenicity of rVSV-nipah virus vaccine candidate PHV02 in healthy adult subjects | ClinicalTrials.gov [Internet]. [cited 2024 Jul 20]. Available from: <https://clinicaltrials.gov/study/NCT05178901?cond=Nipah%20Virus%20Infection&intr=Vaccine&rank=4>
28. ISRCTN. ISRCTN87634044: a study of a new vaccine against Nipah virus in adults aged 18 to 55 years [internet]. [cited 2024 Jul 20]. Available from: <https://www.isrctn.com/ISRCTN87634044>
29. Study details | safety and immunogenicity of a nipah virus vaccine | ClinicalTrials.gov [Internet]. [cited 2024 Jul 22]. Available from: <https://clinicaltrials.gov/study/NCT04199169?cond=Nipah%20Virus%20Infection&intr=Vaccine&rank=1>
30. Study details | dose escalation, open-label clinical trial to evaluate safety, tolerability and immunogenicity of a Nipah virus (NiV) mRNA vaccine, mRNA-1215, in healthy adults | ClinicalTrials.gov [Internet]. [cited 2024 Jul 22]. Available from: <https://clinicaltrials.gov/study/NCT05398796?cond=Nipah%20Virus%20Infection&intr=Vaccine&rank=3>
31. Study details | study to evaluate safety and immunogenicity of a prime-boost regimen of rVSV-nipah virus vaccine candidate PHV02 in healthy adult subjects | ClinicalTrials.gov [Internet]. [cited 2024 Jul 20]. Available from: <https://clinicaltrials.gov/study/NCT06221813?cond=Nipah%20Virus%20Infection&page=1&rank=2>
32. Monath TP, Nichols R, Feldmann F, et al. Immunological correlates of protection afforded by PHV02 live, attenuated recombinant vesicular stomatitis virus vector vaccine against Nipah virus disease. *Front Immunol.* 2023;14:1216225. doi: [10.3389/fimmu.2023.1216225](https://doi.org/10.3389/fimmu.2023.1216225)
33. van Doremalen N, Avanzato VA, Goldin K, et al. ChAdOx1 NiV vaccination protects against lethal Nipah Bangladesh virus infection in African green monkeys. *NPJ Vaccines.* 2022;7(1):171. doi: [10.1038/s41541-022-00592-9](https://doi.org/10.1038/s41541-022-00592-9)
34. Geisbert TW, Bobb K, Borisevich V, et al. A single dose investigational subunit vaccine for human use against Nipah virus and Hendra virus. *NPJ Vaccines.* 2021;6(1):23. doi: [10.1038/s41541-021-00284-w](https://doi.org/10.1038/s41541-021-00284-w)
35. Geisbert JB, Borisevich V, Prasad AN, et al. An intranasal exposure Model of lethal nipah virus infection in African green monkeys. *J Infect Dis.* 2020;221(Suppl 4):S414–S418. doi: [10.1093/infdis/jiz391](https://doi.org/10.1093/infdis/jiz391)
- **This study establishes a more natural non-human primate model for Nipah virus by using intranasal exposure through a laryngeal mask airway mucosal atomization device, leading to uniformly lethal outcomes in African green monkeys that closely resemble human infection, aiding in vaccine and treatment testing.**
36. Monath TP, Nichols R, Tussey L, et al. Recombinant vesicular stomatitis vaccine against Nipah virus has a favorable safety profile: Model for assessment of live vaccines with neurotropic potential. *PloS Pathog.* 2022;18(6):e1010658. doi: [10.1371/journal.ppat.1010658](https://doi.org/10.1371/journal.ppat.1010658)
37. van Doremalen N, Lambe T, Sebastian S, et al. A single-dose ChAdOx1-vectored vaccine provides complete protection against Nipah Bangladesh and Malaysia in Syrian golden hamsters. *PloS Negl Trop Dis.* 2019;13(6):e0007462. doi: [10.1371/journal.pntd.0007462](https://doi.org/10.1371/journal.pntd.0007462)
38. McEachern JA, Bingham J, Cramer G, et al. A recombinant subunit vaccine formulation protects against lethal Nipah virus challenge in cats. *Vaccine.* 2008;26(31):3842–3852. doi: [10.1016/j.vaccine.2008.05.016](https://doi.org/10.1016/j.vaccine.2008.05.016)
39. Pallister JA, Klein R, Arkinstall R, et al. Vaccination of ferrets with a recombinant G glycoprotein subunit vaccine provides protection against Nipah virus disease for over 12 months. *Viol J.* 2013;10(1):237. doi: [10.1186/1743-422X-10-237](https://doi.org/10.1186/1743-422X-10-237)
40. Middleton D, Pallister J, Klein R, et al. Hendra virus vaccine, a one health approach to protecting horse, human, and environmental health. *Emerg Infect Dis.* 2014;20(3):379. doi: [10.3201/eid2003.131159](https://doi.org/10.3201/eid2003.131159)
