

Nipah Research and Development (R&D) Roadmap

Roadmap purpose: To provide a framework for identifying the vision, underpinning strategic goals, and prioritizing areas and activities (from basic research to advanced development, licensure, manufacture, and deployment) 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 severe respiratory illness in pigs and 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, with disease also identified periodically in eastern India; case fatality rates during outbreaks in these countries 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 bat species) and several other bat species in a number of other countries, including Cambodia, Thailand, Indonesia, Madagascar, Ghana, and the Philippines. 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, several other domestic animal species were found to be infected with NiV on the farms involved in the outbreak, including horses, cats, and dogs. 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]), which predominantly causes infection in horses and also can 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 and in healthcare workers who cared for NiV-infected patients. Detailed genomic information for this virus is limited.

In humans, NiV infection 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; these strains provoke distinct but overlapping clinical features in both humans and experimentally infected non-human primates.

The R&D roadmap for NiV infection is a key component of the WHO [R&D Blueprint](#) initiative for accelerating research and product development of medical countermeasures to enable effective and timely emergency response to infectious disease epidemics. NiV is identified in the Blueprint's list of "priority pathogens" (defined as pathogens 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 pathogens 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 the roadmap ranges from basic research to late-stage development, licensure, and early use of MCMs to prevent and control NiV outbreaks and endemic disease.

Other aspects of public health preparedness and response, in addition to R&D for MCMs, are critical to successful NiV infection prevention and control. Examples include enhanced surveillance systems, minimizing zoonotic NiV transmission, improved personal protective equipment (PPE), effective community engagement, adequate infection prevention and control practices, and 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.

VISION

Robust MCMs to detect, prevent, and control 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, accurate, point-of-care 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 TOPICS AND ISSUES

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Economic incentives to invest in Nipah research are not readily apparent, as the disease primarily occurs in under-resourced areas of South Asia and disease incidence is low; therefore, securing funding for Nipah research represents a substantial challenge. The development of a sustainable value proposition for industry and international philanthropic public-private partnerships are needed to secure funding to complete development, licensure, manufacture, and deployment of NiV MCMs. The value proposition would ideally be informed by a robust assessment of the risk of future outbreaks, and will likely require new systematic surveillance studies in humans and susceptible animal hosts in affected areas to strengthen the evidence base.

- Regulatory approval pathways for MCMs can be prohibitively expensive for product developers in the absence of a predictable demand. For example, obtaining regulatory approval for diagnostic tests through the premarket approval (PMA) process is costly, but may be necessary when an Emergency Use Authorization (EUA), which is associated with lower approval costs, is not applicable. Furthermore, licensure of vaccines and therapeutics using alternative regulatory pathways also 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 (BSL-4) conditions. This raises the cost of MCM development.
- To date, NiV spillovers to human communities have occurred almost exclusively in rural communities in Bangladesh and East India; the healthcare 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, Southeast and South Asia, and Madagascar. Evidence also suggests that other fruit bats of the Pteropodidae family may harbor 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 lack of clinical experience with the condition, lack of available laboratory testing, and the occurrence of other diseases that have similar clinical presentations.
- Because NiV infection results in low mortality rates in livestock (e.g., approximately 1% to 5% in pigs), infection in animal herds may not be recognized until after human cases are identified. This delay in diagnosis may lead to an entire herd being infected before livestock are tested for NiV, which could cause large financial losses for livestock owners and increases the likelihood of NiV infection in exposed animal husbandry workers.
- While ferrets, Syrian hamsters, and IFNAR-KO mice are well-established animal models for NiV research applicable to humans, the African green monkey (AGM) is regarded as the most relevant animal model for evaluation of candidate therapeutics and vaccines. 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.
- Conducting phase 1 and phase 2 clinical trials is potentially feasible in endemic regions. However, because NiV infection occurs as relatively small, focal outbreaks, the low disease incidence poses a major challenge for conducting phase 3 clinical trials, in terms of achieving a sufficient sample size to estimate MCM efficacy with adequate statistical power. Therefore, alternative regulatory pathways and/or innovative study designs (e.g., including combining clinical trial data across outbreaks over time) 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 applicable.

