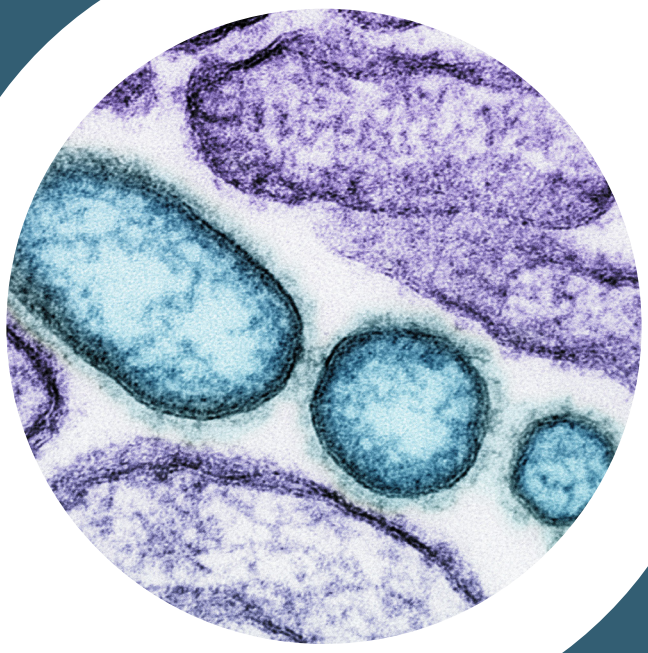
A Research and Development Roadmap for Nipah Virus



2024 Update

CIDRAP

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Acronyms and Abbreviations

AGM	African green monkey
BSL	Biosafety level
CD8 T cells	Cytotoxic T lymphocytes that express CD8 on their surface
CEPI	Coalition for Epidemic Preparedness Innovation
CNS	Central nervous system
CoP	Correlate of protection
EQA	External quality assessment
F glycoprotein	Fusion glycoprotein
G glycoprotein	Attachment glycoprotein
HeV	Hendra virus
HeV-g2	A variant of Hendra virus
HeV-sG	Hendra virus recombinant subunit vaccine
IgG	Immunoglobulin G
IgM	Immunoglobulin M
JE	Japanese encephalitis
mAb	Monoclonal antibody
MCM	Medical countermeasure
mRNA	Messenger RNA
NHP	Non-human primate
NiV	Nipah virus
NiVD	Nipah virus disease
NiV-B	B genotype of Nipah virus, which includes strains from Bangladesh
NiV-I	Nipah virus strains from India, which are part of the B genotype
NiV-M	M genotype of Nipah virus, which includes strains from Malaysia
NRA	National regulatory authority

PEP	Post-exposure prophylaxis
PPE	Personal protective equipment
PREP	Pre-exposure prophylaxis
R&D	Research and development
RCT	Randomized controlled trial
TPP	Target product profile
WALC	West Africa Lassa Fever Consortium
WHO	World Health Organization

Overview

Note: This updated roadmap is an adaptation of an original work titled, "*Nipah Research and Development (R&D) Roadmap: Advanced Draft*" Geneva: World Health Organization (WHO); October 2019 (WHO 2019a). Licence: CC BY-NC-SA 3.0 IGO. This adaptation was not created by WHO and WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition.

Roadmap purpose: To provide a 6-year framework beginning in 2024 for identifying the vision, underpinning strategic goals, and prioritizing areas and activities (from basic research toward advanced development, licensure, manufacture, acceptance and deployment, and assessment) for accelerating the collaborative development of medical countermeasures (MCMs)—diagnostics, therapeutics, and vaccines—against Nipah virus (NiV) infection.

NiV is a paramyxovirus that was first identified as a zoonotic pathogen after an outbreak involving respiratory illness in pigs and severe encephalitic disease in humans occurred in Malaysia and Singapore in 1998 and 1999 (Chew 2000, Chua 1999, Chua 2010, Parashar 2000, Paton 1999). As part of that outbreak, 265 human cases of NiV disease (NiVD) were identified in Malaysia, and 11 abattoir workers in Singapore became ill following contact with imported pigs, with an overall case-fatality rate of 40%. No new outbreaks have been reported in these countries since May 1999. NiVD was subsequently recognized, however, in Bangladesh in 2001, and nearly annual outbreaks have occurred in that country since (Hsu 2004, WHO 2018, Agrawal 2023). NiVD has also been identified periodically in eastern India (2001 and 2007) and in Kerala state in southern India (2018, 2019, 2021, and 2023) (Arunkumar 2019, Chadha 2006, Chattu 2018, Sharma 2018, Soman Pillai 2020, Sudeep 2021, Yadav 2022, Srivastava 2023a). To date, over 400 cases of NiV infection have been identified in Bangladesh and India (Agrawal 2023, Hassan 2024, Satter 2023, Sharma 2018). Case-fatality rates during outbreaks in Bangladesh and India have generally ranged from 50% to 100% (Sharma 2018). NiV infection in humans results in neurological and respiratory syndromes, with fever, headache, altered mental state or unconsciousness, dizziness, cough, and vomiting as the primary presenting clinical features. NiV infection may result in late-onset encephalitis and relapsing encephalitis, and survivors may experience long-term neurological sequelae (Goh 2000, Hossain 2008, Tan 2002). Asymptomatic

or mildly symptomatic infections appear to be relatively uncommon (Kumar 2019, Nikolay 2019).

The primary natural reservoir host for NiV in South Asia, where cases continue to occur, is *Pteropus* bats. A recent study suggests that discrete multiannual local epizootics in bat populations contribute to the ongoing sporadic nature of human NiV outbreaks in South Asia (Epstein 2020). The zoonotic potential of NiV is significant, particularly because of its ability to infect a wide variety of livestock and other domestic animals, which can serve as a source of exposure to humans (Islam 2023). Other regions may be at risk for NiV infection, as serological evidence for NiV has been found in *Pteropus* bats and several other related bat species in Southeast Asia, the Western Pacific, and Madagascar (Anderson 2019, Breed 2010, Epstein 2008, Hasebe 2012, Iehlé 2007, Plowright 2019, Reynes 2005, Sendow 2013, Wacharapluesadee 2005, Yob 2001). In the 1998-99 Malaysia outbreak, NiV spillover occurred from bats to pigs, which led to pig-to-pig, pig-to-human, and suspected, although limited, human-to-human NiV transmission. Additionally, dogs were found to be infected with NiV on the farms involved in the outbreak (Field 2001). In outbreaks in Bangladesh, intermediary hosts between bat and human have not played a major role to date, with the primary modes of NiV transmission being human consumption of bat-contaminated raw date palm sap and subsequent person-to-person transmission (Gurley 2007, Islam 2016, Luby 2009, Nikolay 2019, Rahman 2008). However, a recent study in Bangladesh found NiV antibodies in cattle, dogs, and cats from six sites where human NiVD cases occurred during 2013–2015 (Islam 2023), suggesting the potential of zoonotic spread via intermediary hosts. Respiratory transmission via droplet spread may play an important role in propagating outbreaks (Nikolay 2019, Spiropoulou 2019). The virus could have pandemic potential if a more human-adapted strain, with greater person-to-person transmission, emerges (Luby 2013).

NiV is a member of the Henipavirus genus; this genus also includes another zoonotic pathogen—Hendra virus (HeV)—which predominantly causes infection in horses and also can lead to human disease following contact with infected horses. HeV was initially recognized in 1994, following an outbreak of severe respiratory disease in horses and humans in the Brisbane suburb of Hendra in Queensland, Australia (Murray 1995, Selvey 1995). To date, at least 67 spillover events—all in Australia—involving more than 100 horses and seven humans have been identified (Queensland Government, Wang 2023). The most recent fatal HeV infection in a horse occurred in July 2023 (Queensland Government). A previously unrecognized variant of HeV (HeV-g2) has recently been identified that causes a clinically indistinguishable disease in horses from the prototypic HeV infection of severe neurological and respiratory disease (Annand 2022). HeV-g2 is now detectible following modifications of molecular assay protocols and a contemporary HeV-g2 infection of a horse was reported in 2021 (Taylor 2022). Changes in bat behavior related to habitat loss and climate change appear to have increased the spillover risk of HeV from bats to horses (Eby 2023).