41. Loomis RJ, Stewart-Jones GBE, Tsybovsky Y, et al. Structure-based design of nipah virus vaccines: a generalizable approach to paramyxovirus immunogen development. *Front Immunol.* 2020;11:842. doi: [10.3389/fimmu.2020.00842](https://doi.org/10.3389/fimmu.2020.00842)
42. Loomis RJ, DiPiazza AT, Falcone S, et al. Chimeric fusion (F) and attachment (G) glycoprotein antigen delivery by mRNA as a candidate nipah vaccine. *Front Immunol* [Internet]. 2021;12:12. doi: [10.3389/fimmu.2021.772864](https://doi.org/10.3389/fimmu.2021.772864)
43. Frenck R, Naficy A, Feser J, et al. Safety and immunogenicity of a nipah virus vaccine (hev-sg-v) in adults: a single-centre, randomised, Observer-Blind, placebo-controlled, phase 1 study Available from: <https://ssrn.com/abstract=4845156>
- **This preprint provides the findings from the Phase-1 clinical trial in healthy adults for measuring the safety and immunogenicity of the HeV-sG-V vaccine.**
44. Nikolay B, Ribeiro Dos Santos G, Lipsitch M, et al. Assessing the feasibility of Nipah vaccine efficacy trials based on previous outbreaks in Bangladesh. *Vaccine.* 2021;39(39):5600–5606. doi: [10.1016/j.vaccine.2021.08.027](https://doi.org/10.1016/j.vaccine.2021.08.027)
- **This study assessed the feasibility of Nipah vaccine efficacy trials with different study designs using mathematical modeling and highlighted the challenges in conducting the efficacy trials under current Nipah virus epidemiology.**
45. Pathogens prioritization: a scientific framework for epidemic and pandemic research preparedness [Internet]. World Health Organization. [cited 2024 Aug 12]. Available from: https://cdn.who.int/media/docs/default-source/consultation-rdb/prioritization-pathogens-v6final.pdf?sfvrsn=c98effa7_7&download=true
46. Noad RJ, Simpson K, Fooks AR, et al. UK vaccines network: mapping priority pathogens of epidemic potential and vaccine pipeline developments. *Vaccine.* 2019;37(43):6241–6247. doi: [10.1016/j.vaccine.2019.09.009](https://doi.org/10.1016/j.vaccine.2019.09.009)
47. Gómez Román R, Wang L-F, Lee B, et al. Nipah@20: lessons learned from another virus with pandemic potential. *mSphere* [Internet]. mSphere. 2020 [cited 2024 Apr 22];5(4). doi: [10.1128/msphere.00602-20](https://doi.org/10.1128/msphere.00602-20)
48. WHO-Listed authority (WLA) [Internet]. [cited 2024 Dec 17]. Available from: <https://www.who.int/initiatives/who-listed-authority-reg-authorities>
49. Swenson J, Disbrow G, Johnson RA. How global collaboration can improve the medical countermeasure life cycle for infectious disease outbreaks. *J Infect Dis.* 2024;230(1):e1–e3. doi: [10.1093/infdis/jiae017](https://doi.org/10.1093/infdis/jiae017)
50. Judson SD, Munster VJ. The multiple origins of ebola disease outbreaks. *J Infect Dis.* 2023;228(Suppl 7):S465–S473. doi: [10.1093/infdis/jiad352](https://doi.org/10.1093/infdis/jiad352)

51. Gouglas D, Christodoulou M, Plotkin SA, et al. CEPI: driving progress toward epidemic preparedness and response. *Epidemiol Rev.* 2019;41(1):28–33. doi: 10.1093/epirev/mxz012
52. CEPI Equitable Access Framework [Internet]. CEPI; 2023. Available from: https://static.cepi.net/downloads/2024-03/CEPI_Equitable%20Access%20Framework_May%202023_0.pdf
53. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola ça Suffit!). *Lancet Lond Engl.* 2017;389(10068):505–518. doi: 10.1016/S0140-6736(16)32621-6
54. Chappell KJ, Watterson D, Coyne CB. Fighting Ebola: a window for vaccine Re-evaluation? *PLoS Pathog.* 2017;13(1):e1006037. doi: 10.1371/journal.ppat.1006037
55. Larson GS, Baseler BR, Hoover ML, et al. Conventional wisdom versus actual outcomes: challenges in the conduct of an Ebola vaccine trial in Liberia during the international public health emergency. *Am Soc Trop Med Hyg.* 2017;97(1):10–15. doi: 10.4269/ajtmh.16-1015
56. Gu W, Li J, Zhu F. Immunologic surrogate of protection for inactivated enterovirus 71 vaccines. 2017 [Internet]; p. 1.