Key needs

- Enhanced clinical, laboratory, and public health infrastructure in endemic and at-risk areas to promote early diagnosis, treatment, and implementation of vaccination programs for NiV prevention and control.
- Additional prospective serosurveillance data from susceptible animal species and proximate human populations in areas of predicted risk to determine the level of human spillover and to build preparedness for detection of human cases and for limiting exposure. This is particularly important in areas where public health surveillance programs are not feasible or justifiable.
- Standardized and validated assays, reagents, antibodies, nucleic acids, and stocks of NiV challenge strains for R&D of MCMs for NiV infection. (Assays that can be used at lower biosafety levels are an important priority.)
- Clear criteria for down-selection 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.
- A determination regarding the feasibility of conducting clinical trials of therapeutics and vaccines for NiV infection, which is needed before considering alternative regulatory pathways for licensure (such as the United States Food and Drug Administration's [FDA's] Animal Rule).
- Early and recurrent communications between product developers and the appropriate national regulatory authorities (NRAs) 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 may vary between countries; therefore, early engagement is essential to identify country-specific considerations.
- Outreach and education to clinicians to improve NiV awareness and training, 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 under the authority of local leadership.
- Collaboration between public health authorities in endemic and at-risk areas and international development partners to support NiV surveillance and facilitate effective communication with communities regarding disease prevention 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, manufacture, deployment, and assessment of MCMs, as well as other preventive measures, are dependent 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 refine, standardize, and validate relevant animal challenge models (e.g., ferret, Syrian hamster, IFNAR-KO mouse, and AGM models) to define their role in supporting basic research on the pathogenesis and immunology of NiV infection, which is essential for development and evaluation of MCMs. 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 MCMs should be administered in animal models to best mimic realistic timing of MCM use in humans; (4) bridge NiV MCM data between animal models and humans, such as identifying thresholds of vaccine protection; and (5) identify the best models for studying chronic (relapsing) infection, particularly if investigators use the US FDA's Animal Rule to obtain regulatory approval.
- 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 immunological clearance and cause delayed onset or recurrent encephalitis, identifying factors influencing the development of permanent neurological 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 over time that may impact the epidemiologic and clinical features of disease, 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 viruses 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 at-risk populations (including 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. Efforts are needed to: (1) assess potential barriers for conducting clinical trials, (2) assess MCM acceptability in at-risk populations, (3) determine culturally appropriate messaging to enhance MCM acceptance, and (4) identify public health strategies to promote vaccine use.

Strategic Goals

1. Identify sources of funding and develop appropriate private-sector incentives and competitions to promote R&D of NiV MCMs.

2. Undertake surveillance activities (including research studies) to estimate the relative risk and global spread of NiV outbreaks and public value of MCM development
3. Stimulate and support basic science research for better understanding of NiV virology, pathogenesis, and the immune response to infection in humans and animals.
4. Strategically strengthen laboratory, clinical, and public health infrastructure and capacity at the local and national levels in areas of known or potential NiV spillover.
5. Engage NRAs (particularly in endemic and at-risk areas) to gain guidance on requirements for clinical trials, regulatory pathways, and other considerations that will impact MCM development, acceptance, and post-licensure surveillance.

Landmark Goals/Milestones

[TBD once the strategic goals have been determined.]

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.
- **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, validate, and standardize** relevant animal models to support the development and evaluation of NiV MCMs.
- **Generate** research tools to promote R&D of MCMs for NiV infection (i.e., standardized and validated assays, reagents, antibodies, nucleic acids, and stocks of 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 henipaviruses in order to improve understanding of their global distribution.
- **Determine** the feasibility of conducting phase 3 clinical trials 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.
- **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 down-selection and prioritization of candidate MCMs that should be moved forward.
- **Promote** early communication between developers and appropriate 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 programs 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** 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 programs 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.
- **Clarify** the potential for and possible strategies to promote technology transfer for development and manufacturing of MCMs for NiV infection.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