Another henipavirus, Langya virus, was recently identified as the probable cause of febrile illness among a group of people in China (Zhang 2022). Additionally, a probable outbreak of NiV occurred among horses and humans in the Philippines in 2014, although detailed genomic information for the virus is limited (Ching 2015). This outbreak likely involved spillover of the virus into horses and subsequent disease in humans following consumption of contaminated horsemeat; disease also occurred in healthcare workers who cared for infected patients. Several other henipaviruses

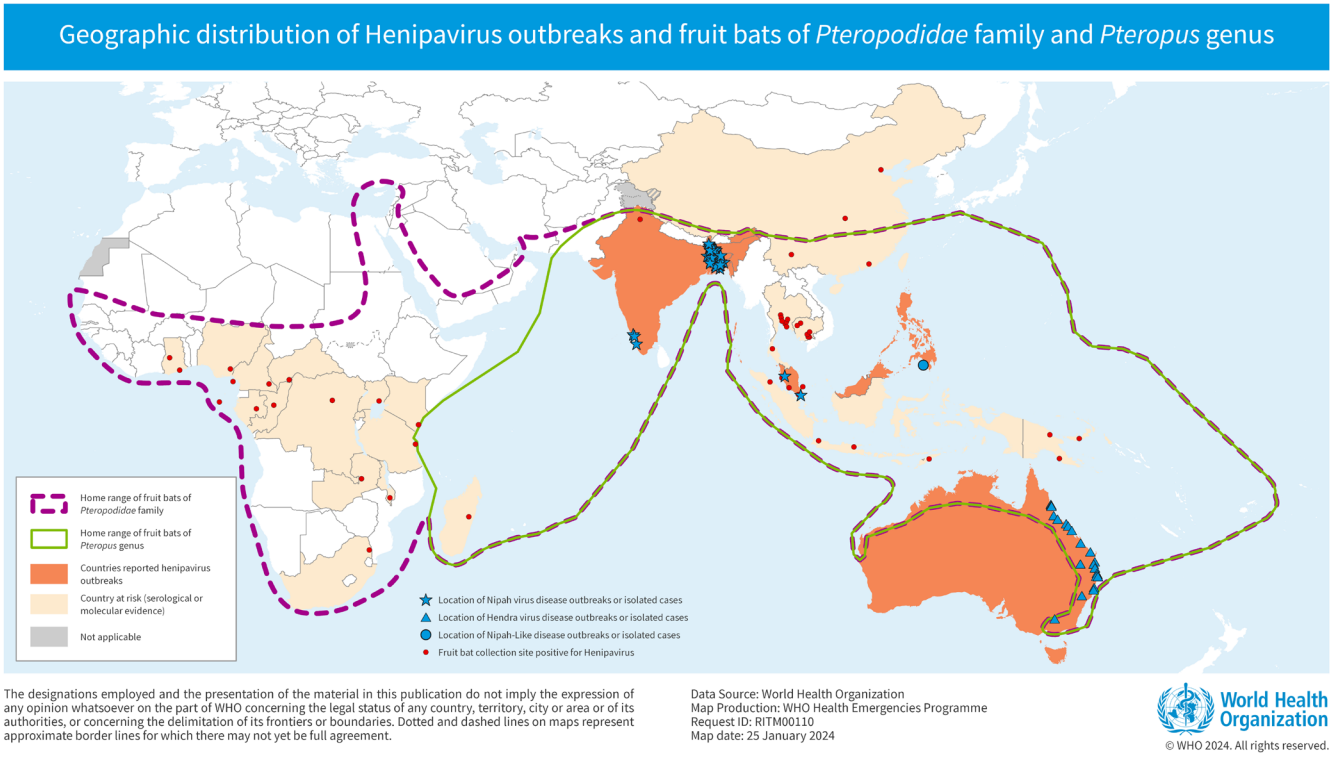


Figure 1. Geographic distribution of henipavirus outbreaks and fruit bats of the Pteropodidae family and *Pteropus* genus. Provided by WHO January 2024.

have been identified, although their zoonotic and pathogenic potential of remains unknown (Kaza 2023, Li H 2023, Zhang 2022); additional research is needed to better understand the global health threat of these viruses.

Additional bat species (such as other fruit bats of the Pteropodidae family that can be found across Africa and parts of the Middle East) may harbor henipaviruses (Bruno 2022, Hayman 2008) and henipa-like viruses have been found in other widely dispersed species (e.g., shrews, rats, and opossums) (Caruso 2023). The geographical range, therefore, of such viruses may be greater than previously recognized and the risk of henipavirus spillover to humans may encompass more than half of the world's population (Figure 1). Although this roadmap is primarily focused on NiV, many of the issues identified also apply to other henipaviruses. While the current incidence of detected disease caused by henipaviruses is low, the COVID-19 pandemic clearly demonstrated that viruses can transform rapidly into serious global threats; therefore, vigilance is needed to better understand the epidemiology of henipaviruses and to monitor their global occurrence (Mishra 2023).

Genomic sequencing has demonstrated that there are two main clades of NiV: the M genotype, which comprises the Malaysian NiV isolates (NiV-M), and the B genotype, which includes Bangladesh (NiV-B) and India NiV isolates (NiV-I) (Liew 2022, Yadav 2019). These three strains share a high percentage of homology, with NiV-M and NiV-B strains sharing 91.8% homology. Similarly, NiV-I strains share 85.14% and 96.15% homology with NiV-M and NiV-B, respectively. Some strain-related differences, however, have been noted in

the clinical features of infection in humans and experimentally infected non-human primates (NHPs), with strains of the B clade appearing to be more pathogenic than those of the M clade (Mire 2016). Recent data indicate that strains from Bangladesh are segregated into two additional distinct sublineages that have intermingled geographically and temporally in that area over time (Rahman 2021, Whitmer 2020). Currently, however, the molecular epidemiology of NiV remains somewhat unclear, and issues around strain diversity and strain evolution require further elucidation (Rahman 2021). One recent summary involving the most comprehensive analysis of available genomic data to date suggests that only about 15% of the overall NiV genetic diversity has been uncovered. Moreover, findings from that analysis demonstrated co-circulation of distinct lineages among bats, coupled with slow migration over large spatial areas (Azuero 2023).

In 2016, WHO designated NiVD a priority disease for epidemic preparedness as part of its *R&D Blueprint for Action to Prevent Epidemics* (WHO 2016) because NiV infection is associated with significant morbidity and mortality, occurs in epidemic patterns that can be disruptive to society, and effective medical countermeasures (MCMs) are generally not available. At the outset of the WHO R&D Blueprint Initiative, pathogen-specific R&D roadmaps were considered an integral component of the program. In 2022, WHO revised its strategy for epidemic/pandemic preparedness, with a renewed focus on entire classes of viruses or bacteria rather than individual pathogens (WHO 2023). However, pathogen-specific roadmaps are still highly valuable to inform future directions and investments in preparedness for pathogens with epidemic potential.

In 2019, WHO published an advanced draft of a research and development (R&D) roadmap for generation of NiV MCMs (WHO 2019a). The roadmap included strategic goals and milestones for creating diagnostics, therapeutics, and vaccines for NiV infection. In July 2023, Wellcome convened a working group of 15 international experts (five from countries affected by NiV or HeV and ten from the US or Europe) to review the 2019 R&D roadmap and generate an updated set of research priorities for promoting development of NiV MCMs by 2030. This updated roadmap reflects scientific developments over the past 5 years and consensus opinion of the expert working group.

The scope of R&D addressed in this roadmap ranges from basic research to late-stage development of MCMs to prevent and control NiV outbreaks and endemic disease in humans. The roadmap is organized into four main sections: cross-cutting issues (for areas that apply broadly to more than one MCM category), diagnostics, therapeutics, and vaccines. (*Note*: These topics are not presented in order of public health priority.) Each section includes barriers (inherent obstacles or technical challenges that may influence the likelihood of success for development of NiV MCMs) and gaps (key needs or unresolved limitations in knowledge that are critical to the development of new NiV MCMs). These are followed by strategic goals and milestones, which build on the gaps and barriers and are focused on achievements for the next 6 years (beginning in 2024) that are necessary for moving NiV MCMs forward. Each section also includes additional ongoing priorities that should be considered for NiV MCM R&D.

Other aspects of public health preparedness and response, in addition to R&D for diagnostics, therapeutics, and vaccines, are critical to successful NiV infection prevention and control. Examples include minimizing zoonotic NiV transmission, improving use of personal protective equipment (PPE), ensuring adequate hand hygiene and environmental hygiene, promoting effective

community engagement, implementing adequate infection prevention and control practices, developing adequate infrastructure (such as cold-chain maintenance) to deploy MCMs, and promoting workforce development and training in endemic and at-risk regions. Many of these issues are beyond the scope of this R&D roadmap, but need to be addressed as part of a broader public health control strategy. Further research of NiV and related henipaviruses in animal species, including development of appropriate MCMs targeted to animal populations, such as vaccines (McLean 2019), also is needed, since disease in animals may amplify occurrence of NiV or a related henipavirus species in humans and virus transmission can occur at the human-animal interface.

Definition of Roadmap Terms

Barriers: Inherent obstacles or technical challenges that may influence the likelihood of success at various stages of coronavirus vaccine development; identifying such barriers helps inform the nature and scope of activities designed to achieve the research and development (R&D) outcomes.

Gaps: Key unresolved issues or limitations in knowledge that are critical to the development of new vaccines and that can be addressed through targeted R&D activities.

Strategic Goals: Long-range high-level research priorities that the roadmap's actions are intended to address during the stated timeframe.

Milestones: Actions deemed necessary to achieve the roadmap's strategic goals; the milestones include target dates for completion and reflect SMART (specific, measurable, achievable, realistic/relevant, and time-sensitive) criteria, to the degree feasible.

Additional Research Priorities: Further topics and issues that are relevant to the achievement of the strategic goals, but are either not high enough priority to be considered milestones or not sufficiently specific or time-bound to be identified with SMART criteria.

Vision

Robust MCMs to detect, prevent, treat, and control human outbreaks of NiV infection (and other closely related henipaviruses) that are readily available and accessible for use in areas of known or potential NiV spillover. These MCMs include (1) rapid and accurate point-of-care or near-patient diagnostics, (2) safe and effective treatment and post-exposure prophylaxis (PEP), and (3) safe and effective vaccines to prevent disease, disability, and death.