57. Markoff L. Points to consider in the development of a surrogate for efficacy of novel Japanese encephalitis virus vaccines. *Vaccine.* 2000;18:26–32. doi: 10.1016/S0264-410X(00)00038-4
58. FDA. Research C for DE and. Table of surrogate endpoints that were the basis of drug approval or licensure. [Internet]. 2022 [cited 2024 Nov 9].
59. Roozendaal R, Hendriks J, Van Effelterre T, et al. Nonhuman primate to human immunobridging to infer the protective effect of an Ebola virus vaccine candidate. *NPJ Vaccines* [Internet]. 2020;5(1). doi: 10.1038/s41541-020-00261-9
60. McLean C, Dijkman K, Gaddah A, et al. Persistence of immunological memory as a potential correlate of long-term, vaccine-induced protection against Ebola virus disease in humans. *Front Immunol* [Internet]. 2023;14:14. doi: 10.3389/fimmu.2023.1215302
61. FDA. Vaccines. 2024. [Internet] [cited 2024 Sep 4]. Available from: <https://www.fda.gov/vaccines-blood-biologics/vaccines>
62. Singh JA, Upshur REG. The granting of emergency use designation to COVID-19 candidate vaccines: implications for COVID-19 vaccine trials. *Lancet Infect Dis.* 2021;21(4):e103–e109. doi: 10.1016/S1473-3099(20)30923-3
63. Baylor NW. Human challenge studies for vaccine development. In: Bagnoli F, Del Giudice G, Phogat S, et al., editors. *Hum chall stud vaccine dev* [Internet]. Cham: Springer Nature Switzerland; 2024. p. 33–40. doi: 10.1007/82_2021_239
64. Hope T, McMillan J. Challenge studies of human volunteers: ethical issues. *J Med Ethics.* 2004;30(1):110–116. doi: 10.1136/jme.2003.004440
65. FDA. Animal Rule Approvals [Internet]. 2023 [cited 2024 Aug 19]. Available from: <https://www.fda.gov/drugs/nda-and-bla-approvals/animal-rule-approvals>
66. Burns DL. Licensure of vaccines using the animal rule. *Curr Opin Virol.* 2012;2(3):353–356. doi: 10.1016/j.coviro.2012.01.004
67. Beasley DWC, Brasel TL, Comer JE. First vaccine approval under the FDA animal rule. *NPJ Vaccines.* 2016;1(1):16013. doi: 10.1038/nnpjvaccines.2016.13
68. Sullivan NJ, Martin JE, Graham BS, et al. Correlates of protective immunity for Ebola vaccines: implications for regulatory approval by the animal rule. *Nat Rev Microbiol.* 2009;7(5):393–400. doi: 10.1038/nrmicro2129
69. Price A, Sizemore D, Hassell T, et al. Nipah virus assays and animal models for vaccine development [Internet]. 2021. Available from: https://media.tghn.org/medialibrary/2021/02/Nipah_Virus_Assays_and_Animal_Models_for_Vaccine_Development_final.pdf
70. De Wit E, Munster VJ. Animal models of disease shed light on Nipah virus pathogenesis and transmission. *J Pathol.* 2015;235(2):196–205. doi: 10.1002/path.4444
71. European Medicines Agency. Guideline on clinical evaluation of vaccines [Internet]. 2023 [cited 2024 Jul 1]. Available from: <https://www.ema.europa.eu/en/clinical-evaluation-new-vaccines-scientific-guideline>
72. Schuster Bruce C, Brhlikova P, Heath J, et al. The use of validated and nonvalidated surrogate endpoints in two European Medicines Agency expedited approval pathways: a cross-sectional study of products authorised 2011–2018. *PLoS Med.* 2019;16(9):e1002873. doi: 10.1371/journal.pmed.1002873
73. Neez E, Hwang TJ, Sahoo SA, et al. European Medicines agency's priority Medicines scheme at 2 years: an evaluation of clinical studies supporting eligible drugs. *Clin Pharmacol Ther.* 2020;107(3):541–552. doi: 10.1002/cpt.1669
74. PRIME: priority medicines | European medicines Agency. [Internet]. [cited 2024 Jul 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/prime-priority-medicines>
75. Exceptional circumstances | European medicines agency (EMA) [Internet]. [cited 2024 Aug 24]. Available from: <https://www.ema.europa.eu/en/glossary-terms/exceptional-circumstances>
76. Directorate General of Drug Administration (DGDA) [Internet]. [cited 2024 Jul 16]. Available from: <https://dgda.gov.bd/site/view/policies/http%3A%2F%2Fdgda.gov.bd%2Fsite%2Fview%2Fpolicies%2FPolicies>
77. Central Drugs Standard Control Organization [Internet]. [cited 2024 Jul 16]. Available from: <https://cdsco.gov.in/opencms/opencms/en/biologicals/Vaccines/>
