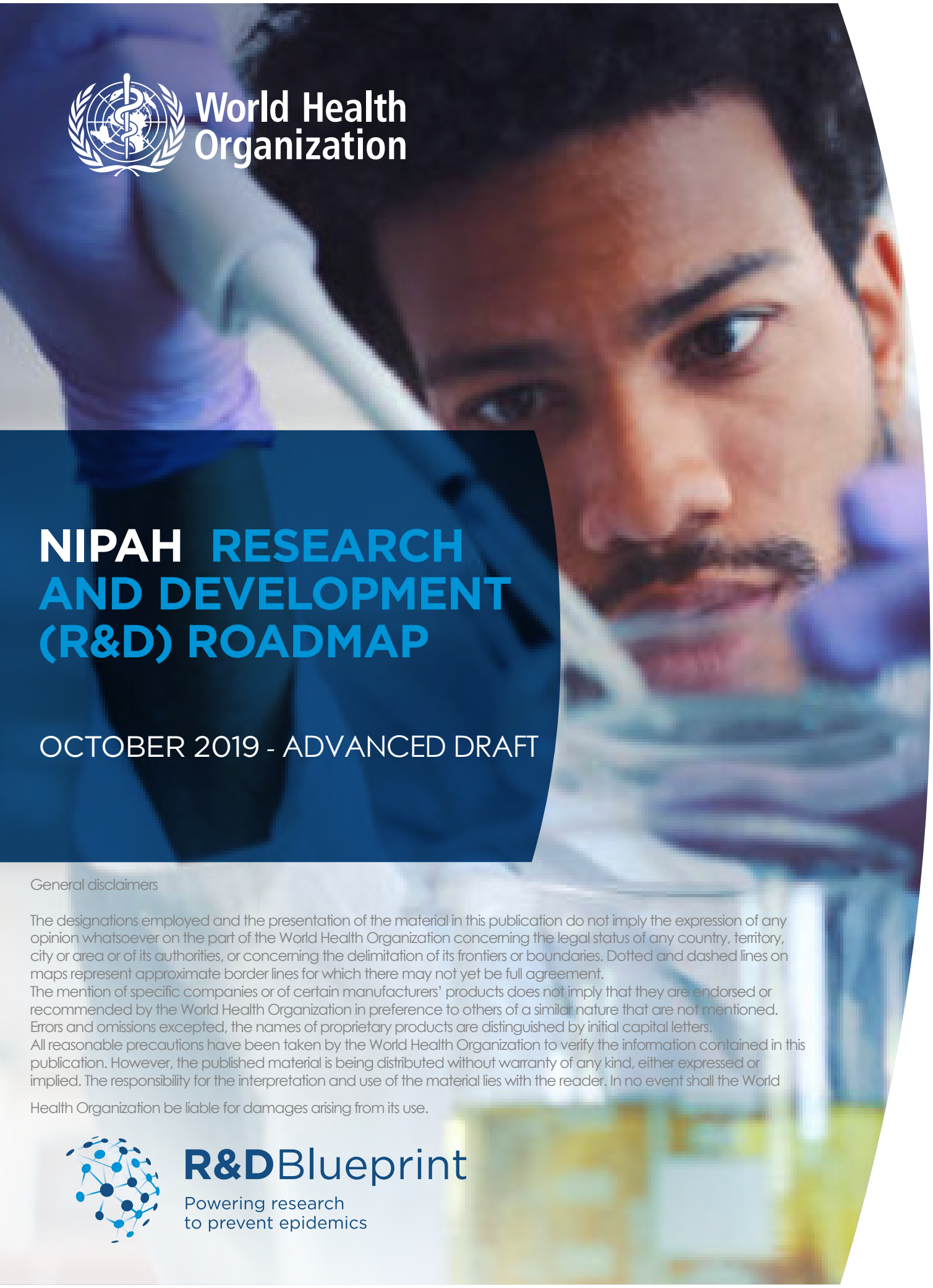


World Health Organization

NIPAH RESEARCH AND DEVELOPMENT (R&D) ROADMAP

OCTOBER 2019 - ADVANCED DRAFT

R&DBlueprint

Powering research
to prevent epidemics

Abbreviationa & Acronyms

AGM	African green monkey
BSL-4	biosafety level 4
CNS	central nervous system
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration (USA)
HeV	Hendra virus
IFNAR-KO	interferon-alpha/beta receptor knockout
mAb	monoclonal antibody
MCM	medical countermeasure
MTA	material transfer agreement
NiV	Nipah virus
NRA	national regulatory authority
PCR	polymerase chain reaction
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PK	pharmacokinetic
POC	point-of-care
PPE	personal protective equipment
R&D	research and development
RCT	randomized control trial
rRT	real-time reverse transcriptase
TPP	target product profile
WHO	World Health Organization

Contents

Roadmap purpose: to provide a 5-year framework for identifying the vision, underpinning strategic goals and prioritizing areas and activities (from basic research towards 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 infection.