Cross-Cutting Issues

Barriers and Gaps

Barriers

- Securing funding for NiV/henipavirus research represents a substantial challenge, since economic incentives to invest in NiV research are not readily apparent because the disease primarily occurs in under-resourced areas of South Asia and reported disease incidence has, so far, been low with only small, sporadic outbreaks (Gómez Román 2020). The development of a sustainable value proposition for industry and international philanthropic public-private partnerships is needed to secure funding to complete development, licensure, manufacture, and deployment of NiV MCMs. The value proposition should be informed by a robust assessment of the risk of future outbreaks of NiV and related henipaviruses and the economic, societal, and health impacts that such outbreaks could generate.
- Demonstrating whether or not a product provides meaningful benefit without undue risk, which is a key aspect of any regulatory approval pathway, can be prohibitively expensive for product developers in the absence of a predictable demand (Gouglas 2018). In addition, licensure of vaccines and therapeutics using alternative regulatory pathways can be very costly, given the regulatory requirements for such approval.
- National regulatory authorities in countries where NiV/henipavirus outbreaks are likely to occur have different regulatory requirements for authorization, licensure, or emergency use of NiV MCMs, which complicates the approval process, particularly for candidate vaccines and therapeutics (Gómez Román 2022). Engagement of international regulators will be an important mechanism for coordinating regulatory issues as NiV MCMs are moved forward (Gómez Román 2020).
- High-level biocontainment requirements may pose an impediment to research on NiV pathogenesis and development of MCMs, as certain materials must be generated under the highest biosafety level (biosafety level 4 [BSL-4] conditions) (Geisbert 2020, Gómez

Román 2022), which can increase the cost and complexity of MCM development.

- To date, NiV spillovers to humans have predominantly been identified in rural communities in Bangladesh and India; the healthcare facilities that serve these communities have limited laboratory and clinical infrastructure for diagnosis and treatment.
- The primary natural reservoir for NiV and henipaviruses is fruit bats of the *Pteropus* genus; these bats have a wide geographical range that stretches across much of the Western Pacific region, Southeast and South Asia, and Madagascar (Bruno 2022). Evidence also suggests that other fruit bats of the Pteropodidae family may harbor NiV or related viruses; such bats can be found across Africa and parts of the Middle East (Bruno 2022). This broad host range increases the likelihood of additional spillover events from bats to humans or livestock in new areas where the disease has not yet been detected, which may make accurate and timely diagnosis, disease recognition, and treatment more difficult owing to the lack of clinical experience with the condition, lack of available laboratory testing, and the occurrence of other diseases that have similar clinical presentations.
- The development and accessibility of animal models that recapitulate human NiV disease are critical for NiV MCM development, given the limitations on clinical samples and the infeasibility of traditional clinical efficacy trials. While ferrets and Syrian golden hamsters are well-established animal models for NiV research, the African green monkey (AGM) is regarded as the most relevant animal model for evaluation of candidate therapeutics and vaccines intended for use in humans (Foster 2022, Geisbert 2010, Geisbert 2020, Geisbert 2021, Johnston 2015, Price 2021, van Doremalen 2022, Woolsey 2023). Studies involving the AGM model may be required for licensure of MCMs via alternative regulatory pathways; however, costs, space requirements (particularly in BSL-4 containment facilities), and ethical concerns constrain the use of NHPs (Arnason 2020, Bossart 2012, Geisbert 2010, Johnston 2015).
- Phase 1 and 2 clinical trials can be conducted in non-endemic regions or in endemic regions; however, phase 3 clinical efficacy trials will need to be conducted in endemic areas. Because NiVD occurs in relatively small, focal outbreaks, the low disease incidence poses a major challenge for conducting such trials, in terms of achieving a sufficient sample size to estimate MCM efficacy with adequate statistical power (Gómez Román 2020, Mishra 2023).
- Patients usually present late in the clinical course of disease, and disease progression is often rapid, making it difficult to collect clinical samples before patients succumb. Additionally, autopsies are often not the standard of care in affected areas, which further reduces opportunities to collect clinical specimens. These barriers hinder the ability to understand disease pathogenesis and immunological responses to infection, which are important for MCM R&D (Amaya 2020, Arunkumar 2019, Gurley 2020, Liew 2022, Mazzola 2019).
- Sociocultural issues may hinder trust in the formal healthcare and public health systems, which could reduce acceptance of NiV vaccines and therapeutics.

Gaps

- Continued R&D, improved manufacturing processes, deployment, and assessment of NiV/henipavirus MCMs, as well as other preventive measures, depend on accurate and current information on the ecology and epidemiology of NiV infection, using a One Health approach. Improved surveillance (or dedicated prospective research with a surveillance focus) is needed to determine the true incidence of human disease in endemic areas and to monitor the occurrence of spillover incidents from bats to humans or livestock in new geographical areas. Improved surveillance might also support the business case for investment in NiV MCMs by identifying a higher incidence of disease than previously demonstrated and revealing a broader geographical range of risk.
- Additionally, continued research is needed to better define and assess the occurrence of NiV and other henipaviruses, including drivers of infection, in the natural reservoir of *Pteropus* bats and potentially other bat species around the globe (Gómez Román 2020, Plowright 2019).
- Additional research is also needed to optimize and further characterize relevant animal challenge models (particularly ferret, Syrian golden hamster, and AGM models) for promoting development and evaluation of NiV MCMs (Geisbert 2020, Gómez Román 2020, Pigeaud 2023, Price 2021, Rockx 2014, Scholte 2023). Examples of additional issues involving animal models include the following:
    - Determine the appropriate animal model(s) for screening assay development.
    - Standardize the challenge strain and dose, and determine the most appropriate lethal NiV dose for MCM development.
    - Identify models for studying chronic (relapsing) infection.
    - Determine if different animal models are needed for different clinical endpoints such as infection, disease, and transmission.
    - Improve overall standardization of the models.
- Furthermore, additional research is needed to explore alternatives to animal model research for R&D of NiV MCMs, such as organoid and microphysiological systems technology (Stewart 2023).
- Other research needs include the following:
    - Improved understanding of the virology, immunology, and pathogenesis of NiV in humans and animals to inform development of NiV MCMs (Gurley 2020, Liew 2022). This includes evaluating the pathophysiological differences between different NiV strains, determining the mechanisms that allow NiV to escape immunological clearance and cause delayed onset or recurrent encephalitis, and identifying factors influencing the development of permanent neurological sequelae (Arunkumar 2019, Gómez Román 2020, Dawes 2019, Gurley 2020, Liew 2022).
    - Ongoing phylogenetic and evolutionary analyses of NiV strains to monitor viral heterogeneity and antigenic changes that may affect the epidemiological and clinical features of disease over time and thereby influence MCM development (Azuero 2023, Gurley 2020, McKee 2022, Rahman 2021).
    - Additional research to determine if: (1) NiV strain variations influence the ability to

detect NiV infections; (2) different strains have different phenotypic characteristics, such as different clinical manifestations or transmission dynamics; and (3) strain variability affects efficacy of vaccines or therapeutics (CEPI 2023, Gurley 2020, Whitmer 2020).

- Whole-genome sequencing of NiV isolates to generate a comprehensive phylogenetic mapping of the global genetic variability among henipaviruses (CEPI 2023).
- Sociological and anthropological research to understand how to best engage populations at high risk of exposure (such as people who consume date palm sap, healthcare workers, and workers at the human-animal interface) and vulnerable populations (such as children, immunocompromised individuals, and pregnant women) for participation in clinical trials and to ensure acceptance of new NiV MCMs, especially if therapeutics and vaccines do not consistently prevent disease (Singhai 2021, The Lancet 2018).
- Prospective serosurveillance of henipavirus exposure from susceptible animal species and proximate human populations in areas of predicted risk to assess the potential of human spillover and to build preparedness for detection of human cases and for limiting exposure (Daszak 2020, Deka 2018, Gómez Román 2020, Plowright 2019).
- Expanded use of machine-learning approaches can facilitate an improved understanding of the risk of NiV/henipavirus spillover events (Plowright 2019). Ecological studies are also needed to enhance understanding of the dynamics governing prevalence and shedding of NiV and other henipaviruses in bats (Plowright 2019).

- Other important needs include the following:
  - Funding sources (such as public-private partnerships, government agencies, and philanthropic organizations) and industry incentives and competitions for non-dilutive funding to encourage innovation and secure private-sector commitments to develop and manufacture NiV MCMs (Gómez Román 2020).
  - Enhanced clinical, laboratory, and public health infrastructure in endemic and at-risk areas to promote early diagnosis, treatment, surveillance, and implementation of vaccination programmes for NiV prevention and control (Bruno 2022).
  - Advocacy to policy makers in affected countries and to global stakeholders to ensure they understand the potential health, societal, and economic benefits of devoting resources to improving NiV surveillance, detection, prevention, and control measures (Gómez Román 2020).
  - Intensive awareness programmes regarding NiV transmission from NiV-contaminated fruit and subsequent person-to-person spread in the vicinities around areas where cases have previously occurred in India and Bangladesh. Such programmes should be targeted to the community and to all hospital settings.
  - Scenario planning to clarify regulatory pathways for product approval in countries where NiV/henipavirus outbreaks are likely

to occur, including determining whether or not efficacy data from animal models is sufficient for regulatory approval. Such planning should take into consideration the local epidemiology of NiV infection and the different requirements of local national regulatory authorities for product approval and emergency use authorization (Gómez Román 2022).

