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World Health Organization

Paramyxoviridae Research & Development Roadmap

March 2026

R&DBlueprint
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Contents

EXECUTIVE SUMMARY

Paramyxoviridae comprise of large, enveloped RNA viruses infecting mammals, birds, reptiles, and fish, with marked diversity in receptor usage, replication strategies, host range, immune evasion mechanisms, and disease severity. The Paramyxovirus R&D roadmap developed by this CORC identifies seven prototype viruses to represent the diversity of this family and ensure R&D expands beyond lethal zoonotic infections to provide maximum coverage against pathogen X. The roadmap is thus aligned with WHO's transition from a pathogen-specific approach to a broader family-based framework for pandemic preparedness and has been developed with inputs from global subject experts over a series of 15 meetings.

The document is divided into 4 chapters representing 4 key themes: (i) selection of prototype viruses; (ii) disease epidemiology, non-human reservoirs of disease, sociobehavioural frameworks; (iii) laboratory & assays, basic research, disease models and; (iv) development of medical countermeasures. The latter three chapters each categorically identify the key needs, challenges and knowledge gaps, research priorities, and strategic goals and milestones for R&D against this virus family.

The prototype viruses have been identified through literature review, information from previously published multi-criteria frameworks for pathogen prioritization, and expert consultations. Disease burden, pathogen transmission dynamics (including inter-species spread) and virulence, epidemiological urgency, existing structural knowledge of viruses, genetic diversity, laboratory tractability, pathogen risk, and availability of medical countermeasures were some of the key determinants for prototype identification. This approach identified seven prototype viruses across the *Orthoparamyxovirinae*, *Rubulavirinae*, and the *Avulavirinae* subfamilies. These seven prototypes include three pathogens known to cause substantial diseases in humans- Measles virus, Nipah virus and Human Parainfluenzavirus-3, and 4 viruses causing nil-to-minimal human disease: Cedar Virus, Menangle Virus, Parainfluenza Virus-5 and Newcastle Disease Virus. This approach strikes a balance between high-consequence pathogens (Nipah virus), laboratory-tractable surrogates (Cedar virus), prototypes representing extreme transmissibility and immune modulation (Measles virus), clinically relevant human respiratory pathogens with substantial pediatric disease burden (Human parainfluenza virus type 3 [HPIV3]), emerging pathogens (Menangle virus), and proven viral vector platforms for accelerated

vaccine development (PIV-5 and Newcastle Disease Virus). R&D on this diverse virus panel is intended to maximize preparedness, and fast-track medical countermeasure development, licensure, and deployment against Pathogen "X".

From an epidemiological perspective, Paramyxoviruses span varied transmission systems driven by complex ecological and socio-behavioural factors. While substantial knowledge exists for certain prototypes such as Measles and Nipah viruses, significant gaps persist across the family. Disease burden remains poorly quantified for many Paramyxoviruses due to existing surveillance systems that are biased to detect severe disease, and the paucity of sero-epidemiological data capturing mild or asymptomatic infections. Surveillance architectures are fragmented, with absence of standardized case definitions, limited laboratory capacity at spillover sites, and weak linkages across human, animal, and environmental interface, limiting early detection of spillover events and coordinated response. Critical knowledge gaps also exist in reservoir ecology, host range, transmission dynamics, and socio-behavioural determinants of exposure, particularly at the animal–human interface where spillovers occur. The natural history and full clinical spectrum of many Paramyxovirus infections remain incompletely characterized, and global data-sharing mechanisms are weak, further constraining comparative analysis and preparedness. Additionally, maintaining operational readiness during inter-epidemic periods remains a persistent challenge, with declining surveillance sensitivity and workforce capacity undermining timely outbreak detection. To overcome these challenges, the CORC endorses establishment of One Health surveillance mechanisms with standardized case definitions, sentinel and event-based surveillance platforms, and strengthened detection capacity at spillover sites. Harmonization of epidemiological, clinical, and genomic data systems is emphasized to enable real-time tracking of transmission and viral evolution. The integration of genomic epidemiology into routine surveillance, coupled with longitudinal cohort studies and sero-epidemiological investigations, is essential to accurately estimate disease burden, describe natural history of the disease, and identify immunity gaps. Parallel efforts are required to characterize reservoir hosts, amplification pathways, and environmental drivers of spillover, while embedding socio-behavioural research into outbreak investigations to inform culturally appropriate and regionally relevant prevention strategies. The roadmap further calls for the development of predictive modelling frameworks integrating epidemiological, ecological, and environmental data, alongside sustained inter-epidemic preparedness efforts through continuous sentinel surveillance, trained rapid response teams,