Introduction

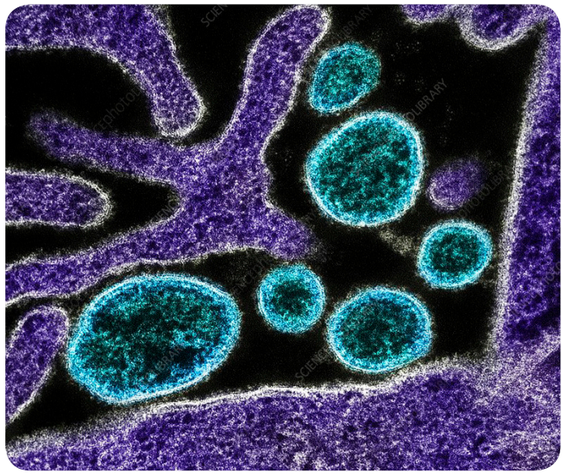
Nipah virus (NiV) is a paramyxovirus that was first identified as a zoonotic pathogen after an outbreak involving respiratory illness in pigs and severe encephalitic disease in humans occurred in Malaysia and Singapore in 1998 and 1999. As part of that outbreak, 265 human cases were identified in Malaysia, 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. NiV infection was subsequently recognized, however, in Bangladesh in 2001, and nearly annual outbreaks have occurred in that country since.

NiV infection has also being recognized periodically in eastern India and, in 2018, was identified for the first time in southern India. Case-fatality rates during outbreaks in Bangladesh and India have ranged from 75% to 100%. Other regions may be at risk for NiV infection, as serologic evidence for NiV has been found in the known natural reservoir (Pteropus species and several other bat species) in a number of other countries, including Cambodia, Thailand, Indonesia, Madagascar, Ghana and the Philippines. In the 1998 to 1999 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, several other domestic animal species on the farms involved in the outbreak (including horses, cats and dogs), were found to be infected with NiV. In the outbreaks in Bangladesh, intermediary hosts between bat and human have not played a major role, with the primary modes of NiV transmission being human consumption of bat-contaminated raw date-palm sap, and subsequent person-to-person transmission.

The zoonotic potential of NiV is significant, particularly because of its ability to amplify in livestock, which can serve as a source of exposure to humans. NiV is part of the Henipavirus genus; this genus also includes another zoonotic pathogen – Hendra virus (HeV) – that predominantly causes infection in horses and can also lead to human disease (usually following contact with infected horses). HeV was initially recognized in 1994 following an outbreak of fatal cases of severe respiratory disease in horses and humans in the Brisbane suburb of Hendra in Queensland, Australia. To date, confirmed HeV disease has been confined to Australia. An outbreak of an unidentified henipavirus (possibly NiV, or a closely related virus) occurred among horses and humans in the Philippines in 2014. This outbreak likely involved spillover of NiV into horses and subsequent disease in humans following consumption of contaminated horsemeat; disease also occurred in health-care workers who cared for NiV-infected patients. Detailed genomic information for this virus is limited.

NiV infection in humans results in neurologic 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. Genomic sequencing has demonstrated that there are multiple strains of NiV; for example, the strain responsible for the outbreak in Malaysia is different from those identified in Bangladesh and India. Some differences have been noted in the clinical features of infection, with different strains in humans and experimentally infected non-human primates.

NIPAH RESEARCH AND DEVELOPMENT (R&D) ROADMAP



The R&D roadmap for NiV infection is a key component of the World Health Organization (WHO) R&D Blueprint initiative for accelerating research and product development of MCMs to enable effective and timely emergency response to infectious disease epidemics. NiV infection is identified in the Blueprint's list of "priority diseases" (defined as diseases that are likely to cause severe outbreaks in the near future and for which few or no MCMs exist). The Blueprint calls for the development of R&D roadmaps for the priority diseases to align and stimulate R&D of new or improved countermeasures, such as rapid diagnostic assays, novel therapeutics and effective vaccines. 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 to more than one MCM category), diagnostics, therapeutics and vaccines. (Note: these topics are not presented in order of public-health priority). The strategic goals and milestones identified in the roadmap are focused on key achievements for the next five years; the roadmap milestones will be tracked over time, with periodic assessment of progress and updating as needed.

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 the R&D roadmap, but need to be addressed as part of a broader public-health control strategy. Further research of NiV in animal species, including development of appropriate MCMs targeted to animal populations, is also needed, since disease in animals may amplify occurrence of NiV (or related henipavirus species) in humans, and virus transmission can occur at the human-animal interface.

VISION

Ready availability and accessibility of robust MCMs to detect, prevent and control human outbreaks of NiV infection (and other closely related henipaviruses) for use in areas of known or potential NiV spillover. These MCMs include: (1) rapid and accurate, point-of-care (POC) diagnostics; (2) safe and effective treatment and post-exposure prophylaxis (PEP); (3) safe and effective vaccines to prevent disease, disability and death.

Cross-cutting issues

Primary challenges, key needs and knowledge gaps

Primary challenges

- Securing funding for Nipah research represents a substantial challenge, since economic incentives to invest in Nipah 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 small and sporadic outbreaks. 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 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. In addition, licensure of vaccines and therapeutics using alternative regulatory pathways can be very costly, given the regulatory requirements for such approval.
- 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, which can increase the cost of MCM development.