- Regulatory pathways and capabilities of national regulatory authorities (NRAs) vary among countries; therefore, early engagement, potentially with support from WHO and other key international stakeholders, is essential to identify country-specific considerations. While it is critical to focus on approaches that make ethical and scientifically valid clinical trials feasible whenever possible, alternative regulatory pathways may need to be considered for licensure of NiV vaccines or therapeutics, if classic clinical trial designs (e.g., randomized controlled trials [RCTs]) are not feasible.
- Standardized and well-characterized assays (to be further defined based on end use), reagents, antibodies, nucleic acids, and stocks of NiV challenge strains for R&D of MCMs for NiV infection (Price 2021, Rampling 2019, Satterfield 2016). Assays that can be used at lower biosafety levels are an important priority. WHO international standards, when available, should be used to harmonize assay results.
- Outreach and education to clinicians and community health workers to improve NiV awareness, training, and outbreak preparedness (e.g., disease diagnosis, clinical management, and infection prevention and control) and to ensure availability of diagnostic tools in endemic areas to increase the likelihood of accurate and timely diagnosis and treatment of NiV infection (Mishra 2023, Singhai 2021).
- Enhanced capacity for data sharing and analysis (particularly of NiV sequence data) to support collaborative clinical research, including methods for collecting, standardizing, and sharing clinical data.
- Implementation of standardized case-investigation protocols and post-mortem minimally invasive tissue sampling for investigating NiV-related deaths to enhance understanding of NiV disease pathogenesis (Bassat 2021, Hegde 2024).
- Collaboration between public health authorities in endemic and at-risk areas and international development partners to support NiV surveillance and strengthen disease prevention and preparedness activities. This effort could involve linking NiV surveillance with other surveillance efforts, such as surveillance for Japanese encephalitis (JE). Human health, animal health, and wildlife officials should be engaged as part of a long-term collaborative effort.
- Clarification regarding the potential for and possible strategies to promote technology transfer for NiV MCM development and manufacturing to endemic and at-risk areas.
- Efforts to reduce the cost of medical countermeasure development and ongoing production.

Strategic Goals and Aligned Milestones

Strategic Goal 1.1: Identify additional and ongoing sources of private- and public-sector funding and develop appropriate incentives and competitions to promote R&D of NiV MCMs.

Milestone 1.1.a: By 2024, develop a public value proposition to effectively advocate for the development and sustainability of NiV MCMs that (1) articulates the global threat of NiV and related henipaviruses, (2) demonstrates the need for global engagement to address the threat, and (3) outlines the global social and economic benefits of generating accessible and affordable NiV MCMs.

Milestone 1.1.b: By 2025, create a funding plan—based on the global value proposition—for moving NiV diagnostics, therapeutics, and vaccines toward clinical evaluation, licensure/approval, acceptance, and sustainable access.

Milestone 1.1.c: By 2025, develop a coordinated strategy (to include addressing indirect costs and shortfalls) for promoting and incentivizing greater industry engagement in R&D for NiV MCMs, particularly in affected countries.

Strategic Goal 1.2: Improve understanding of the epidemiology and ecology of NiV and related henipaviruses to better define the disease burden, risk factors for infection, reservoir hosts, and risk of spillover events in at-risk countries.

Milestone 1.2.a: By 2024, generate and implement standardized protocols for case investigation in at-risk countries, using a One Health approach, that are aimed at identifying risk factors for primary NiV infection and at conducting case-contact studies to better understand chains of transmission.

Milestone 1.2.b: By 2025, assess country-level capacity in at-risk countries for implementing standardized clinical protocols for case investigation, and develop plans for addressing key gaps in implementation.

Milestone 1.2.c: By 2025, develop and initiate a plan for enhancing human surveillance for NiV and related henipaviruses in India and Bangladesh outside of existing surveillance areas (i.e., where cases previously have been identified). This should include securing funding, identifying additional surveillance catchment areas, engaging key partners in those areas, generating standardized surveillance protocols, conducting training for implementation, and leveraging other surveillance activities, such as for JE.

Milestone 1.2.d: By 2025, develop plans for conducting human surveillance for NiV and related henipaviruses in at-risk countries other than India and Bangladesh.

Milestone 1.2.e: By 2025, develop plans for conducting animal surveillance for NiV and related henipaviruses in at-risk countries other than India and Bangladesh.

Milestone 1.2.f: By 2025, develop plans for conducting additional research in at-risk countries to identify the potential for and drivers of spillover events for NiV and related henipaviruses, using a One Health approach, particularly in areas where NiV cases have not yet been identified.

Milestone 1.2.g: By 2026, establish capacity at selected surveillance sites in India and Bangladesh to investigate NiV-related deaths by using post-mortem minimally invasive tissue sampling to enhance understanding of NiV disease pathogenesis.

Strategic Goal 1.3: Determine the requirements for clinical trials, regulatory pathways, and other considerations that will affect licensure or approval of NiV MCMs by engaging international regulators representing NRAs in affected areas and other key international stakeholders.

Milestone 1.3.a: By 2024, conduct scenario planning to identify gaps, clarify regulatory procedures, and determine the acceptable pathways for approval and emergency use authorization of NiV MCMs (including vaccines, novel candidate therapeutics, repurposed therapeutics, and diagnostics) in countries at highest risk for NiV outbreaks through an international forum of regulators.

Milestone 1.3.b: By 2025, develop strategies to address gaps in regulatory approval and emergency use authorization of candidate NiV MCMs, with specified timelines for completion.

Milestone 1.3.c: By 2025, assess capacity in affected countries to conduct clinical trials and field studies of MCMs, particularly during outbreaks.

Milestone 1.3.d: By 2026, create a system for monitoring regulatory issues related to licensure or use of candidate NiV MCMs over time.

Milestone 1.3.e: By 2026, develop protocols for emergency use of candidate NiV MCMs during outbreaks.

Strategic Goal 1.4: Support basic science research to improve understanding of NiV virology, pathogenesis, and the immune response to infection.

Milestone 1.4.a: By 2024, generate standardized and well-characterized assays, reagents, antibodies, nucleic acids, and stocks of NiV challenge strains to facilitate R&D of NiV MCMs.

Milestone 1.4.b: By 2026, develop a standardized human pathology investigation protocol (with minimally invasive tissue sampling) for improving understanding of NiV pathogenesis.

Milestone 1.4.c: By 2027, conduct additional research to further optimize animal models that recapitulate disease in humans for use in preclinical studies of NiV MCMs.

Milestone 1.4.d: By 2027, conduct research to determine if strain variability affects efficacy of promising NiV MCMs or the accuracy of diagnostic tests.

Additional Priority Areas/Activities

Research

Continue to expand research to further understand the ecology and epidemiology of NiV and other pathogenic henipaviruses in human and animal populations (wild and domestic) over time and across geographical areas, using a One Health approach. Such research should include serosurveys in different animal species and ecological studies in bats, and should employ computational approaches, such as machine-learning.

Continue to perform phylogenetic and evolutionary analyses, using whole-genome sequencing, of NiV strains to monitor antigenic changes and characterize genetic diversity over time.

Continue to conduct sequencing of NiV strains from existing clinical samples obtained from past NiV cases to assess variability of NiV strains in India and Bangladesh (CEPI 2023).

Incorporate, on an ongoing basis, additional NiV strains into preclinical research as newer strains become available.

Continue to conduct basic science research on the virology, pathogenesis, and immunology of NiV infections to inform development of MCMs.

Continue to explore alternative strategies to using animal models for research (e.g., use of organoids, other in-vitro approaches, computational modelling).

Determine key differences in pathogenesis for different NiV strains that may have implications for the development of safe and effective NiV vaccines or therapies.

Conduct research studies to enable a more comprehensive mapping of genetic variability of henipaviruses to improve understanding of their global distribution.

Conduct social science research to determine strategies for engaging communities for participation in clinical trials and to support acceptance of MCMs for NiV infection as they become available.

Product development

Promote early communication between developers and appropriate NRAs for clarity and guidance on the regulatory aspects of MCM development for NiV infection, including potential regulatory pathways for MCM licensure and approval.

Key capacities

Create international partnerships to fund, support, and promote enhanced laboratory capacity, public health surveillance capacity, and infrastructure in endemic and at-risk areas to promote early diagnosis, treatment, and implementation of vaccination programmes for NiV prevention and control.

Improve active and passive surveillance capacity to (1) better define the incidence of disease in NiV-endemic and at-risk areas and (2) promote targeted research in non-endemic areas to identify evidence of spillover of NiV or other related henipaviruses from the natural reservoir to human or animal populations.

Develop an open-access shared data platform to facilitate sharing of NiV sequence and strain data.

Collaborate with local governmental authorities (including human health, animal health, and wildlife representatives) to support NiV surveillance and disease prevention activities in affected and at-risk areas.

Promote community- and hospital-based outreach programs in India and Bangladesh that focus on transmission risks in the vicinities around areas where NiV cases have previously occurred.

Strengthen infrastructure and capacity for post-marketing pharmacovigilance of licensed NiV therapeutics and vaccines.

Policy and commercialization

Support plans for adequate manufacturing and subsequent distribution of NiV diagnostics, therapeutics, and vaccines to endemic and at-risk areas. These should include efforts to reduce production costs and ensure equitable global access as needed.

Support the development of affordable pricing mechanisms to promote accessibility of NiV MCMs in low- and middle-income at-risk countries. (*Note*: According to WHO, an "affordable and fair" price is one that can reasonably be paid by patients and health budgets and simultaneously sustains research and development, production, and distribution within a country.)

Clarify the potential for and possible strategies to promote technology transfer for development and manufacturing of MCMs for NiV infection.