operational clinical trial sites, and strengthened laboratory capacity. Strategic goals over a five-year horizon include establishing foundational surveillance infrastructure, operationalizing integrated One Health systems, generating robust evidence on disease trends (including molecular epidemiology), developing predictive algorithms for outbreak forecasting, and sustaining inter-epidemic preparedness through community engagement, training of skilled workforce, and operationalizing clinical trial-ready cohorts and sites.

Pandemic preparedness efforts rely greatly on strengthened laboratory capacity. Standardized laboratory procedures, supported by robust quality control systems, are critical for understanding virus biology, undertaking effective surveillance and outbreak response, and accelerating the development of medical countermeasures. However, research in this domain is constrained by the extensive genetic and structural diversity of Paramyxoviruses, stringent biosafety requirements for high-risk pathogens, limited structural virology data, and limitations of commonly available assay formats. Lack of standardized laboratory assays, reference reagents, pathogen strains, and well-characterized disease models further hinder research, complicating diagnostic product development and commercialization. Addressing these challenges requires comprehensive characterization of viral proteins, identification of key targets for countermeasure development, standardization of sampling techniques and assay protocols, and establishment of experimental models of disease with defined end-points. Use of surrogate systems is also encouraged to reduce reliance on high-containment facilities and promote research equity. The diagnostic industry also requires guidance and support through target product profiles and establishment of biorepositories for clinical sample sharing. Development of reference standards, strengthening of laboratory networks, and continued capacity building through global collaborations and open resource sharing are other key needs for harmonization of laboratory assays and evaluation of the efficacy/effectiveness of medical countermeasures. Strategic goals over a 5-year timeframe include standardization of laboratory assays, research on Paramyxovirus structure and function, establishment of biorepositories for samples/ strains, development of Target Product Profiles for diagnostics, defining validation and regulatory approval pathways of newer assays, and identification of focus areas to guide Paramyxovirus R&D funding.

The crux of pandemic preparedness lies in the development of medical countermeasures: antivirals, vaccines and therapeutics face a distinct set of scientific, operational, and regulatory challenges. A key limitation is the lack of defined immune correlates of protection and universally accepted clinical/ immunological endpoints, coupled with antigenic variability among Paramyxoviruses, unavailability of reliable disease models, uncertainty regarding immune response (including mucosal immunity) and duration of protection. Balancing safety and immunogenicity is critical; manufacturing scalability, vaccine stability and cold-chain dependence are other major constraints to vaccine deployment. There is also limited understanding of vaccine cross-protection across genera, and regulatory frameworks need to incorporate non-traditional evaluation pathways (such as animal models, immunobridging studies) for vaccines that cannot undergo conventional efficacy trials. The roadmap highlights several key needs to address these gaps, including development of broadly protective vaccines, and establishment of correlates of protection and trial endpoints. Safe, immunogenic, and durable plug-and-play vaccine platforms designed to integrate seamlessly with existing immunization infrastructure and supported by scalable manufacturing and robust accelerated regulatory frameworks are critical for licensure and immediate deployment of vaccines against Pathogen "X". Medical countermeasure development will need to be supported through continued genomic surveillance of pathogens and standardized well-performing laboratory assays and reagents; integrated cross-species vaccination frameworks, robust information/education/communication modules, and culturally acceptable newer vaccine delivery systems are also critical for vaccine uptake during pandemics. As a short-term goal, the CORC endorses foundational immunology research, harmonization of wet-lab techniques, R&D on novel vaccine platforms, and defining clinical trial/regulatory pathways of prototype virus vaccines which are in advanced stages of development. The next focus should be on validation of disease models, and establishment of immune evaluation pathways against candidate vaccines. Accelerated licensure of plug-and-play vaccine platforms, and sustained preparedness and deployment readiness should be long-term goals. The roadmap also describes possible clinical trial designs for the seven prototype Paramyxoviruses identified by the CORC.