- To date, NiV spillovers to human communities have been identified most commonly in rural communities in Bangladesh and India; the health-care facilities that serve these communities have limited laboratory and clinical infrastructure for diagnosis and treatment.
- The natural reservoir for NiV is fruit bats of the Pteropus genus; these bats have a wide geographic range that stretches across much of the Western Pacific region, South-East and South Asia and Madagascar. Evidence also suggests that other fruit bats of the Pteropodidae family may harbour NiV; such bats can be found across Africa and parts of the Middle East.
- 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.
- While ferrets, Syrian hamsters and interferon-alpha/beta receptor knockout (IFNAR-KO) mice 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. Additionally, studies involving the AGM model may be required for licensure of MCMs via alternative regulatory pathways. Costs, space requirements (particularly in BSL-4 containment facilities) and ethical concerns constrain the use of AGMs.
- 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 NiV infection 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. It may be possible to address this issue by enhancing case detection through improved surveillance and by combining clinical trial data over time, including across outbreaks. 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 (for example, randomized controlled trials [RCTs]) are not feasible.

Key needs

- 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.

- 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.

- 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.

- Obtaining additional prospective serosurveillance data of henipavirus exposure from susceptible animal species and proximate human populations in areas of predicted risk, should be explored as a strategy to assess the potential of human spillover and to build preparedness for detection of human cases and for limiting exposure.

- Standardized and well-characterized assays (to be further defined based on end use), reagents, antibodies, nucleic acids and NiV challenge strains for R&D of MCMs for NiV infection. Assays that can be used at lower biosafety levels are an important priority. The WHO international standards should be used (when available) as calibrators and reported in units/ml to harmonize assay results.

- Clear criteria for downselection and prioritization of candidate MCMs to move forward into clinical trials versus those that need additional preclinical research. Such criteria should align with desired characteristics outlined in the target product profiles (TPPs), and should address aspects of sustainable MCM production, stockpiling and access.

- Early and recurrent communications between product developers and the appropriate national regulatory authorities (NRAs), or other regulatory agencies, to obtain clarity and guidance on clinical trial requirements, regulatory pathways and requirements, and other considerations for NiV MCMs during the pre-licensure and post-licensure periods. Regulatory pathways and NRA capabilities will vary between countries; therefore, early engagement, potentially with support from the WHO, is essential to identify country-specific considerations.

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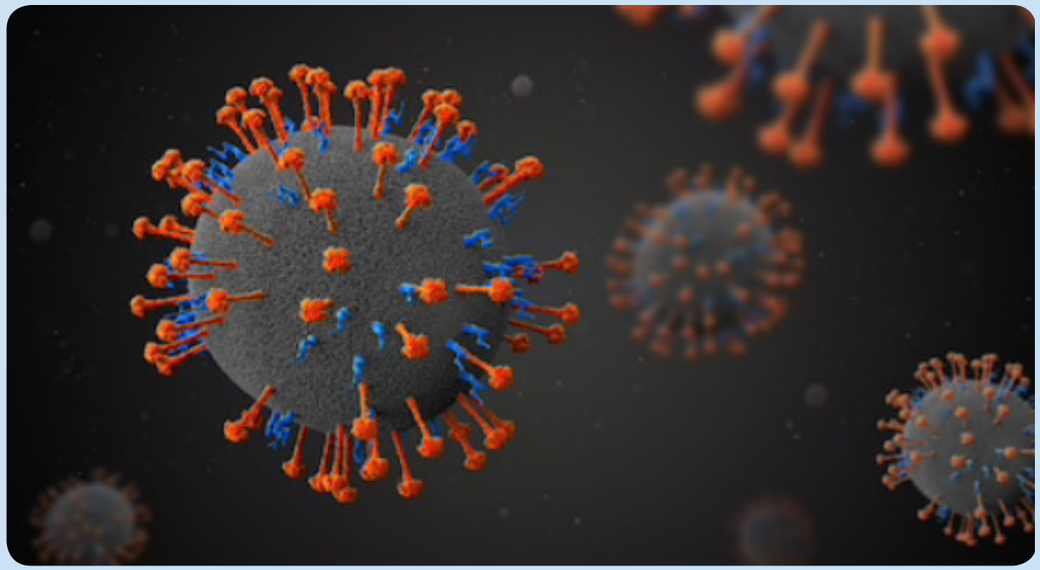
- Outreach and education to clinicians and community health workers to improve NiV awareness, training and outbreak preparedness (for example, disease diagnosis, clinical management and infection prevention and control), and to ensure availability of diagnostic tools in endemic areas to increase the likelihood of accurate and timely diagnosis and treatment of NiV infection.

- 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.

- 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. 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.



Knowledge gaps

- Continued R&D, improved manufacturing processes, deployment and assessment of 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 disease in endemic areas and to monitor the occurrence of spillover incidents from bats to humans, or livestock, in new geographic areas. 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.
- Additional research is needed to optimize relevant animal challenge models (such as, ferret, Syrian hamster, IFNAR-KO mouse and AGM models) for promoting development and evaluation of MCMs, particularly if investigators are required to use an alternative pathway (such as the United States Food and Drug Administration's [FDA's] Animal Rule) to obtain regulatory approval. For example, efforts are needed to: (1) determine the appropriate animal model(s) for screening assay development; (2) standardize the challenge strain and dose, and determine the most appropriate lethal NiV dose for MCM development; (3) determine when after-challenge MCMs should be administered in animal models to best mimic realistic timing of MCM use in humans; (4) bridge NiV MCM data from animal models to humans, such as identifying thresholds of vaccine protection to determine appropriate human MCM doses; (5) identify the best models for studying chronic (relapsing) infection.
- Additional information is needed on the virology, immunology and pathogenesis of NiV in humans and animals to inform development of NiV MCMs. This includes evaluating the pathophysiologic differences between different NiV strains, determining the mechanisms that allow NiV to escape immunologic clearance and cause delayed onset or recurrent encephalitis, identifying factors influencing the development of permanent neurologic sequelae and further characterizing cell-mediated and humoral immune responses to NiV infection. In addition, identifying aspects of the immune response that are absent or counter-effective during human NiV infection may lead to the development of novel targeted intervention strategies.
- Ongoing phylogenetic and evolutionary analyses of NiV strains are needed to monitor viral heterogeneity and antigenic changes that may affect the epidemiologic and clinical features of disease over time and thereby influence MCM development.
- Further research is needed to better understand viruses in the henipavirus genus, including their reservoir hosts and pathogenicity.
- Additional studies, applying whole-genome sequencing of NiV, are needed to generate a comprehensive phylogenetic mapping of the global genetic variability among henipaviruses.
- Sociological and anthropological research is needed to understand how to best engage populations at high risk of exposure (such as persons who consume date palm sap, health-care 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.