Diagnostics

Barriers and Gaps

Barriers

- Initial signs and symptoms of NiV infection are nonspecific, and infection is often not suspected at the time of presentation. This can hinder accurate diagnosis and creates challenges in outbreak detection and implementation of effective and timely infection control measures and outbreak response activities. Additionally, latent infection can last for months to years after initial exposure, which can complicate epidemiological investigations.
- The accuracy of laboratory results can be affected by a variety of factors, such as clinical sample quality, quantity, type, timing of collection, and the time necessary to transfer the sample from the patient to the laboratory (WHO 2019b, Mazzola 2019).
- The time required to perform diagnostic testing using conventional laboratory methods is problematic, given the potential for rapid disease progression of NiV infection (Sayed 2019).
- Diagnostic needs vary across the latent, acute, and convalescent phases of NiV infection (Bruno 2023).
- Limited laboratory infrastructure and diagnostic capabilities in peripheral settings can lead to delays in diagnosis and in outbreak investigation and response (Bruno 2022, Chua 2013, Gómez Román 2020, Wang 2012, WHO 2019b).
- Owing to the high biosafety precautions necessary when working with NiV, diagnostic testing of clinical specimens for NiV poses safety and logistical challenges in under-resourced areas with regard to collection, handling, transport, and laboratory analysis (Watanabe 2020, Widerspick 2022).
- Limited NiV-positive clinical samples are available, which are important for validation of diagnostic tests (Mazzola 2019).
- *Pteropus* species (and likely other bat species) may carry other henipaviruses in addition to NiV and HeV, some of which could be pathogenic in humans and livestock.

- Antibodies to different henipaviruses appear to be highly cross-reactive, making it difficult to discriminate, using serological assays, the particular henipaviruses that are in circulation, which is critical to ensuring diagnostic preparedness to respond to future outbreaks (Mazzola 2019, Wang 2012, WHO 2019b, Yang 2022).

Gaps

- Further research is needed to:
    - Improve understanding of the kinetics of NiV detection in urine, respiratory secretions, cerebrospinal fluid, blood, and tissue samples to enhance the ability to diagnose infection at different stages of disease (Arunkumar 2019, Gómez Román 2020, Mazzola 2019, Thakur 2019).
    - Determine criteria for test performance and further evaluate performance characteristics (including sensitivity, specificity, limits of detection, cross-reactivity, and quantitative vs. qualitative data) for NiV assays, particularly for newer tests, such as rapid diagnostic tests, and tests that are designed to detect more than one henipavirus. Further testing of diagnostics should be conducted in animal models before field trials in humans are pursued.
    - Continue to develop commercialized or standardized rapid nucleic acid tests that can quickly confirm active NiV infection at the point of care or at the level of near-patient care (Gómez Román 2020, Pollak 2023, WHO 2019b). This effort may require clarification of the regulatory pathways for commercialization of NiV diagnostic tests. To date, only one rapid test has been approved for emergency use in India during an outbreak that occurred in 2018 (Yadav 2021).
    - Generate international reference standards to calibrate diagnostic assays to ensure proficiency testing of new diagnostics (Gómez Román 2020, WHO 2019b).
    - Clinically validate the performance and operational suitability of new promising diagnostics, particularly rapid diagnostic tests, in endemic geographical regions (Pollak 2023).
    - Continue to assess and operationally validate safe and simple methods of inactivation for various types of clinical samples that do not interfere with diagnosis and that can be used at peripheral sites (Pollak 2023, WHO 2019b, Watanabe 2020, Widerspick 2022, Yadav 2021).
    - Establish operational suitability at the point of care (i.e., at peripheral community settings) for NiV diagnostic tests by developing an integrated approach to facilitate rapid, accurate, and safe testing procedures (Pollak 2023).This could include a minimal protocol or best practices approach for sample inactivation before testing (WHO 2019b).
- Other needs include the following:
    - Development of a virtual repository (with specimens being held and maintained in the countries of origin) of clinical samples to assess and validate diagnostic tests (Gómez Román 2020, WHO 2019b). As part of this process, a clear approach is needed to (1) determine what clinical samples should be collected, based on what would be most useful (e.g., plasma,

whole blood, urine, cerebrospinal fluid); (2) outline the purposes of sample collection; (3) determine what organizations will be responsible for the activities related to creating and maintaining the repositories; (4) establish standardized protocols for sample collection and maintenance; (5) establish an appropriate governance structure; (6) identify who would have access to the samples; (7) prioritize use of samples and sample distribution; and (8) ensure that material transfer agreements are in place. (Samples obtained from laboratory animals also can be used to assess diagnostic assays during the timeframe when the virtual repository is being created.)

- Optimal deployment strategies for diagnostics in different geographical areas based on the risk and epidemiology of NiV infection (WHO 2019b).
- In-country laboratories able to conduct proficiency testing to monitor reproducibility and performance of NiV diagnostic assays in the field.
- Systems for external quality assessment (EQA) monitoring of tests using up-to-date clinical specimen panels and reference standards (Mazzola 2019).
- A sufficient number of laboratories committed to using the diagnostics regularly to support the business case for NiV diagnostics, particularly given the costs of regulatory approval.
- Improvement of diagnostic preparedness in at-risk areas to detect NiV, HeV, and other emergent henipaviruses as they arise (Wang 2012).
- Ongoing efforts to develop affordable and easy-to-use multiplex panels for detection of a range of pathogens using a syndromic approach, if such panels can be deemed cost-saving (Mazzola 2019).

- Use cases and target product profiles (TPPs) have been drafted for NiV diagnostics (WHO 2019b); however, these need to be finalized and the criteria may need to be modified over time as new lineages are identified (Mazzola 2019).
- Since NiV strains continue to evolve, it's possible that current diagnostic tests could fail to detect an emergent NiV variant. Recently, a novel strain of HeV was identified in Australia that was not detected through conventional polymerase chain reaction testing owing to gene sequence mismatches (Annand 2022). Diagnostic tools that can detect a broader range of NiV, HeV, or related viruses capable of spillover may be needed to advance the ability to forecast spillover risks and to detect emergent viruses (Peel 2022).

Strategic Goals and Aligned Milestones

Strategic Goal 2.1: Support development of diagnostic assays through creation of repositories of clinical samples from NiV-infected patients.

Milestone 2.1.a: By 2024, develop and standardize plans and protocols (including the governance structure) for creating repositories of well-characterized acute and convalescent clinical samples to include a recommended set of metadata (e.g., age, sex, days since symptom onset), as feasible, and to be maintained in the two primary NiV-affected countries, Bangladesh and India.

Milestone 2.1.b: By 2025, identify sustainable, long-term funding, determine sites for sample storage, and initiate creation of the repositories in Bangladesh and India, with samples and associated metadata to be collected during future outbreaks.

Strategic Goal 2.2: Continue to develop and assess affordable, highly sensitive and specific (as needed, depending on intended use), point-of-care and near-patient NiV diagnostic tests that are suitable for use in peripheral settings, have extended shelf lives, and have minimal requirements for biosafety precautions and staff training.

Milestone 2.2.a: By 2024, finalize the draft use cases and TPPs for NiV diagnostics.

Milestone 2.2.b: By 2024, engage appropriate regulatory agencies and NRAs to inform commercialization pathways for NiV diagnostic assays. This effort should include clarifying regulatory pathways for approval (including approval for emergency use) of NiV diagnostics.

Milestone 2.2.c: By 2024, generate a call to accelerate the development of point-of-care and near-patient diagnostic testing for NiV.

Milestone 2.2.d: By 2024, develop a validated (at BSL-4) protocol or set of best practices that biosafety committees will accept for inactivation of clinical samples from humans and animals that are being tested for NiV.

Milestone 2.2.e: By 2025, create international reference standards for calibrating and harmonizing NiV diagnostic assays.

Milestone 2.2.f: By 2026, complete preclinical evaluation for at least two of the most promising NiV point-of-care or near-patient diagnostic assays that align with the TPP and can be used in peripheral sites.

Milestone 2.2.g: By 2027, complete clinical validation of performance and operational suitability for at least two of the most promising NiV point-of-care or near-patient diagnostic assays that align with the TPP and can be used in peripheral sites.

Milestone 2.2.h: By 2028, promote international regulatory approval for at least one rapid, point-of-care or near-patient-care NiV diagnostic test that can be commercialized and standardized.

Strategic Goal 2.3: Enhance laboratory diagnostic preparedness in areas of known spillover risk to promote early detection of NiV.

Milestone 2.3.a: By 2025, continue to expand national laboratory networks for NiV detection in at-risk countries that include plans for enhancing laboratory preparedness to enable earlier and timely detection of NiV infection during future outbreaks.

Milestone 2.3.b: By 2026, generate well-characterized and up-to-date proficiency panels and network quality controls for NiV diagnostic testing to be used in selected laboratories in at-risk countries.

Milestone 2.3.c: By 2026, implement routine EQA monitoring of NiV diagnostic testing at selected laboratories in at-risk countries.

Additional Priority Areas/Activities

Research

Continue to explore new diagnostic approaches that may allow earlier detection of infection.

Further evaluate the kinetics of NiV detection to enhance the ability to diagnose NiV infection at different stages of disease.

Determine criteria for test performance and **continue to evaluate** performance characteristics for promising new assays for diagnosis of NiV infection.

Continue to conduct field evaluation studies to assess and validate new diagnostic tests for NiV infection as they become available.