DIAGNOSTICS

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Initial signs and symptoms of NiV infection are nonspecific and the diagnosis often is not suspected at the time of presentation. This can hinder accurate diagnosis and creates challenges in outbreak detection and institution of effective and timely infection control measures and outbreak response activities. Additionally, latent disease can occur months to years after initial infection.
- Laboratory infrastructure and diagnostic capabilities in endemic and at-risk areas are often limited, and etiologic diagnosis 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, which can complicate diagnostic needs and capabilities.
- Owing to the biosafety precautions necessary when working with the NiV virus, 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.
- The time required to perform diagnostic testing using conventional laboratory methods poses challenges, given the rapid disease progression of NiV infection.
- Pteropus bat 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 to discriminate which henipaviruses are in circulation using serologic assays. Capacity to identify additional pathogenic henipaviruses is an important challenge for ensuring diagnostic preparedness to respond to future outbreaks.

Key needs

- A TPP for NiV diagnostics, identifying optimal and desirable characteristics to guide the development of promising diagnostic assays.
- A biobank of human and animal clinical samples to assess and validate diagnostic tests and a process for how best to judiciously use the samples. 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, etc.); (2) outline the purposes of sample collection; (3) identify who would have access to the samples; and (4) prioritize use of samples and sample distribution.
- Clarification regarding the use cases for different diagnostic assays and what viruses are targeted (i.e., NiV, NiV and HeV, or all henipaviruses), since the corresponding performance, validation, and regulatory approval requirements may differ depending on how and in which population (i.e., human or animal) the test will be used. For example, it may be desirable to have a point-of-care screening test that is highly sensitive and a confirmatory test that is highly

specific. In animals, it may be desirable to have a diagnostic test with high sensitivity to screen reservoir populations and a highly specific test for livestock. Diagnostic use cases need to be considered in tandem with the use of therapeutics and other interventions.

- Rapid point-of-care diagnostic tests for NiV that involve minimal requirements for laboratory infrastructure, can detect disease early in the clinical course, are robust for use under a variety of conditions (e.g., varying humidity, temperature, etc.), can be applied in both human and animal populations, and have a high degree of sensitivity and specificity for different NiV strains.
- Optimal deployment strategies for diagnostics in different geographic areas based on the risk and epidemiology of NiV infection.
- International reference standards to calibrate diagnostic assays.
- Validation of promising diagnostics in endemic and at-risk geographic regions.
- Diagnostic preparedness to detect NiV, HeV, and other emergent henipaviruses in humans and animals as they arise.
- 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, given the costs of regulatory approval.
- If feasible, multiplex syndrome-based assay panels for use in humans and animals that can detect NiV infection while simultaneously screening for the presence of other henipaviruses or other pathogens of public health concern that may cause similar clinical syndromes in endemic or at-risk areas. Since validation and regulatory approval of multiplex assays can prove challenging, an alternate approach would be the development of multiple single assays that can be run in parallel.
- If NiV or HeV vaccines become widely used in livestock, serological testing to differentiate vaccinated animals from infected animals (such as the Differentiating Infected from Vaccinated Animals (DIVA) test) will be needed.

Knowledge gaps

- Further research is needed on the kinetics of NiV detection in cerebrospinal fluid, blood, saliva, other body fluids (e.g., urine and respiratory secretions), and tissue samples to enhance the ability to diagnose infection at different stages of disease. Additionally, further research on the kinetics of NiV in the animal reservoirs is needed.
- More information is needed regarding the performance characteristics (including sensitivity, specificity, limits of detection, cross-reactivity, and quantitative vs. qualitative data) for NiV assays, particularly for newer tests (such as pseudotyped neutralization assays and antigen-capture 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.
- A clear understanding is needed of the potential for cross-reactivity of diagnostic tests in animal populations to allow accurate interpretation of test results, since substantive economic consequences (such as trade restriction for livestock) could be triggered by positive results.