Strategic goals and aligned milestones

Strategic Goal 1

To identify sources of private- and public-sector funding and develop appropriate incentives and competitions to promote R&D of NiV MCMs.

Milestones

1. By 2019, develop a public value proposition to effectively advocate for the development and sustainability of NiV MCMs that: (1) articulates the potential global threat of NiV infection; (2) outlines the social and economic benefits of generating accessible and affordable NiV MCMs; (3) details the positive impact on the health systems in affected areas.

2. By 2019, create a funding plan for moving NiV diagnostics, therapeutics and vaccines towards clinical evaluation, licensure/approval, acceptance and sustainable access.

Strategic Goal 2

To improve understanding of NiV epidemiology and ecology to estimate the relative risk and potential for global spread of NiV outbreaks.

Milestones

1. By 2021, develop a plan for enhancing NiV surveillance, including securing funding, identifying surveillance catchment areas, engaging key partners in those areas, generating a standardized protocol and conducting training for implementation.

2. By 2022, initiate enhanced NiV surveillance to better characterize NiV epidemiology (including the potential for spillover events), enhance case detection and better define the disease burden in different geographic areas.

Strategic Goal 3

To support basic science research to improve understanding of NiV virology, pathogenesis and the immune response to infection in humans and animal models.

Milestones

1. By 2020, generate standardized and well-characterized assays, reagents, antibodies, nucleic acids and NiV challenge strains to facilitate R&D of NiV MCMs.

2. By 2021, optimize animal models that recapitulate disease in humans for use in preclinical studies of NiV MCMs and that may be necessary for licensure of MCM products (particularly vaccines) via non-traditional regulatory pathways.

Priority areas/activities

Research

- **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 geographic areas, using a One Health approach.
- **Continue** to perform phylogenetic and evolutionary analyses of NiV strains to monitor antigenic changes and characterize genetic diversity over time.
- **Continue** to conduct basic science research on the virology, pathogenesis and immunology of NiV infections to inform development of MCMs.
- **Determine** key differences in pathogenesis for different NiV strains that may have implications for the development of safe and effective NiV vaccines or therapies.
- **Refine and optimize** relevant animal models to support the development and evaluation of NiV MCMs, particularly as needed for licensure, if alternative regulatory pathways are considered.
- **Generate** research tools to promote R&D of MCMs for NiV infection (such as, standardized and validated assays, reagents, antibodies, nucleic acids and NiV challenge strains), particularly those that can be used at lower biosafety levels.
- **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

- **Define** criteria for downselection and prioritization of candidate MCMs that should be moved forward.
- **Promote** early communication between developers and appropriate national regulatory authorities (NRAs) for clarity and guidance on the regulatory aspects of MCM development for NiV infection.

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; (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** a shared data platform to facilitate sharing of NiV sequence and strain data.
- **Collaborate** with local government authorities (including human health, animal health and wildlife representatives) to support NiV surveillance and disease prevention activities in endemic and at-risk areas.
- **Promote** community-based outreach programmes that transfer skills and knowledge for the prevention and early recognition of NiV disease in areas of known or potential NiV spillover risk.
- **Strengthen** infrastructure and capacity for post-marketing pharmacovigilance of licensed NiV therapeutics and vaccines.