Continue to research methods of diagnostic testing that are able to differentiate between various pathogenic henipaviruses.

Continue to develop affordable and easy-to-use multiplex panels for detection of a range of pathogens using a syndromic approach.

Consider development of diagnostic tools that can detect a broader range of NiV, HeV, or related viruses capable of spillover.

Product development

Refine over time, as needed, criteria in the existing TPPs to include identification of different NiV lineages/strains.

Continue to develop and evaluate point-of-care and near-patient rapid diagnostic tests for NiV infection that are affordable, highly sensitive and specific (as needed, depending on their intended use), can capture antigenically diverse strains of the virus, and can be performed accurately and safely in peripheral settings under a variety of circumstances.

Expand diagnostic test development for other henipaviruses over time.

Key capacities

Establish operational suitability in peripheral laboratories of rapid diagnostic tests over time, as new tests become available.

Enhance diagnostic preparedness in areas of known or potential henipavirus spillover risk to promote early detection of NiV, HeV, and other emergent henipaviruses as needed.

Policy and commercialization

Develop guidance on optimal strategies for the deployment and use of new NiV diagnostic tests across different geographical areas, as such tests become available.

Therapeutics

Barriers and Gaps

Barriers

- Patients typically present late in the clinical course of disease, which decreases the likelihood of successful treatment.
- A limiting constraint to assessing the effectiveness of promising therapeutics is the number of patients with NiV infection who can be enrolled in clinical trials over time, given the few cases that are identified annually.
- The absence of improved diagnostic assays for timely diagnosis and surveillance of infection creates an important challenge in providing early treatment of patients and PEP for exposed people, which can significantly affect clinical evaluation of therapeutic candidates.
- NiV can infect the central nervous system (CNS), which creates challenges for generating therapeutic agents that cross the blood-brain barrier to inhibit virus replication and prevent severe neurological disease.
- Healthcare systems in affected countries often do not have adequate infection control–programmes in place to prevent person-to-person transmission. They also lack the ability to rapidly identify contacts most likely to benefit from PEP.
- One promising therapy is the monoclonal antibody (mAb) m102.4; however, the projected cost per patient for this agent is expected to be more than $1,000 (Gómez Román 2022); this high cost poses an important barrier to its use. Cold-chain storage and specialized training of local staff to deliver the drug add additional costs.

Gaps

- Patients may benefit from optimal supportive care, independent of treatment with specific NiV therapeutic agents. Key research areas include obtaining data on the safety and efficacy of components of supportive care for NiVD, such as optimal fluid and respiration

management strategies, diagnosis and treatment of organ dysfunction, and the use of empiric antibiotics and/or antimalarials to inform best-practice guidelines and evidence-based policy decisions. Standard-of-care guidelines will be important for conducting clinical efficacy trials of therapeutic agents.

- Studies in animals have evaluated the usefulness of several agents (including remdesivir, favipiravir, and fusion inhibitory peptides) when delivered prior to disease onset or early during the disease course (Dawes 2018, Lo 2019, Mathieu 2018). One recent study showed that AGMs were only partially protected when remdesivir was administered 3 days post-inoculation; therefore, early administration seems critical for effective treatment (de Wit 2023b). Patients with NiV infection are often detected late in the clinical course, which creates challenges for predicting how well a therapeutic agent will work in the field. Additional challenge studies in animals, therefore, are needed to (1) assess the clinical benefit of these therapeutics as treatment options when administered after symptom onset or at least more than 24 hours after initial exposure, (2) determine whether these agents may be appropriate for PEP, and (3) clarify the most feasible and cost-effective route of administration (e.g., oral, intranasal, intravenous) appropriate for real-world conditions, particularly if being considered for mass prophylaxis in an outbreak setting (Gómez Román 2022).
- m102.4 has demonstrated protection against lethal NiV challenge in animal models and has been provided under compassionate use programmes for a few people exposed to either HeV or NiV (Broder 2012, Guillaume 2004, Playford 2020). Several other mAbs also have been assessed in animal models and appear promising (Gómez Román 2022).

  A phase 1 clinical trial for m102.4 with 40 human participants was completed in Australia during 2015 and 2016 (Playford 2020). In that trial, m102.4 was well tolerated and safe, with no evidence of an immunogenic response. Although these findings are promising, additional research needs for mAbs as treatment or PEP for NiV infection include:

  - Additional clinical trials in endemic areas to further assess the safety, tolerability, efficacy, and pharmacokinetic parameters of m102.4 (and possibly other mAbs with adequate preclinical data) for PEP and potentially early treatment of clinical disease.
  - Additional research to determine the likelihood of escape mutants with mAb use. While evidence of escape mutants has not been found to date with m102.4, it may be necessary to consider mAb cocktails (Borisevich 2016, Playford 2020).
  - Animal studies to determine if mAb cocktails that combine several different mAbs into one formulation are more efficacious than administering one mAb alone (Dang 2021).
  - Future studies to ascertain the efficacy of m102.4 for treatment and prophylaxis against different viral strains of NiV and HeV, particularly among populations living in settings where the potential for an outbreak exists.
  - Adequate stockpiles of m102.4 (or potentially other mAbs) to ensure urgent access at the onset of an NiV outbreak.
- Given the limited number of NiV cases identified each year, a transparent and collaborative process is needed to determine

which therapeutics are most appropriate for study in future clinical trials and how best to allocate scarce resources for conducting such trials.

- A prepositioned, agreed-upon protocol for conducting clinical trials of promising therapeutics during NiV outbreaks would be of value in advancing clinical evaluation of such agents (Spiropoulou 2019).
- Diagnostic criteria and standardized testing are needed for including patients in clinical trials of therapeutics.
- Additional research needs include the following:
    - Further research to broaden the number of novel antiviral candidates (including repurposed drugs) for treating NiVD to strengthen the therapeutic pipeline. Computational-aided drug design may prove helpful for this research (Yang 2023).
    - Additional data to establish the pharmacokinetic/pharmacodynamic relationship of promising therapeutic candidates.
    - Additional data to determine the role of PEP and to inform development of guidance on the types of exposures that warrant such intervention and the most appropriate agents to administer. This determination should include feasibility for PEP stockpiling and distribution in both affected and at-risk areas, particularly Bangladesh, which has hundreds of potentially exposed people annually that could be candidates for PEP.
    - Additional information to determine whether or not strain differences will affect the response to therapeutic candidates and results from clinical trials.
    - Additional data to determine the therapeutic windows for promising therapeutics for the different NiV strains, as highlighted by a study in AGMs that showed that the therapeutic window for m102.4 against a strain from Bangladesh/India was shorter than for a strain from Malaysia (Mire 2016).

Strategic Goals and Aligned Milestones

Strategic Goal 3.1: Enhance preparedness to conduct clinical trials of therapeutic agents during future outbreaks of NiV or related viruses.

Milestone 3.1.a: By 2024, convene a consortium of key stakeholders—in affected areas and internationally—to address the primary challenges with conducting clinical trials of therapeutic agents during future outbreaks of NiV or related henipaviruses. This consortium could be modelled after the West Africa Lassa Fever Consortium (WALC) (ISARIC 2023).

Milestone 3.1.b: By 2024, develop NiV infection control and standard-of-care guidelines to be used in affected countries and disseminate the guidelines.

Milestone 3.1.c: By 2024, complete an agreed-upon generic prepositioned protocol for conducting safety and efficacy trials of promising therapeutic candidates (mAbs and small molecules, including repurposed drugs) to be implemented in NiV-affected areas during outbreaks and develop plans for operationalizing the protocol.

Milestone 3.1.d: By 2024, complete an agreed-upon generic prepositioned protocol for conducting PEP (and potentially pre-exposure prophylaxis [PREP]) trials of promising therapeutic candidates (mAbs and small molecules, including repurposed drugs) to be implemented in NiV-affected areas during outbreaks and develop plans for operationalizing the protocol.

Milestone 3.1.e: By 2025, conduct outreach and training to clinicians on the NiV infection control and standard-of-care guidelines in India and Bangladesh.

Milestone 3.1.f: By 2026, generate a reliable source or stockpile of an mAB (m102.4 or other mAbs) to be used in outbreak-related clinical trials for PEP, possibly PREP, and early clinical treatment.

Strategic Goal 3.2: Develop and evaluate therapeutic agents for treatment of NiVD and for PEP to prevent NiVD.

Milestone 3.2.a: By 2025, create and implement a prioritization process, with a governance structure, for determining which promising NiV therapeutic candidates should be further evaluated in clinical trials, once adequate animal data demonstrating safety and efficacy are available.

Milestone 3.2.b: By 2025, complete at least one additional phase 1 clinical trial in an NiV-affected area of a promising mAb or mAb cocktail to assess safety and tolerability.

Milestone 3.2.c: By 2026, complete preclinical evaluation in animal models—with administration of the therapeutic agent more than 24 hours after challenge and potentially after symptom onset—of the preliminary safety, tolerability, and efficacy of at least two promising small-molecule therapeutic candidates or combination therapies for the treatment of NiV infection.

Milestone 3.2.d: By 2027, complete at least one phase 2/3 clinical trial in an NiV-affected area of a promising mAb or mAb cocktail to further assess safety, tolerability, and potentially efficacy, if NiV incidence allows efficacy assessment.

Milestone 3.2.e: By 2028, complete at least one phase 1 clinical trial of the preliminary safety and tolerability of at least two promising small-molecule therapeutic candidates or combination therapies for treating NiVD.