78. IXCHIQ. FDA [Internet]. 2024 [cited 2024 Jul 29].
79. Ixchiq | European Medicines Agency [Internet]. [cited 2024 Jul 29]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/ixchiq>
80. Health Canada. Regulatory decision summary for ixchiq [Internet]. [cited 2024 Dec 15]. Available from: <https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS1719926004455>
81. Maure C, Khazhidinov K, Kang H, et al. Chikungunya vaccine development, challenges, and pathway toward public health impact. *Vaccine.* 2024;42(26):126483. doi: 10.1016/j.vaccine.2024.126483
82. Roques P, Fritzer A, Dereuddre-Bosquet N, et al. Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera. *J Clin Investig Insight* [Internet]. 2022 [cited 2024 Jun 5];7(14). doi: 10.1172/jci.insight.160173
- This study demonstrated the novel approach of using passive transfer of human sera for evaluating vaccine efficacy, which enabled faster approval of Chikungunya vaccine.
83. Yoon I-K, Alera MT, Lago CB, et al. High rate of subclinical Chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. *PLoS Negl Trop Dis.* 2015;9(5):e0003764. doi: 10.1371/journal.pntd.0003764
84. Schneider M, Narciso-Abraham M, Hadl S, et al. Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2023;401(10394):2138–2147. doi: 10.1016/S0140-6736(23)00641-4
85. WHO Target Product Profile for Nipah virus Vaccine [Internet]. 2017 [cited 2024 Jul 6]. Available from: https://www.who.int/csr/research-and-development/priority_disease_list_review_short_summary_25Jan2017.pdf
86. Qian GY, Edmunds WJ, Bausch DG, et al. A mathematical model of Marburg virus disease outbreaks and the potential role of vaccination in control. *BMC Med.* 2023;21(1):439. doi: 10.1186/s12916-023-03108-x
87. Vesga JF, Métras R, Clark MHA, et al. Vaccine efficacy trials for Crimean-Congo haemorrhagic fever: insights from modelling different epidemiological settings. *Vaccine.* 2022;40(40):5806–5813. doi: 10.1016/j.vaccine.2022.08.061
88. Carlson CJ, Garnier R, Tiu A, et al. Strategic vaccine stockpiles for regional epidemics of emerging viruses: a geospatial modeling framework. *Vaccine.* 2024;42(23):126051. doi: 10.1016/j.vaccine.2024.06.019
89. Zeng W, Cui Y, Jarawan E, et al. Optimizing immunization schedules in endemic cholera regions: cost-effectiveness assessment of vaccination strategies for cholera control in Bangladesh. *Vaccine* [Internet]; 2021;39(43):6356–6363. doi: 10.1016/j.vaccine.2021.09.044

90. Wells C, Yamin D, Ndeffo-Mbah M, et al. Harnessing case isolation and ring vaccination to control Ebola. *PLOS Negl Trop Dis* [Internet]. 2015;9(5):e0003794. doi: [10.1371/journal.pntd.0003794](https://doi.org/10.1371/journal.pntd.0003794)
91. Smith DRM, Turner J, Fahr P, et al. Health and economic impacts of Lassa vaccination campaigns in West Africa. *Nat Med*. 2024;30(12):3568–3577. doi: [10.1038/s41591-024-03232-y](https://doi.org/10.1038/s41591-024-03232-y)
92. Dzau V, Swaminathan S, Baker C, et al. The 100 days mission: how a new medical-countermeasures network can deliver equity and innovation. *Lancet*. 2023;402(10412):1507–1510. doi: [10.1016/S0140-6736\(23\)01775-0](https://doi.org/10.1016/S0140-6736(23)01775-0)
93. WHO. Diagnostics laboratory emergency use listing [Internet]. [cited 2024 Dec 18]. Available from: <https://www.who.int/teams/regulation-prequalification/eul>