Policy and commercialization

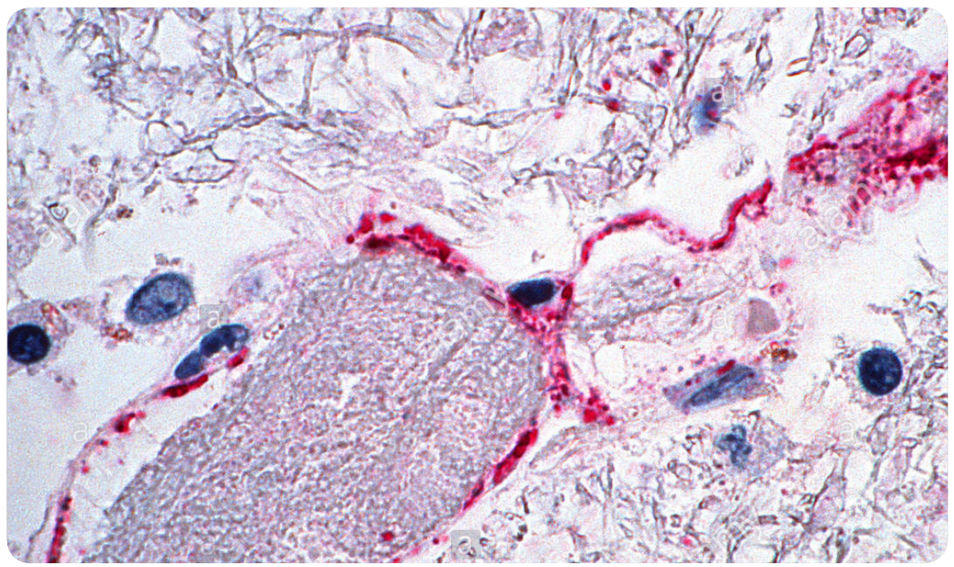
- **Establish** a sustainable value proposition and secure funding to complete development, licensure, manufacture, deployment and use of affordable MCMs for NiV infection.
- **Support** plans for adequate manufacturing and subsequent distribution of NiV diagnostics, therapeutics and vaccines to endemic and at-risk areas.
- **Ensure** access to regulatory guidance, oversight, review and authorization from appropriate NRAs for NiV MCMs. This should be done when clinical trials and approaches for regulatory approval are being determined.
- **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 that 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

Primary challenges, key needs and knowledge gaps

Primary challenges

- Initial signs and symptoms of NiV infection are nonspecific, and the diagnosis 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 disease can occur months to years after initial infection, which can complicate epidemiologic investigation.
- Laboratory infrastructure and diagnostic capabilities, in endemic and at-risk areas, are often limited and investigation into the cause of infection is not always pursued; these issues can lead to delays in diagnosis, and outbreak investigation and response.
- Clinical sample quality, quantity, type, timing of collection and the time necessary to transfer the sample from the patient to the laboratory can affect the accuracy of laboratory results.
- Various types of test methods and platforms are required to test patients at different phases of NiV infection, and this can complicate diagnostic needs and capabilities.
- Owing to the biosafety precautions necessary when working with NiV, diagnostic testing of clinical specimens for NiV in under-resourced areas poses safety and logistical challenges with regard to collection, handling, transport, and laboratory analysis.
- The time required to perform diagnostic testing using conventional laboratory methods, is problematic given the rapid disease progression of NiV infection.
- Currently, no approved tests for diagnosis of NiV infection are commercially available.
- Pteropus species (and perhaps other bat species) appear to carry other henipaviruses in addition to NiV and HeV, some of which may prove to be pathogenic in humans and livestock. Antibodies to different henipaviruses are highly cross-reactive, making it difficult using serologic assays to differentiate which henipaviruses are in circulation. Capacity to identify additional pathogenic henipaviruses is an important challenge for ensuring diagnostic preparedness to respond to future outbreaks.



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Key needs

- Clarification regarding the use cases for different diagnostic assays, since the corresponding performance, validation and regulatory approval requirements may differ depending on how the tests will be used. For example, it may be desirable to have a POC screening test that is highly sensitive and a confirmatory test that is highly specific.
- A TPP for NiV diagnostics that identifies the key use cases and optimal and desirable characteristics to guide the development of promising diagnostic assays.
- A virtual repository (with specimens being held and maintained in the countries of origin) of clinical samples, to assess and validate diagnostic tests. 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 (for example, 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; (8) ensure that material transfer agreements (MTAs) are in place. (Samples obtained from laboratory animals also can be used to assess diagnostic assays during the time frame when the virtual repository is being created).
- Rapid POC or near-patient diagnostic tests for NiV, which involve minimal requirements for laboratory infrastructure, can detect disease early in the clinical course, are robust for use under a variety of conditions (such as, varying humidity, temperature) and have a high sensitivity and specificity for different NiV strains, as needed, depending on the use cases for each test. Rapid diagnostic capability is needed for early case detection to promote outbreak detection, ensure early implementation of infection control measures and, ultimately, to improve patient outcomes, once therapeutic options are available.
- International reference standards to calibrate diagnostic assays.
- Validation of promising diagnostics in endemic and at-risk geographic regions.
- Diagnostic criteria and standardized testing for including patients in clinical trials of therapeutics.
- Improved diagnostic preparedness in at-risk areas to detect NiV, HeV and other emergent henipaviruses as they arise.
- Optimal deployment strategies for diagnostics in different geographic areas based on the risk and epidemiology of NiV infection.
- In-country laboratories able to conduct proficiency testing to monitor reproducibility and performance of NiV diagnostic assays in the field.
- A sufficient number of laboratories committed to using the diagnostics on a regular basis to support the business case for Nipah diagnostics, particularly given the costs of regulatory approval.

Knowledge gaps

- Further research is needed on the kinetics of NiV detection in cerebrospinal fluid, blood, saliva, other body fluids (for example, urine and respiratory secretions) and tissue samples, to enhance the ability to diagnose infection at different stages of disease.
- More information is needed regarding the performance characteristics (including sensitivity, specificity, limits of detection, cross-reactivity and quantitative versus qualitative data) for NiV assays, particularly for newer tests (such as pseudotype neutralization assays and antigen-capture enzyme-linked immunosorbent assays [ELISAs]) 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.

Strategic goals and aligned milestones

Strategic Goal 1

To support development of diagnostic assays through creation of a virtual reference repository of clinical samples from NiV-infected patients.