Additional Priority Areas/Activities

Research

Continue to research the safety, tolerability, and efficacy of available investigational therapies (such as m102.4, other mAbs, remdesivir, and favipiravir) for treating and preventing NiV infection, including conducting additional studies in animal models and clinical trials as appropriate and feasible. This should include determining the therapeutic windows for use of therapeutic agents as treatment or PEP.

Clarify, in animal models, the potential for development of escape mutants from use of mAbs.

Continue to conduct preclinical research on mAbs other than m102.4 and on mAb cocktails to assess safety, tolerability, and efficacy for treating NiV infection.

Continue to expand the pipeline of new therapeutic options for treating and preventing NiV infection that should undergo further evaluation, potentially using pseudotyped viruses or chimeric henipaviruses for initial screening of compounds or mAbs (Amaya 2021, Amaya 2023, Li T 2023).

Research optimal treatment and supportive care strategies for NiV infection and determine best-practice guidelines.

Product development

Continue to develop, evaluate, and license safe and effective therapeutic agents for the treatment of NiV infection that are active against different NiV strains and other henipaviruses, and that can cross the blood-brain barrier to treat or prevent CNS disease.

Identify therapeutic approaches for PEP that are broadly active against different NiV strains and other pathogenic henipaviruses that may emerge.

Key capacities

Ensure that clinical trial protocols are in place and are ready to be operationalized in advance of outbreaks, including obtaining appropriate approvals and conducting necessary training.

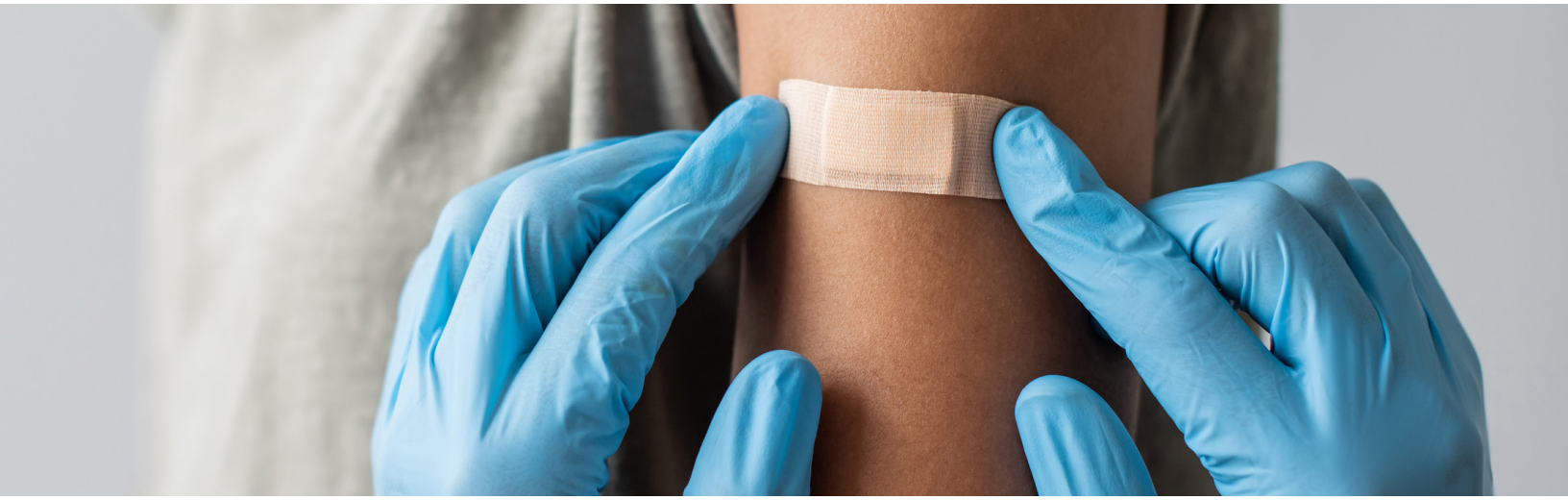
Promote enhancements to the healthcare delivery systems in affected areas to improve clinical management and supportive care of patients with NiVD and to improve infection control practices to limit person-to-person spread.

Ensure that mechanisms are in place to finance, generate, and maintain stockpiles of NiV therapeutics for further clinical testing and outbreak control.

Policy and commercialization

Explore strategies for decreasing the costs associated with m102.4 or other mAbs, such as exploring the possibility of administering mAbs subcutaneously rather than intravenously.

Develop guidance for the use of therapeutics for disease treatment and PEP as new therapies become available.



Vaccines

Barriers and Gaps

Barriers

- Large clinical efficacy trials, which typically are required for vaccine licensure, will likely not be feasible for NiV vaccines, owing to the sporadic and unpredictable nature of NiV outbreaks and the low case numbers usually involved (Gómez Román 2022, Nikolay 2021, Satterfield 2016).
- In the absence of large clinical efficacy trials, authorization and licensure will likely involve nontraditional regulatory pathways to guide the evaluation of safety and efficacy (Gómez Román 2022). However, experience is limited with these routes (such as the US Food and Drug Administration's Animal Rule or Accelerated Approval Program, and the European Medicines Agency's conditional market authorization and authorization under exceptional circumstances), and there are few successful models for vaccine authorization and approval.
- The limited commercial value of NiV vaccines may impede industry's involvement in developing and producing NiV vaccines without significant financial support (e.g., through partnerships with organizations such as the Coalition for Epidemic Preparedness Innovations (CEPI), PATH, and government agencies in high-income countries) (Gómez Román 2022).
- The affordability of creating and maintaining an NiV vaccine stockpile and deploying vaccines during outbreaks is a key issue for low- and middle-income countries; supplementary funding will likely be required to ensure vaccine preparedness for NiV outbreaks (Gómez Román 2022). Given the severity of NiV/HeV disease and the potential for outbreaks in other geographical areas, such global public investment is justified.
- The absence of improved diagnostic assays for the timely diagnosis of infection creates an important challenge by delaying implementation of a rapid reactive vaccination strategy for NiV outbreak control.

Gaps

- NiV vaccines are needed that (1) are readily accessible with adequate supply chains, particularly in low-resourced areas, (2) can protect against different NiV strains, and (3) provide rapid onset of immunity to prevent and control outbreaks quickly.
- Use cases for NiV vaccines need to be better defined, because how vaccines are to be used will affect vaccine deployment and manufacturing plans.
- Reference standards for NiV antibodies are needed to evaluate candidate NiV vaccines.
- Expanded partnerships among researchers, funders, and regulators are needed to advance the development of promising NiV vaccine candidates (Amaya 2020, Gómez Román 2022).
- NiV vaccine candidates in preclinical development target the fusion (F) and attachment (G) glycoproteins, and a variety of platform technologies are being considered (e.g., virus vectors, protein subunits, messenger RNA (mRNA), DNA, and virus-like particles) (Amaya 2020, Geisbert 2021, Gómez Román 2022, Loomis 2021, Monath 2022). NiV vaccine candidates based on several different platforms are in phase 1 clinical trials (Auro Vaccines 2022, NIAID 2023, Public Health Vaccines 2023, Oxford Vaccine Group 2023).
- Demonstrating vaccine-induced protection against NiV infection or disease in an animal model will require an immune correlate of protection (CoP) or immune surrogate that can predict the likelihood of protective efficacy and that reflects the protective immune responses generated in humans (Amaya 2020, Escudero-Pérez 2023, Price 2021).
    - Accurate and reliable CoPs for determining the protective efficacy of NiV vaccines have not yet been identified (Loomis 2021). Neutralizing antibody is generally used as a CoP, although the protective threshold still needs to be defined to allow additional vaccine testing in animal challenge models and eventual immunobridging of antibody responses to humans, through phase 1/2 clinical studies (Escudero-Pérez 2023, Price 2021).
    - Once the protective threshold for neutralizing antibodies is determined, the most appropriate and feasible assays (e.g., assays that are developed using live NiV vs. assays developed using pseudoviruses expressing the NiV F and G glycoproteins) (Luo 2023) need to be identified and standardized for use in animal models (Price 2021).
    - NiV vaccines can also be protective even in the absence of detectable neutralizing antibodies depending on the vector, antigen, time, and source of challenge and vaccination route, pointing to mechanisms of protection other than neutralizing antibodies (de Wit 2023a, Welch 2023). Further research is needed to better understand these mechanisms. Different types or titers of CoPs may ultimately be needed for different vaccine platforms, antigens, clinical outcomes (e.g., protection against infection, severe disease, chronic disease, or death) and potentially host or population characteristics to support the assessment of candidate NiV vaccines using immunogenicity and efficacy data from preclinical studies.
    - Other humoral immune responses that may be relevant as COPs include

specific titers of immunoglobulin M (IgM) antibodies, and numbers of plasmablasts and activated B cells (Escudero-Pérez 2023). With regard to cellular immune responses, cytotoxic T lymphocytes that express CD8 on their surface (CD8+ T-cell) measurements may be useful as a CoP (Escudero-Pérez 2023). Additional research is needed to better define these potential CoPs, which may be particularly important for next-generation vaccines.