Strategic Goals

1. Obtain a better understanding of the kinetics of NiV detection at various points during the clinical course of illness to allow improved diagnostic capability across the disease spectrum.
2. Develop and assess affordable, highly sensitive and specific, point-of-care NiV diagnostic tests for use in humans and animals that are sufficiently robust for the conditions in which they will be used and that have minimal requirements for biosafety precautions and staff training. Consideration also should be given to development of multiplex assays that can detect related henipaviruses, in addition to NiV, or that can detect other pathogens of concern in endemic and at-risk areas.
3. Generate guidance on deployment strategies and use of diagnostic tests for NiV detection in areas of known or potential henipavirus spillover risk.
4. Enhance diagnostic preparedness in areas of known or potential henipavirus spillover risk to promote early detection of NiV, HeV, and other emergent henipaviruses in humans and animals.

Landmark Goals/Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Explore** new diagnostic approaches that may allow for 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.
- **Create** a biobank of clinical human and animal samples for use in researching new diagnostic agents.
- **Continue to research** cross-reactivity of diagnostic tests in animal populations.

Product development

- **Generate** a TPP for NiV diagnostics.
- **Define** use cases for diagnostic assays.
- **Develop, evaluate, and validate** point-of-care rapid diagnostic tests for NiV infection that are affordable, highly sensitive and specific, available for use in humans and animals, and can capture antigenically diverse strains of the virus and be performed accurately and safely in remote areas under a variety of circumstances.
- **Develop** multiplex syndrome-based assay panels that can detect NiV infection while simultaneously screening for the presence of other henipaviruses or other pathogens of concern in the geographic region that cause similar clinical syndromes.

- **Develop** diagnostics applicable to mass testing in livestock to identify NiV infection early and to reduce the likelihood of transmission of NiV from livestock to humans.
- **Develop** serologic testing to differentiate vaccinated from infected animals (such as a DIVA test), if NiV or HeV vaccines become widely used (long-term consideration).

Key capacities

- **Generate** international reference standards to calibrate diagnostic assays.
- **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 in humans and animals.

Policy and commercialization

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

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

THERAPEUTICS

Current 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.
- The absence of improved diagnostic assays for timely diagnosis of infection creates an important challenge in providing early treatment and PEP to exposed persons.
- In the NiV-endemic region of Bangladesh, hundreds of patients are admitted to hospitals annually with a diagnosis of encephalitis, but do not have NiV infection. In the absence of confirmatory testing, treating all patients with encephalitis and their contacts for NiV infection would be costly and labor intensive, with relatively little benefit; therefore accurate and rapid diagnosis is critical.
- Studies in animals often evaluate usefulness of therapeutics when delivered prior to disease onset or early during the disease course. Patients with NiV infection often are detected later in the clinical course, which creates challenges for predicting how well an agent will work in the field.
- Nipah virus 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.

- Healthcare systems in endemic countries often do not have adequate infection control systems in place to prevent person-to-person transmission. They also lack the ability to rapidly identify contacts most likely to benefit from PEP therapy.

Key needs

- A TPP for NiV therapeutic agents, identifying optimal and desirable characteristics to guide the development of promising treatment approaches in the context of individual and community priorities.
- 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, easily administered, well-tolerated, and effective therapeutic agents that treat chronic (relapsing) NiV infection to decrease associated 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 healthcare workers, family caregivers, and persons exposed to infected livestock.
- Improved patient care in endemic areas (such as the ability to provide ventilator support for seriously ill patients).

Knowledge gaps

- Ribavirin may be an option for treatment of NiV infection, but animal studies in hamsters and AGMs have not supported efficacy for ribavirin. Further research into the potential effectiveness of ribavirin for NiV infection may be warranted.
- The human monoclonal antibody (mAb) m102.4 has demonstrated protection against lethal NiV challenge in animal models and has been provided as a compassionate use for a small number of individuals exposed to either HeV or NiV. Recently, a phase 1 clinical trial for m102.4 with 40 human participants was completed in Australia, but results are not yet available. Additional animal studies using different NiV strains and clinical trials in endemic areas are needed to 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, and GS-4734 [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 the therapeutic window for m102.4 against a strain from Bangladesh/India to be shorter than for a strain from Malaysia.
- Further research is needed to broaden the number of novel antiviral candidates for treatment of NiV infection.
- Additional data are needed to establish the pharmacokinetic/pharmacodynamics (PK/PD) relationship of promising therapeutic candidates.