Overall, this roadmap presents a comprehensive and integrated framework for Paramyxovirus R&D, built on a multi-prototype strategy that spans epidemiological research, laboratory science, and medical countermeasure development. By aligning global research efforts around standardized procedures, harmonized data systems, and

coordinated surveillance, it seeks to overcome existing fragmentation and accelerate translational impact. The emphasis on family-wide preparedness, One Health integration, scalable plug-and-play vaccine platform technologies, and sustained inter-epidemic readiness provides a robust foundation for responding to both current Paramyxovirus threats and emerging pathogens.

CHAPTER 1: Prototype Selection

Introduction

Prototype pathogen identification is a strategic component of the World Health Organization (WHO) R&D Blueprint, shifting from a reactive approach focused on individual pathogens to a proactive strategy centred on entire viral families. This process involves the selection of representative viruses within a family to serve as pathfinders or models for foundational and translational research. The prototype approach aims to generate generalizable knowledge, validated assays, and platform technologies that can be rapidly adapted to counter other known members of the same family or unanticipated emerging threats, referred to as "Pathogen X".

The utility of this framework is demonstrated by its ability to facilitate the rapid creation of medical countermeasures, such as vaccines and monoclonal antibodies, by leveraging established research from model organisms. These prototypes are selected based on their potential to provide insights into viral replication, pathogenesis, and immune correlates of protection that are broadly applicable across a phylogenetic group. The *Paramyxoviridae* family represents a persistent global health security threat, comprising pathogens with extreme transmissibility and high case fatality rates. The potential for a novel paramyxovirus to emerge with these characteristics underscores the urgent need for a strategic pandemic preparedness plan. By focusing intensive research and development on a strategically selected portfolio of representative viruses, it is possible to generate the knowledge and platform technologies needed to rapidly counter any member of the viral family, including an unknown "pathogen X".

Paramyxoviridae Family

The family *Paramyxoviridae* comprises large, enveloped RNA viruses that infect mammals, birds, reptiles, and fish. *Paramyxoviridae* is a prominent family within the order *Mononegavirales*. This order encompasses a diverse group of enveloped viruses that share a common genomic architecture: a non-segmented, single-stranded RNA genome of negative polarity (*Amarasinghe et al, 2019*). According to the current taxonomy, *Paramyxoviridae* is placed within the Realm *Riboviria*, Phylum *Negarnaviricota*, and Class

Monjiviricetes (*Rima et al, 2019*). The family itself is further subdivided into subfamilies and genera based on phylogenetic analysis of the complete amino acid sequence of the large (L) protein, the most conserved protein in the viral genome. The subfamilies include *Avulavirinae, Metaparamyxovirinae, Orthoparamyxovirinae*, and *Rubulavirinae*. Viruses of the subfamilies *Orthoparamyxovirinae* and *Rubulavirinae* infect humans as well as a wide range of mammals and some birds. The important genera under *Orthoparamyxovirinae* that infect humans include *Morbillivirus* (Measles virus), *Henipavirus* (Nipah and Hendra viruses), and *Respirovirus* (HPIV-1 and HPIV-3). Under *Rubulavirinae*, the relevant genera are *Orthorubulavirus* (Mumps virus, HPIV-2, and HPIV-4) and *Pararubulavirus* (Menangle virus and Sosuga virus). *Avulavirinae* primarily infect birds, with Newcastle disease virus (NDV) causing occasional mild conjunctivitis in humans. Viruses of the subfamily *Metaparamyxovirinae* primarily infect reptiles (e.g., ferlaviruses in snakes and lizards) and some mammals. To date, no confirmed human infections have been reported (*Rima et al, 2019*).