- Most current NiV vaccine candidates target the immunodominant F and G glycoproteins, which elicit potent neutralizing antibody responses (Byrne 2023, Geisbert 2021, Ithinji 2022, Loomis 2020, Loomis 2021, van Doremalen 2022, Wang 2022, Woolsey 2023). Data are needed on the potential role of additional immunogens, such as nucleoproteins and other non-envelope proteins, in stimulating B- and T-cell responses that contribute to viral clearance, cross-protection, or immune memory. Robust vaccine-induced humoral and cell-mediated immunity to NiV might include protective antibodies with durable immunological memory and rapid and efficient effector functions (Escudero-Pérez 2023).
- Additional immunological research is needed to assess the following key elements of protective immunity against NiV infection and disease:
    - The relative contributions of innate, cell-mediated, and humoral immune responses that lead to protective immunity against NiV.
    - Specific cell types and interactions between different immune compartments in achieving viral clearance, surviving acute disease, and modulating chronic infection (Escudero-Pérez 2023, Liew 2022).
    - The roles that neutralizing and non-neutralizing or binding antibodies play in protecting against NiVD (Liew 2022).
    - Mechanisms and cell subsets of cellular immune responses (e.g., CD8 T-cell activation) that play a role in cross-neutralizing (heterologous) protection against co-circulating NiV strains (e.g., NiV-M, NiV-B, and NiV-I) (Amaya 2020, Arunkumar 2019, Escudero-Pérez 2023, Liew 2022).
- If researchers and regulators agree that a nontraditional regulatory pathway is appropriate for licensure of NiV vaccines, then a number of issues need to be addressed, such as the following (Price 2021):
    - Generate a fully characterized and controlled virus challenge stock (or potentially one each for NiV-M and NiV-B) for assessing candidate vaccines in animal models.
    - Further characterize, as needed, at least one animal model suitable for vaccine efficacy evaluation.
    - Standardize the challenge strain and dose, and determine the most appropriate lethal NiV dose for MCM development. Challenge strains used in experimental research also need to be compared against any circulating strains in humans (CEPI 2023).
    - Determine the most appropriate CoP or surrogate marker (e.g., neutralizing antibodies) for measuring protection and generate standardized assays for measurement.

- Bridge NiV vaccine efficacy data from animal models to humans, including identifying thresholds of vaccine protection, to determine appropriate human vaccine doses.
- If the accelerated approval process is deemed an acceptable regulatory approval pathway for NiV vaccines, then plans will be needed to conduct well-controlled clinical trials to establish that vaccines have an effect on an appropriate surrogate endpoint that is likely to predict clinical benefit against NiVD.
- Post-licensure clinical trials will also be needed to confirm the clinical benefit of any NiV vaccines that are approved via nontraditional pathways.

- Additional research is also needed to address the following areas:
  - Clarification of vaccine attributes (such as time from administration to immune protection, duration of immunity, and the need for booster doses) and to determine safety profiles of candidate vaccines.
  - Alternative vaccine delivery approaches, such as oral tablets or transdermal patches, to facilitate rapid NiV vaccine deployment in response to NiV outbreaks in low-resource settings.
  - Further evaluation of optimal NiV antigen combinations (e.g., including stabilized prefusion F protein trimers, multimeric G constructs, and chimeric proteins containing both pre-F and G glycoproteins), and antigen/vaccine platform combinations for generating rapid and durable protective responses to NiV infection (Byrne 2023, Loomis 2020, Loomis 2021, Srivastava 2023b).
  - Research in animal models to determine if vaccine candidates are cross-protective between different NiV strains, including recently identified strains; only a few studies demonstrating cross-protection have been performed to date.
- Mathematical modelling and forecasting may be useful in (Nikolay 2021) (1) assessing whether or not disease incidence is high enough in endemic areas for conducting clinical trials of candidate vaccines, (2) simulating various epidemiological scenarios for development of vaccination strategies, (3) estimating the potential impact of NiV vaccines (once vaccines become available), (4) estimating disease risk based on risk behaviors and practices in communities or specific population groups, and (5) estimating the vaccine quantity that may be necessary to maintain stockpiles.
- Researchers should consider efforts towards developing pan-henipavirus vaccines to maximize potential benefit, similar to projects aimed at developing pan-coronavirus vaccines or universal influenza vaccines (Tan 2023). One strategy for developing broadly protective henipavirus vaccines involves identifying conserved epitopes or cross-reactive antibodies targeting henipavirus F proteins (Byrne 2023, Dang 2019, Dang 2021, Ithinji 2022, Mire 2020). Notably, a Hendra virus recombinant subunit vaccine (HeV-sG) that protects against both NiV (Malaysia and Bangladesh strains) and HeV is in clinical development (Geisbert 2021).
- Public communication outreach strategies are needed that address possible vaccine

uptake hesitancy in target populations and guidance for community sensitization to vaccine acceptation and promotion within the community.

- Once vaccines are available, the following will be needed:
    - Guidance on the use of NiV vaccines to include vaccination strategies for special populations (such as children, immunocompromised people, and pregnant women), different epidemiological scenarios, and different vaccine attributes.
    - Enhanced surveillance capacity to assess the impact of vaccination programmes and to refine vaccination strategies over time.
    - Strategic planning for stockpiling and deploying NiV vaccines.

Strategic Goals and Aligned Milestones

Strategic Goal 4.1: Develop the tools and policies necessary for evaluating and potentially approving one or more NiV candidate vaccines through a nontraditional regulatory pathway.

Milestone 4.1.a: By 2024, generate a fully characterized and controlled virus challenge stock (preferably using an NiV-B strain) for assessing candidate vaccines in animal models.

Milestone 4.1.b: By 2025, generate standardized assays to measure immunoglobulin G (IgG) antibodies for NiV vaccine R&D, with a particular focus on assays to be used for regulatory approval via nontraditional pathways.

Milestone 4.1.c: By 2025, in conjunction with regulatory authorities, establish benchmark parameters (e.g., route of challenge, timing of challenge, and challenge dose) for testing NiV candidate vaccines in well-characterized animal models, with particular focus toward meeting criteria necessary for approval via a nontraditional pathway, including identifying surrogate markers that correlate with vaccine efficacy.

Milestone 4.1.d: By 2025, describe the range of possible protective thresholds against NiV infection for serum neutralizing antibodies or other functional CoPs, which can be used in animal studies and for immunobridging to humans.

Strategic Goal 4.2: Continue to move the current NiV vaccine pipeline forward through clinical trials.

Milestone 4.2.a: By 2024, complete current phase 1 clinical trials for at least three promising NiV candidate vaccines.

Milestone 4.2.b: By 2025, define use cases for NiV vaccines to inform vaccine deployment and manufacturing plans.

Milestone 4.2.c: By 2025, initiate phase 2 clinical trials, preferably in affected areas, to further assess immunogenicity and safety for at least two of the most promising NiV candidate vaccines.

Milestone 4.2.d: By 2028, conduct additional well-controlled phase 2 clinical trials in affected areas to assess a surrogate endpoint in human subjects—including children and pregnant women—for at least two NiV candidate vaccines.

Milestone 4.2.e: By 2029, complete a regulatory dossier for licensure or emergency use for at least one NiV vaccine candidate based on a suitable animal model with subsequent immunobridging to humans for review via a nontraditional approval pathway.

Additional Priority Areas/Activities

Research

Improve understanding of humoral (e.g., NiV-specific IgG and IgM antibodies) and cellular (e.g., CD8+ T-cell) immune responses to NiV infection in animal models to inform the design of vaccines and the identification of correlates of protection (Arunkumar 2019, Escudero-Pérez 2023).

Improve understanding of innate immune responses (e.g., involving interferon impairment and pro-inflammatory cytokine release) in relation to humoral and cellular immune responses to NiV infection (Escudero-Pérez 2023).

Continue research on identifying the key NiV antigens (including surface glycoproteins and internal proteins) that modulate the host immune response to NiV infection to inform future vaccine design (Escudero-Pérez 2023).

Continue to research different types of CoPs (both humoral and cell-mediated) for NiV vaccines that are currently in the R&D pipeline and next-generation vaccines, taking into consideration different vaccine platforms, antigens, and clinical outcomes.

Generate international reference standards to calibrate serological assays for vaccine potency analyses.

Continue to conduct preclinical evaluation of promising candidate NiV vaccines (current and future vaccines) for safety, immunogenicity,

efficacy in animal models, correlates of protection, and durability.

Further study the cross protection of various vaccine candidates against different NiV strains, and between NiV strains and HeV strains.

Conduct mathematical modelling to estimate the potential impact of NiV vaccines and inform strategies for vaccine use.

Explore the possibility of creating pan-henipavirus vaccines that will protect against NiV, HeV, and other henipaviruses.

Product development

Continue to develop and clinically evaluate safe and effective monovalent NiV vaccines for humans.

Expand partnerships among researchers, government agencies, and industry to provide the resources necessary for ongoing R&D of NiV vaccines.

Define vaccine attributes (such as time from administration to immune protection, durability of protection, and the need for booster doses) for the most promising candidate vaccines.

Key capacities

Improve surveillance capabilities to assess the impact of vaccine use and vaccination strategies once vaccines become available.

Support plans for adequate manufacturing and stockpiling of NiV vaccines for further clinical evaluation and use when outbreaks occur.

Policy and commercialization

Provide guidance on vaccination strategies for various target populations and epidemiological scenarios that align with vaccine attributes, once vaccines are available.

Develop guidance for community sensitization to vaccine acceptance and promotion within the community.

Consider developing a strategy for vaccine surge capacity to rapidly ramp up the vaccine supply, if NiV is used as a bioterrorism agent or if an NiV strain emerges with increased capacity for person-to-person transmission and potential for faster spread.

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