- Additional studies, as needed, of therapeutic candidates in the AGM model, followed by human clinical trials for safety, feasibility, and efficacy.
- 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 hundreds of potentially-exposed persons annually that could be candidates for PEP.
- 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.

Strategic Goals

1. Develop, evaluate, and license therapeutic agents for treatment of NiV infection and for PEP to prevent NiV infection, and ensure that therapies are readily available, affordable, and accessible in areas of known or potential NiV spillover.
2. Develop guidance for the use of therapeutics for disease treatment and PEP as new therapies become available.

Landmark Goals/Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Continue to research** the safety, tolerability, and efficacy of investigational therapies (such as ribavirin and m102.4) for treating and preventing NiV infection, including conduct of animal studies and clinical trials as appropriate and feasible.
- **Continue to identify** 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

- **Generate** a TPP for NiV infection therapeutics.
- **Develop, evaluate, and license** safe and effective therapeutic agents for 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

- **Promote** enhancements to the healthcare delivery systems in impacted 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 outbreak control.

Policy and commercialization

- **Identify** a company to advance therapeutic use of m102.4 and **secure** financing for its manufacture and distribution.
- **Develop** guidance for the use of therapeutics for disease treatment and PEP, as new therapies become available.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

VACCINES

Current Primary Challenges, Key Needs, and Knowledge Gaps

Primary challenges

- Sociocultural issues may hinder trust in the formal human, veterinary, and public health systems, which could impact acceptance of NiV vaccines for use in humans or animals.
- The absence of improved diagnostic assays for timely diagnosis of infection creates an important challenge in implementing a rapid reactive vaccination strategy for NiV outbreak control.

Key needs

- Nipah vaccines that can protect against different NiV strains in humans and animals, and that provide rapid onset of an immune response to adequately prevent and control outbreaks.
- Guidance on use of NiV vaccines (or broader henipavirus vaccines) to include vaccination strategies, potentially in both humans (including special populations such as children, immunocompromised individuals, and pregnant women) and animals, for different epidemiologic scenarios and different vaccine attributes.
- Once vaccines are available, enhanced surveillance capacity to assess the impact of vaccination programs and to refine vaccination strategies over time.

Knowledge gaps

- While neutralizing antibodies are likely a primary mediator of protection against NiV infection, cellular immunity appears to also play a role. Additional research is needed regarding the innate, cell-mediated, and humoral immune responses that constitute protective immunity against NiV.
- 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 (i.e., the recombinant subunit vaccine Equivac® HeV from Zoetis).
- Additional research is needed 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.
- The identification of specific correlates or surrogates of protection in humans and animals and standardized assays for measuring immune correlates are needed to facilitate research on promising NiV vaccine candidates, and expedite possible licensing through nontraditional regulatory pathways, such as the US FDA's Animal Rule and accelerated approval mechanisms.
- Evaluation of vaccine safety in target populations is needed to better understand the risk of adverse incidents associated with vaccine use.
- If evidence at some point 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 [MV]) for use in NiV endemic areas.
- Mathematical modelling 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), and (4) estimating the vaccine quantity that may be necessary to maintain vaccine stockpiles.
- Because livestock (e.g., pigs and horses) are intermediary hosts for NiV and HeV, vaccination of livestock populations has been suggested as a possible mitigation strategy for preventing secondary transmission to humans. Currently, one HeV vaccine is available for horses and available evidence suggests this vaccine is cross-protective against NiV. Ongoing research into developing NiV/HeV vaccines for livestock (or other animals) and the potential for their use in endemic regions is needed to further assess the merit of this potential control strategy.
- Additional research is needed to determine if development of multivalent vaccines for animals (that protect against more than one disease) would increase the likelihood of vaccine uptake by food animal producers and the broader veterinary community.

Strategic Goals

1. Develop, evaluate, license, and deploy NiV vaccines for use in humans and potentially animals (e.g., livestock, companion animals).
2. Continue to research cross-protection of candidate vaccines against NiV and HeV (and potentially other emergent henipaviruses as needed).
3. Develop and refine guidance on vaccine use in humans and animals that aligns with current NiV epidemiology and takes into consideration attributes of new vaccines as they become available.