Milestones

1. By 2019, develop and standardize plans and protocols (including the governance structure) for creating a virtual reference repository of well-characterized clinical samples to be maintained in the two primary NiV-affected countries: Bangladesh and India.
2. By 2021, identify funding and initiate creation of the virtual reference repositoryin Bangladesh and India, with samples to be collected during future outbreaks and possibly as part of future clinical trials.

Strategic Goal 2

To develop and assess affordable, highly sensitive and specific (as needed depending on intended use) POC or near-patient NiV diagnostic tests that are sufficiently robust for the conditions in which they will be used and that have minimal requirements for biosafety precautions and staff training.

Milestones

1. By 2019, generate a TPP for NiV diagnostics that identifies the primary use cases and optimal and desirable characteristics to guide the development of promising NiV diagnostic assays.
2. By 2019, engage appropriate regulatory agencies and NRAs to inform commercialization pathways for NiV diagnostic assays.
3. By 2021, complete preclinical evaluation for at least two of the most promising NiV POC or near-patient diagnostic assays that align with the TPP.
4. By 2022, complete field studies for at least two of the most promising NiV POC or near-patient diagnostic assays that align with the TPP.

Strategic Goal 3

To enhance laboratory diagnostic preparedness in areas of known or potential spillover risk to promote early detection of NiV.

Milestones

1. By 2021, develop national laboratory strategies for NiV detection, in the primary affected countries, that include plans for enhancing laboratory preparedness to diagnose NiV infection during future outbreaks.

Priority areas/activities

Research

- **Create** a virtual repository of clinical reference samples for use in researching new diagnostic agents.
- **Explore** new diagnostic approaches that may allow earlier detection of infection.
- **Further evaluate** the kinetics of NiV detection in cerebrospinal fluid, blood, saliva, other body fluids and tissue samples to enhance the ability to diagnose NiV infection at different stages of disease.
- **Determine** performance characteristics for promising new assays for diagnosis of NiV infection and **develop** appropriate standards for their use in different contexts.
- **Conduct** field evaluation studies to assess and validate new diagnostic tests for NiV infection.

Product development

- **Generate** a TPP for NiV diagnostics that defines the use cases and addresses the optimal and preferred performance characteristics for different use cases.
- **Develop and evaluate** POC or 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 remote areas under a variety of circumstances.

Key capacities

- **Generate** international reference standards to calibrate diagnostic assays.
- **Develop** national laboratory strategies for NiV diagnosis and detection in the primary NiV-affected countries.
- **Support** in-country laboratories in monitoring performance of NiV diagnostics in the field.
- **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 geographic areas, as such tests become available.

Therapeutics

Primary challenges, key needs and knowledge gaps

Primary challenges

- Patients typically present late in the clinical course of disease, which decreases the likelihood of successful treatment.
- Sociocultural issues may hinder trust in the formal health-care and public-health systems, which could reduce acceptance of NiV therapeutics.
- The absence of improved diagnostic assays for timely diagnosis and surveillance of infection creates an important challenge in providing early treatment of patients and post-exposure prophylaxis (PEP) for exposed persons.
- In NiV-endemic areas, hundreds of patients annually are admitted to hospitals with a diagnosis of encephalitis but do not have NiV infection. Treating all patients with encephalitis, and their contacts, for NiV infection, would be costly and labour intensive, with relatively little benefit; hence, accurate and rapid diagnosis is critical.
- Studies in animals often evaluate the usefulness of therapeutics when delivered prior to disease onset or early during the disease course. Patients with NiV infection are often detected later in the clinical course, which creates challenges for predicting how well a therapeutic agent will work in the field.
- NiV can infect the central nervous system (CNS), which creates challenges for generating therapeutic agents that cross the blood-brain barrier to inhibit viral replication and prevent severe neurologic disease.
- Health-care systems in endemic countries often do not have adequate infection-control programmes in place to prevent person-to-person transmission. They often also lack the ability to rapidly identify contacts most likely to benefit from PEP therapy.
- A limiting constraint to assessing the effectiveness of promising therapies is the number of patients with NiV infection that can be enrolled in clinical trials, given the small number of cases that are detected annually.

Key needs

- Protocols for conducting safety and efficacy clinical trials of promising therapeutic candidates, to be implemented in NiV-affected areas, particularly during future outbreaks.
- Safe, easily administered, well-tolerated and effective therapeutic agents that treat acute NiV infection, to improve survival and decrease associated morbidity and long-term disability.
- Safe and effective PEP, to prevent infection following exposure to NiV, and guidance on PEP use. PEP could be used to prevent illness in health-care workers, family caregivers and individuals exposed to infected livestock.
- Improved patient care in endemic areas (such as the ability to provide ventilator support for seriously ill patients).
- A transparent and collaborative process is needed to determine which agents are most appropriate for study in future clinical trials, given the limited number of cases that could potentially be enrolled in trials each year.