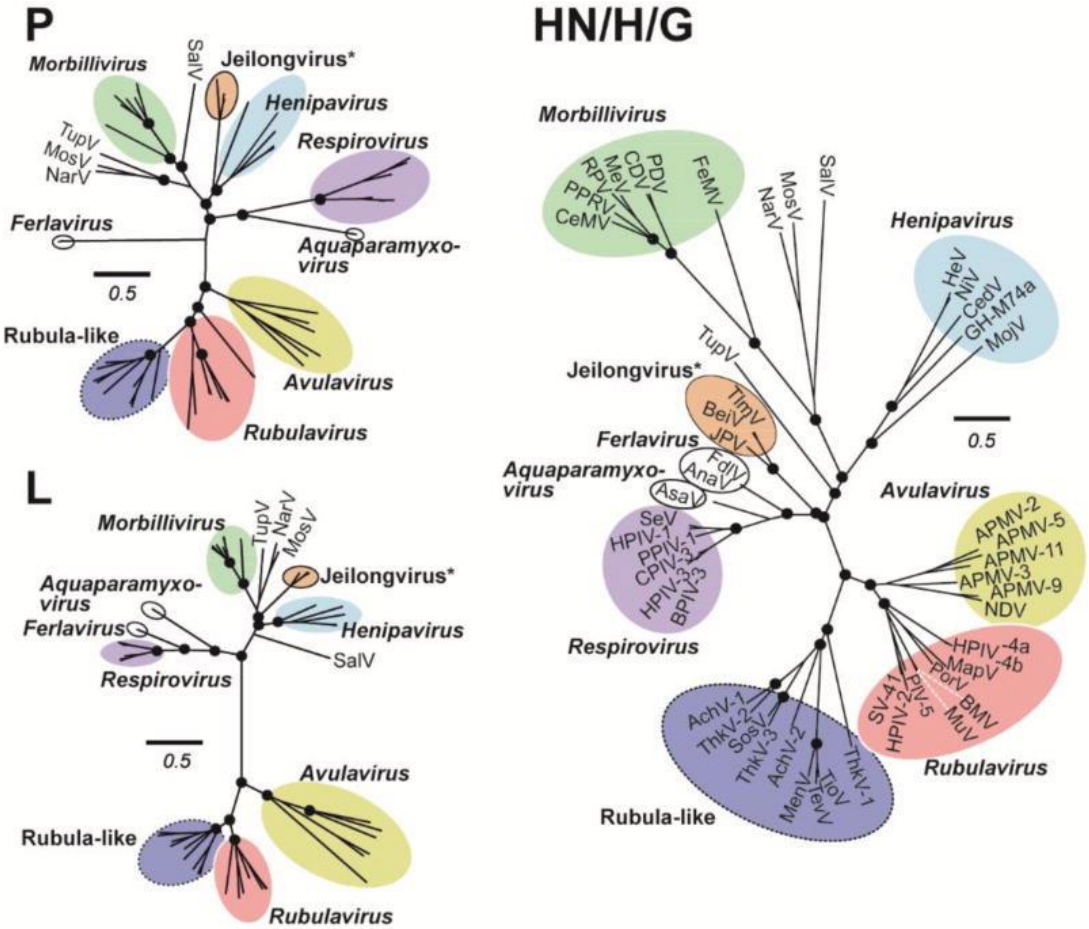

Fig. Maximum likelihood phylogenetic trees of P, L and attachment (HN/H/G) protein sequences of Paramyxoviridae. Coloured circles encompass phylogenetic groupings best characterized as genera. Citation: Thibault PA, Watkinson RE, Moreira-Soto A, Drexler JF, Lee B. Zoonotic Potential of Emerging Paramyxoviruses: Knowns and Unknowns. Adv Virus Res. 2017;98:1-55. doi:10.1016/bs.aivir.2016.12.001