Landmark Goals/Milestones

[TBD once the strategic goals have been determined.]

Priority Areas/Activities

Research

- **Determine** the innate, cell-mediated, and humoral immune responses that contribute to protective immunity against NiV infection for use in developing and evaluating NiV vaccines.
- **Identify and standardize** correlates and/or surrogates of protection, which are necessary for ongoing research into candidate vaccines and also may be important for vaccine licensure.
- **Complete** preclinical evaluation of promising candidate NiV vaccines for safety, immunogenicity, efficacy in animal models, 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.
- **Explore** whether multivalent vaccines for animal populations would increase vaccine acceptability and uptake by food-animal producers and the broader veterinary community.
- **Conduct** mathematical modelling to estimate the potential impact of NiV vaccines and inform strategies for vaccine use.

Product development

- **License** safe and effective monovalent NiV vaccines for humans and animals.
- **License** safe and effective multivalent vaccines for use in humans that protect against more than one disease for use in human populations (e.g., vaccines that protect against both NiV and MV or HeV), if broader population-based vaccination is warranted at some point in the future.
- **Develop, clinically evaluate, and license** safe and effective multivalent vaccines that protect against more than one disease for use in animal populations, if this is deemed to be a sustainable approach.

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.
- **Support** plans for adequate manufacturing and stockpiling of licensed NiV vaccines for 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.
- **Consider** development of 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 thus more rapid spread.

Schedule of Resources, Coordination, and Implementation

[TBD; will obtain input later in the process.]

Critical Path Analysis

[TBD once the primary activities have been vetted by subject matter experts.]

BACKGROUND INFORMATION

World Health Organization R&D Roadmap documents and guidance:

WHO. Nipah Baseline Situational Analysis. Nov 2017

WHO. WHO target product profile for Nipah virus vaccine. Jun 2017

Other Publications:

Angeletti S, Presti AL, Cella E, et al. Molecular epidemiology and phylogeny of Nipah virus infection: a mini review. Asian Pac J Trop Dis 2016;9(7):630-4. doi: 10.1016/j.apjtm.2016.05.012 [\[Full text\]](#)

ANZCTR (Australian New Zealand Clinical Trials Registry). Trial ACTRN 12615000395538. Last updated 2016 Nov 29; site accessed 2017 Dec 12 [\[Web page\]](#)

Baseler L, Scott, DP, Saturday G, et al. Identifying early target cells of Nipah virus infection in Syrian hamsters. PLoS Negl Trop Dis 2016 Nov; 10(11): e0005120. Published online 2016 Nov 3 [\[Full text\]](#)

Bossart KN, Rockx B, Feldmann F, et al. A Hendra virus G glycoprotein subunit vaccine protects African green monkeys from Nipah virus challenge. Sci Transl Med 2012 Aug 8;4(146): 146ra107. [\[Full text\]](#)

Broder CC. Passive immunization and active vaccination against Hendra and Nipah viruses. Dev Biol (Basel) 2013 May 14;135:125-38 [\[Abstract\]](#)

Broder CC, Weir DL, Reid PA. Hendra virus and Nipah virus animal vaccines. Vaccine 2016 Jun 24;34(30):3525-34 [\[Full text\]](#)

Broder CC, Xu K, Nikolov DB, et al. A treatment for and vaccine against the deadly Hendra and Nipah viruses. Antivir Res 2013 Oct;100(1):8-13. doi: 10.1016/j.antiviral.2013.06.012. [\[Full text\]](#)

CDC (Centers for Disease Control and Prevention). Nipah virus (NiV) signs and symptoms. Last updated 2014 Mar 20 [\[Web page\]](#)

Chen F, Zhao D, Jiao Z. Nipah virus encephalitis. In: Li H, ed. Radiology of Infectious Diseases: Volume 1. Springer, Dordrecht; 2015. 541-7

Chiang CF, Lo MK, Rota PA, et al. Use of monoclonal antibodies against Hendra and Nipah viruses in an antigen capture ELISA. Virol J 2010 Jun 3;7(115). doi: 10.1186/1743-422X-7-115. [\[Full text\]](#)