NIPAH RESEARCH AND DEVELOPMENT (R&D) ROADMAP

Knowledge gaps

- The human monoclonal antibody (mAb) m102.4 has demonstrated protection against lethal NiV challenge in animal models and has been provided as part of compassionate use programmes for a small number of individuals exposed to either HeV or NiV. Recently, a phase 1 clinical trial for m102.4 was completed in Australia with 40 human participants. Additional animal studies, using different NiV strains and clinical trials in endemic areas, are needed to further assess the safety, tolerability and efficacy of m102.4 (and possibly other mAbs) for PEP and potentially early treatment of clinical disease.
- Additional research is needed regarding the likelihood of escape mutants with mAb use. While evidence of escape mutants has not been found to date with mAb 102.4, it may be necessary to consider mAb cocktails.
- Preclinical and clinical data are needed on the safety, tolerability and efficacy of the most promising novel treatments (such as fusion inhibitory peptides, antifusion peptides, favipiravir [an RNA-dependent RNA polymerase inhibitor] and GS-5734 [a broad-spectrum agent being used to treat Ebola virus disease survivors]) used alone, or in combination with other therapies. Additionally, the therapeutic windows of each therapy should be determined for different NiV strains, as highlighted by a recent 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.
- Further research is needed to broaden the number of novel antiviral candidates for treatment of NiV infection and to strengthen the therapeutic pipeline.
- Additional data are needed to establish the pharmacokinetic/pharmacodynamic (PK/PD) relationship of promising therapeutic candidates.
- Additional data are needed 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 distribution in both endemic and at-risk areas, including Bangladesh, which has annually hundreds of potentially exposed persons that could be candidates for PEP.
- Additional information is needed regarding whether or not strain differences will affect the response to therapeutic candidates and results from clinical trials.
- 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 NiV, 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.

Strategic goals and aligned milestones

Strategic Goal 1

To enhance preparedness to conduct clinical trials of therapeutic agents during future NiV outbreaks.

Milestones

1. By 2019, complete a protocol for conducting safety and efficacy clinical trials of promising therapeutic candidates, to be implemented in NiV-affected areas, and develop plans for operationalizing the protocol.
2. By 2019, complete a protocol for conducting PEP trials of promising therapeutic candidates, to be implemented in NiV-affected areas, and develop plans for operationalizing the protocol.
3. By 2019, identify an approach for downselecting promising therapeutic candidates for further study in clinical trials, given limited annual case numbers for enrolment.
4. By 2020, complete a broader, regional protocol for conducting clinical trials of promising therapeutic candidates, to be implemented in NiV-affected areas, and develop plans for operationalizing the protocol.
5. By 2020, generate a reliable source of m102.4 (or other promising agent[s] or agent combinations) to be assessed in clinical trials.

Strategic Goal 2

To develop and evaluate therapeutic agents for the treatment of NiV infection and for PEP to prevent NiV infection.

Milestones

1. By 2019, create and implement a prioritization process for evaluating promising NiV therapeutic candidates.
2. By 2021, complete preclinical evaluation of the preliminary safety, tolerability and efficacy of at least two promising therapeutic candidates, or combination therapies, for the treatment of NiV infection.
3. By 2023, complete clinical evaluation of the preliminary safety, tolerability and (possible) efficacy of at least two promising therapeutic candidates, or combination therapies, for the treatment of NiV infection.

NIPAH RESEARCH AND DEVELOPMENT (R&D) ROADMAP

Priority areas/activities

Research

- **Continue to research** the safety, tolerability and efficacy of available investigational therapies (such as m102.4 and favipiravir) for treating and preventing NiV infection, including conducting studies in animal models and clinical trials as appropriate and feasible.
- **Continue to expand** the pipeline of new therapeutic options for treating and preventing NiV infection that should undergo further evaluation.
- **Research** optimal treatment and supportive care strategies for NiV infection and determine best-practice guidelines.

Product development

- **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, including obtaining appropriate approvals and conducting necessary training.
- **Promote** enhancements to the health-care delivery systems in affected areas to improve clinical management and supportive care of patients with NiV infection.
- **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

- **Generate** a reliable source of m102.4 to be used in clinical trials.
- **Develop** guidance, for the use of therapeutics for disease treatment and PEP, as new therapies become available.

Vaccines

Primary challenges, key needs and knowledge gaps

Primary challenges

- Currently, there is no candidate vaccine that is in late-stage development, and few companies are willing to invest in the generation of new NiV vaccines.
- Sociocultural issues may hinder trust in the formal human and veterinary clinical and public- health systems, which could diminish the acceptance of NiV vaccine use.
- The absence of improved diagnostic assays for the timely diagnosis of infection creates an important challenge in implementing a rapid reactive vaccination strategy for NiV outbreak control.

Key needs

- Nipah vaccines that: (1) are readily accessible with adequate supply chains; (2) can protect against different NiV strains; (3) provide rapid onset of an immune response to adequately prevent and control outbreaks.
- Guidance on the use of NiV vaccines to include vaccination strategies for special populations (such as children, immunocompromised individuals and pregnant women), different epidemiologic scenarios and different vaccine attributes.
- Public communication outreach strategies that address possible vaccine uptake hesitancy in target populations, and guidance for community sensitization to vaccine acceptance and promotion within the community.
- Once vaccines are available, enhanced surveillance capacity to assess the impact of vaccination programmes and to refine vaccination strategies over time.