Different genera within the subfamilies *Orthoparamyxovirinae* and *Rubulavirinae* exhibit significant differences in their receptor usage, replication strategies, and immune evasion mechanisms. *Morbillivirus* (e.g., Measles virus) primarily utilizes SLAM/CD150 on immune cells and Nectin-4 on epithelial cells (*Rima et al, 2019*). *Henipavirus* members such as Nipah and Hendra viruses exploit ephrin-B2 and ephrin-B3, while the related Cedar viruses ephrin-B2, ephrin-B1, ephrin-A2, and ephrin-A5, but not ephrin-B3, and is notably non-pathogenic with limited interferon antagonism (*Marsh et al, 2012; Laing et al, 2019*). *Respiroviruses* (e.g., HPIV-1, Sendai virus) and *Orthorubulaviruses* (e.g., Mumps virus, HPIV-2, HPIV-4) attach to host cells via sialic acid residues (*ICTV, 2019*). In contrast, many *Pararubulaviruses*, such as Menangle and Sosuga viruses, appear not to rely on neuraminidase-mediated sialic acid interactions, and their precise cellular receptors remain unidentified (*Duprex and Dutch, 2023*). Immune evasion also varies: *Morbillivirus* and *Henipavirus* encode multiple accessory proteins (V, C, W) that strongly suppress interferon responses, whereas interferon antagonism in *Rubulavirinae* and *Respirovirus* is comparatively weaker and often more localized (*Pisanelli et al. 2022*). Collectively, these genus- and virus-specific differences explain the variation in host range, pathogenesis, and disease severity within the *Paramyxoviridae* family.

Prototype for Paramyxoviridae

The objective of a prototype-driven research strategy is to establish a representative model that encapsulates the core characteristics and inherent diversity of a virus family. The goal is to accelerate the development of vaccines, therapeutics, and diagnostics through focused research, using knowledge from prototype viruses to enable rapid responses against emerging or unknown viruses. Furthermore, this aims to identify and address critical gaps in our understanding of viral pathogenesis, refine animal models, and understand immune correlates of protection. It involves the generation of standardized platforms and assays, supporting risk assessment and surveillance of lesser-known or newly discovered family members. Ultimately, these integrated efforts should

strengthen pandemic preparedness.

Viruses in *Paramyxoviridae* family exhibit diversity in structure and genes, which impacts their life cycles and host interactions. They enter hosts via respiratory droplets, direct contact, and use distinct cellular machinery. Their evasion mechanisms challenge immune responses and antiviral therapies by manipulating host processes, mimicking proteins, or suppressing the activity of immune cells. Due to these varied features, entry strategies, and evasion tactics, a single prototype virus is an insufficient countermeasure for development and other studies.

Through a literature review and expert discussion, the major viruses in the family, that cause infections in humans and/or animals. were identified, as listed in Table No. 1.

99 Table No.1 Viruses of importance in the *Paramyxoviridae* family:

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Subfamily	Genus	Virus	Disease to humans
Orthoparamyxovirinae	*Henipavirus*	• Hendra virus (HeV)	rare
		• Nipah virus (NiV)	sporadic/ outbreak
		• Mòjiāng virus (MojV)	not reported
		• Langya virus (LaV)	rare
		• Cedar virus (CedPV)	not reported
	Morbillivirus	• Measles virus (MV)	routine
		• Canine distemper virus (CDV)	not reported
		• Phocine morbillivirus (PDV)	not reported
		• Bat morbillivirus	not reported
	Respirovirus	• Human respirovirus 3 (HPIV-3)	routine
		• Human respirovirus 1 (HPIV-1)	routine
		• Sendai virus (SeV)	rare
Rubulavirinae	*Orthorubulavirus*	• Mumps virus (MuV)	routine
		• Parainfluenza virus 5 (PIV-5)	rare
		• Human rubulavirus 4 (HPIV-4)	routine
		• Human rubulavirus 2	routine

Subfamily	Genus	Virus	Disease to humans
		(HPIV-2)	
	Pararubulavirus	• Menangle virus (MenPV)	sporadic/ outbreak
		• Tioman virus (TioPV)	rare
		• Sosuga virus (SOSV)	rare

Identification of key drivers for prototype selection

The selection of prototype pathogens within the *Paramyxoviridae* family presented a unique challenge because of the diversity of candidate viruses and the multiple, sometimes competing, considerations involved. On one hand, there are well-studied human pathogens such as measles virus (MV) and mumps virus (MuV), for which vaccines and extensive immunological knowledge already exist. On the other hand, there are zoonotic viruses, such as Nipah virus (NiV), with demonstrated epidemic and pandemic potential, as well as animal viruses like Sendai virus (SeV) or canine distemper virus (CDV), which provide valuable models but differ in their relevance to human disease. Further complicating the process was the existence of safer BSL-2 agents such as Cedar virus (CedPV), which could facilitate laboratory research but do not reproduce the severe disease phenotypes required for translational countermeasure testing.