Ching PG, de los Reyes V, Sucaldito M, et al. Outbreak of Henipavirus infection, Philippines, 2014. Emerg Infect Dis 2015;21(2):328-331. doi: 10.3201/eid2102.141433. [\[Full text\]](#)

Chong HT, Kamarulzaman A, Tan CT, et al. Treatment of acute Nipah encephalitis with ribavirin. Ann. Neurol 2001;49:810–813. [\[Abstract\]](#)

Chua KB, Gubler DJ. Perspectives of public health laboratories in emerging infectious diseases. Emerg Microbes Infect 2013 Jun;2(6): doi: 10.1038/emi.2013.34. [\[Full text\]](#)

680 Clayton BA. Nipah virus: transmission of a zoonotic paramyxovirus *Current Opinion in Virology* 2017;
681 22:97–10 [[Abstract](#)]

682 Daniels P, Ksiazek T, Eaton BT. Laboratory diagnosis of Nipah and Hendra virus infections. *Microbes*
683 *Infect* 2001Apr;3(4):289-95 [[Abstract](#)]

684 DeBuysscher BL, de Wit E, Munster VJ, et al. Comparison of the pathogenicity of Nipah virus isolates
685 from Bangladesh and Malaysia in the Syrian hamster. *PLoS Negl Trop Dis* 2013 Jan 17;7(1):e0002024.
686 [[Full text](#)]

687 DeBuysscher BL, Scott D, Marzi A, et al. Single-dose live-attenuated Nipah virus vaccines confer
688 complete protection by eliciting antibodies directed against surface glycoproteins. *Vaccine* 2014 May
689 7;32(22):2637-44 [[Full text](#)]

690 Dhondt KP, Horvat B. Henipavirus infections: lessons from animal models. *Pathogens* 2013 Apr
691 9;2(2):264-87 [[Full text](#)]

692 de Wit E, Munster VJ. Nipah virus emergence, transmission, and pathogenesis. In: Shapshak P, Sinnott
693 JT, Somboonwit C, Kun JH, eds. *Global Virology I – Identifying and Investigating Viral Diseases*. New York,
694 NY: Springer US; 2015. 125-46

695 Foord AJ, White JR, Colling A, et al. Microsphere Suspension Array Assays for Detection and
696 Differentiation of Hendra and Nipah Viruses. *Biomed Res Int*. 2013; 2013: 289295. Published online 2013
697 Feb 6. doi: 10.1155/2013/289295. [[Full text](#)]

698 Freiberg AN, Worthy MN, Lee B, et al. Combined chloroquine and ribavirin treatment does not prevent
699 death in a hamster model of Nipah and Hendra virus infection. *J Gen Virol* 2010 Mar;91(Pt 3):765-72
700 [[Full text](#)]

701 Geisbert TW, Daddario-DiCaprio KM, Hickey AC, et al. Development of an acute and highly pathogenic
702 nonhuman primate model of Nipah virus infection. *PLoS ONE* 2010 May 18;5(5):e0010690. [[Full text](#)]

703 Geisbert TW, Mire CE, Geisbert JB, et al. Therapeutic treatment of Nipah virus infection in nonhuman
704 primates with a neutralizing human monoclonal antibody. *Sci Transl Med* 2014 June 25; 6(242): 242ra82
705 [[Full text](#)]

706 Georges-Corbot MC, Contamin H, Faure C, et al. Poly(I)-poly(C12U) but not ribavirin prevents death in a
707 hamster model of Nipah virus infection. *Antimicrob Agents Chemother* 2016 May;50(5):1768-72. doi:
708 10.1127/AAC.50.5.1768-1772.2006. [[Full text](#)]

709 Guillaume V, Contamin H, Loth P, et al. Nipah virus: vaccination and passive protection studies in a
710 hamster model. *J Virol* 2004 Jan;78(2):834-40 [[Full text](#)]

711 Hayman DTS, Johnson N. Nipah virus: a virus with multiple pathways of emergence. In: Johnson N, ed.
712 *The Role of Animals in Emerging Viral Diseases*. Elsevier 2014; 293-315 [[Abstract](#)]