Knowledge gaps

- Additional research is needed regarding the innate, cell-mediated and humoral immune responses that constitute protective immunity against NiV. Since neutralizing antibodies are likely the primary mediator of protection against NiV infection, research in this area should focus primarily on the humoral immune response for driving vaccine development.
- Further research is needed to clarify 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.
- Further research is needed to determine the cross-protection efficacy for NiV of the HeV-sG subunit vaccine (that is, the recombinant subunit vaccine Equivac® HeV from Zoetis).
- Additional research is needed in animal models to determine if vaccine candidates are cross-protective between different NiV strains, including recently identified strains, as only a few studies demonstrating cross-protection have been performed to date.
- The identification of specific correlates, or surrogates of protection, and standardized assays for measuring immune correlates, are needed to facilitate research on promising NiV vaccine candidates and to expedite possible licensing through nontraditional regulatory pathways, such as the US FDA's Animal Rule and accelerated approval mechanisms. These specific correlates may vary by vaccine platform and antigen and hence multiple assays may need to be standardized.
- Pre-licensure evaluation of vaccine safety is needed to better understand the risk of adverse incidents associated with vaccine use. While phase 1 and phase 2 trials can be performed in non-affected countries, safety trials will also be needed involving target populations in endemic regions.
- Further epidemiologic research is needed to better define at-risk populations and identify additional areas of potential NiV spillover.
- Additional sociological research is needed to explore perceptions and concerns of at-risk populations regarding NiV vaccine implementation.
- If, at some point, evidence supports the need for a broader, population-based vaccination strategy (beyond reactive use for outbreak control in affected communities), additional research may be warranted on the development of multivalent vaccines that protect against more than one infection (such as a combined vaccine against NiV and HeV, or NiV and measles virus) for use in NiV endemic areas.
- Mathematical modelling and forecasting may be useful in: (1) assessing whether or not disease incidence is high enough in endemic areas for conducting clinical trials of candidate vaccines; (2) simulating various epidemiologic 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 behaviours and practices in communities or specific population groups; (5) estimating the vaccine quantity that may be necessary to maintain vaccine stockpiles.

Strategic goals and aligned milestones

Strategic Goal 1

To engage NRAs (particularly in endemic and at-risk areas) and the WHO, to gain guidance on requirements for clinical trials, regulatory pathways and other considerations that will affect licensure of a vaccine against NiV.

Milestones

1. By 2019, convene an expert working group to assess the feasibility of conducting clinical efficacy trials of NiV vaccines and to determine the most appropriate regulatory pathways for licensure.
2. By 2020, convene a regional consultation to clarify in-country issues around conducting clinical trials (if deemed feasible) and the need for licensure, and future use of NiV vaccines. This consultation should include representatives from in-country regulators, other regulatory agencies (such as the FDA or the European Medicines Agency), national and international public- health agencies and organizations and local and international researchers.

Strategic Goal 2

To develop and evaluate NiV vaccines for prevention of NiV disease in humans

Milestones

1. By 2021, complete preclinical evaluation of the preliminary safety, tolerability and efficacy of at least two promising NiV vaccine candidates.
2. By 2023, complete phase 1 and phase 2 clinical trials for at least one of the most promising NiV candidate vaccines.
3. By 2023, complete the following if phase 3 trials are considered feasible: (1) develop a framework for conducting phase 3 clinical trials of NiV vaccine candidates; (2) develop a regional protocol for conducting phase 3 trials and plans for operationalizing the protocol; (3) create a collaborative and transparent strategy for determining which candidate vaccines will go forward into phase 3 trials.

Priority areas/activities

Research

- **Improve understanding** of the humoral immune response to infection, to inform development and evaluation of NiV vaccines.
- **Identify and standardize** correlates and/or surrogates of protection that are necessary for ongoing research into candidate vaccines and may also be important for vaccine licensure.
- **Generate** international reference standards to calibrate serologic assays for vaccine potency analyses.
- **Complete** preclinical evaluation of promising candidate NiV vaccines for safety, immunogenicity and efficacy in animal models (such as through serum transfer studies), correlates of protection and durability.
- **Further study** cross-protection of various vaccine candidates against different NiV strains, and between NiV strains and HeV strains.
- **Perform** clinical trials to assess safety and immunogenicity in phase 1 and 2 trials, and undertake animal studies for immune bridging to facilitate regulatory licensing.
- **Conduct** mathematical modelling to estimate the potential impact of NiV vaccines and inform strategies for vaccine use.
- **Explore** possible strategies for conducting clinical vaccine efficacy trials, in affected areas, that are ethical, interpretable and feasible, or identify alternative approaches for assessing efficacy of new NiV vaccines and therapeutics in coordination with the appropriate NRAs.
- **Establish** a plan for conducting phase 3 clinical trials in endemic regions, in coordination with local government agencies, if clinical trials are considered to be a feasible option for efficacy assessment.
- **Evaluate** the feasibility of generating multivalent vaccines (that is, that protect against more than one disease) and determine whether or not such vaccines would be useful in future NiV control efforts.

Product development

- **Develop and clinically** evaluate safe and effective monovalent NiV vaccines for humans.

Key capacities

- **Improve** surveillance capabilities to assess the impact of vaccine use and vaccination strategies (once vaccines become available).
- **Prepare** clinical trial sites and NRAs in affected countries for future clinical trials with NiV vaccines, if clinical trials are considered feasible.
- **Identify and address** issues with licensure and use of NiV vaccines in affected areas through a coordinated process involving key stakeholders, including in-country NRAs and public-health authorities.
- **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 epidemiologic 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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Background information

Primary challenges, key needs and World Health Organization R&D Roadmap documents and guidance

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