National Institute of Allergy and Infectious Diseases (NIAID) organized a workshop titled "Pandemic Preparedness: The Prototype Pathogen Approach to Accelerate Medical Countermeasures" (*Deschamps et al, 2023*). Duprex and Dutch reviewed the *Paramyxoviridae* family and proposed a pathogen prioritization matrix centred on seven key decision drivers: high transmission, high genetic diversity, population naivety, zoonotic potential, disease progression, therapeutic availability, and laboratory tractability to identify prototypes (*Duprex and Dutch 2023*).

Based on this evaluative framework, prototypes were identified (Table 2), primarily prioritizing agents handled in Biosafety Level 2 (BSL-2) settings to maximize laboratory

tractability and research participation. Prototypes were not established for the remaining subfamilies within the *Paramyxoviridae* family. The *Avulavirinae*, which primarily infect avian species, were triaged from consideration because they are not considered zoonotic. Additionally, the *Metaparamyxovirinae* were deemed unsuitable for the prototype approach because no members of this subfamily have been isolated to date; they currently exist only as sequence information.

S No	Genera	Suggested prototypes	Rationale
1	*Henipavirus*	Cedar virus	Non-pathogenic *Henipavirus* with BSL-2+ designation, enabling wider laboratory access and experimental tractability compared with BSL-4 Nipah or Hendra viruses.
2	*Morbillivirus*	Canine distemper virus (CDV)	BSL-2 agent; highly transmissible, strong cross-species infection history, well-established animal models, and close relevance to measles virus biology.
3	*Respirovirus*	Human parainfluenza virus 1 or 3 (HPIV-1 / HPIV-3)	BSL-2 respiratory viruses; clinically relevant, tractable in vitro systems, representative of respiratory-restricted paramyxovirus infections.
4	*Rubulavirus*	Human parainfluenza virus 2 or Parainfluenza virus 5 (Orthorubulavirus)	BSL-2 agents; genetically and biologically representative rubulaviruses with extensive laboratory, animal model, and vaccine research background.
		Menangle, Sosuga, Tioman, or Achimota virus (Pararubulavirus)	BSL-2 zoonotic viruses; bat-associated, genetically diverse, documented zoonotic potential, and useful for studying emergence and spillover.

Table 2: Prototypes suggested in previous literature (*Duprex and Dutch, 2023*)

The 2024 update of the WHO R&D Blueprint marked a strategic transition from focusing on individual high-risk threats to a comprehensive "Family approach," evaluating evidence across 28 viral families. This framework introduced the formal categorization of prototype pathogens to generate generalizable knowledge and platform technologies. These prototypes are identified based on their potential to serve as models for fundamental and translational research, facilitating the rapid development of medical countermeasures

(MCMs) that can be applied to other family members or unanticipated emerging threats, referred to as "Pathogen X" (*Koaka et al, 2024*).

For the *Paramyxoviridae* family, the 2024 update specifically identified Nipah virus (*Henipavirus nipahense*) as both a priority pathogen and a prototype pathogen. Its status as a priority pathogen is based on established knowledge of its high virulence, significant case fatality rates, and the current lack of effective medical countermeasures. Simultaneously, its role as a prototype pathogen is intended to guide research into shared structural and functional properties within the family. Because the *Paramyxoviridae* family is genetically and ecologically diverse, the framework notes that a single prototype may be insufficient to cover all research needs, necessitating a broader portfolio of prototype viruses to accelerate the creation of vaccines and therapeutics that can be adapted across the entire family during future public health emergencies.