713 Johnston SC, Briesse T, Bell TM, et al. Detailed analysis of the African green monkey model of Nipah virus
714 disease. *PLoS One* 2015 Feb 23;10(2):e0117817. [[Full text](#)]

715 Ksiazek TG, Rota PA, Rollin PE. A review of Nipah and Hendra viruses with an historical aside. *Virus*
716 *Research* 2011;162(1-2):173-83 [[Abstract](#)]

- 717 Kulkarni DD, Tosh C, Venkatesh G, et al. Nipah virus infection: current scenario. Indian J Virol 2013
718 Dec;24(3):398-408 [[Full text](#)]
- 719 Luby SP. The pandemic potential of Nipah virus. Antiviral Res 2013;100(1):38-43 [[Full text](#)]
- 720 Mathieu C, Horvat B. Henipavirus pathogenesis and antiviral approaches. Expert Rev Anti Infect Ther
721 2015;13(3):343-54 [[Abstract](#)]
- 722 McEachern JA, Bingham J, Crameri G, et al. A recombinant subunit vaccine formulation protects against
723 lethal Nipah virus challenge in cats. Vaccine 2008 Jul 23;26(31):3842-52 [[Abstract](#)]
- 724 Mire CE, Satterfield BA, Geisbert JB, et al. Pathogenic differences between Nipah virus Bangladesh and
725 Malaysia strains in primates: implications for antibody therapy. Sci Rep 2016 Aug 3;(6). doi: srep30916.
726 [[Full text](#)]
- 727 Mire CE, Versteeg KM, Cross RW, et al. Single injection recombinant vesicular stomatitis virus vaccines
728 protect ferrets against lethal Nipah virus disease. Virol J 2013 Dec 13. pii: 1743-422X-10-353. [[Full text](#)]
- 729 Pernet O, Schneider BS, Beaty SM, et al. Evidence for henipavirus spillover into human populations in
730 Africa. Nat Commun. 2014 Nov 18;5:5342 [[Full text](#)]
- 731 Prescott J, de Wit E, Feldmann H, et al. The immune response to Nipah infection. Arch Virol 2012
732 September; 157(9): 1635–1641 [[Full text](#)]
- 733 Rahman SA. National Guideline for Management, Prevention and Control of Nipah Virus Infection
734 including Encephalitis 2011 [[Full text](#)]
- 735 Satterfield BA, Geisbert TW, Mire CE. Inhibition of the host antiviral response by Nipah virus: current
736 understanding and future perspectives. Future Virol 2016 Apr 15;11(5):331-34 [[Abstract](#)]
- 737 Sazzad HM, Luby SP, Ströher U, et al. Exposure-based screening for Nipah virus encephalitis, Bangladesh.
738 Emerg Infect Dis 2015 Feb;21(2):349-51 [[Full text](#)]
- 739 Steffen DL, Xu K, Nikolov DB, Broder CC. Henipavirus mediated membrane fusion, virus entry and
740 targeted therapeutics. Viruses 2012 Feb;4(2):280-308 [[Full text](#)]
- 741 Tan KS, Tan CT, Goh KJ. Epidemiological aspects of Nipah virus infection. Neuro J Southeast Asia
742 1999;4:77-81 [[Full text](#)]
- 743 van den Pol AN, Mao G, Chattopadhyay A, et al. Chikungunya, Influenza, Nipah, and Semliki Forest
744 Chimeric viruses with Vesicular Stomatitis Virus: actions in the brain. J Virol 2017 Feb 28;91(6). pii:
745 02154-16. [[Full text](#)]
- 746 Wang LF, Daniels P. Diagnosis of henipavirus infection: current capabilities and future directions. Curr
747 Top Microbiol Immunol 2012;359:179-96 [[Abstract](#)]
- 748 Weatherman S, Feldman H, de Wit E. Transmission of henipaviruses. Curr Opin Virol 2018 Feb;28:7-11.
749 doi: 10.1016/j.coviro.2017.09.004 [[Full text](#)]