Framework for Prototype Selection

Building on established prioritization frameworks and the 2024 update of the WHO R&D Blueprint, the selection process considered pathogen's importance as a human or animal pathogen, including its disease burden, transmissibility, and pathogenicity, existing research knowledge of its replication, pathogenesis, and genomic and structural data. The framework also considered whether a pathogen is zoonotic, the existence of animal reservoirs causing cross-species infections, the availability of animal models, and the current status of countermeasure development. While laboratory tractability remains a critical factor for ensuring widespread scientific collaboration, it was not the primary determinant for identifying prototypes.

The strategy identified at least one prototype pathogen for each priority genus within the *Orthoparamyxovirinae* and *Rubulavirinae* subfamilies, and a prototype virus from the *Avulavirinae* subfamily. This genus-based approach ensures that the chosen prototypes fully capture the genetic diversity, distinct host-entry mechanisms, and immune evasion mechanisms, as well as other unique properties particularly important in therapeutic development. Establishing validated platform technologies for multiple genera creates a plug-and-play infrastructure, allowing the existing platforms and strategies to be immediately adapted to accelerate the deployment of countermeasures whenever a novel member of any genus emerges.

Rationale for each recommended prototypes:

1. Nipah virus (*Henipavirus*, *Orthoparamyxovirinae*)

Nipah virus (NiV) is recommended as the primary *Henipavirus* prototype because it uniquely combines public health relevance, enables the development of laboratory platforms, and has validated translational models. NiV has repeatedly caused human outbreaks in Malaysia, Bangladesh, and India, with high case fatality rates and confirmed person-to-person transmission. These characteristics align with the profile of a potential "Disease X" and underscore its importance as a realistic model of pandemic and epidemic risk within the *Henipavirus* genus (*Luby 2013*).

Despite its BSL-4 classification, Nipah research has advanced substantially through the development of safe laboratory tools and protocols. Minigenome replicons allow replication and transcription studies under BSL-2 conditions, supporting mechanistic work and antiviral screening (*Freiberg et al, 2008; Wang et al, 2025*). Pseudovirus systems, in which Nipah F and G glycoproteins are expressed on surrogate viral backbones, enable neutralization assays, immunogenicity studies, and vaccine evaluation without handling infectious virus (*Nie et al, 2019*). In addition, reverse genetics systems permit the rescue of recombinant NiV from cDNA, genetic manipulation of viral genes, and creation of reporter viruses, which are crucial for vaccine design and therapeutic evaluation (*Yun et al, 2015*).

Importantly, Nipah has also been validated in animal models, including hamsters, ferrets, and non-human primates, to reproduce the hallmark systemic and neurological features of the disease. These models have already been used to test vaccines and monoclonal antibodies, thereby accelerating translational pipelines from in vitro studies to preclinical validation (*Bossart et al, 2012; Geisbert et al,. 2021*). Several medical countermeasures (MCMs) against Nipah are in advanced stages of development, further strengthening its position as a practical and scientifically valuable prototype.

Nipah virus combines epidemiological urgency, robust laboratory platforms, and validated animal models, making it the most appropriate prototype for the *Henipavirus* genus. Its selection ensures that platform technologies for vaccines, therapeutics, and diagnostics are developed in a way that directly supports pandemic preparedness against

future emergent *Henipaviruses*.

2. Cedar Virus (*Henipavirus, Orthoparamyxovirinae)*

Cedar virus was selected as a second prototype for the genus *Henipavirus* because its biosafety level 2 status significantly enhances laboratory tractability and research equity, allowing a broader global network of researchers to contribute to *Henipavirus* research without the restrictive requirement for high-containment facilities. Cedar virus (CedV), identified in 2012 in Australian Pteropus fruit bats, is a member of the genus *Henipavirus* and is genetically related to the highly pathogenic NiV and HeV. Unlike these zoonotic pathogens, CedV is apathogenic in animal models and has not been associated with confirmed human disease. Its close phylogenetic relationship to NiV and HeV, combined with intrinsic attenuation and lower biosafety requirements, makes CedV a potential protoype, alternate to NiV for *Henipavirus* research.

Cedar virus exhibits over 60% amino acid identity in the nucleoprotein (N) and matrix (M) proteins along with substantial conservation of the polymerase gene (L) when compared to pathogenic *Henipaviruses*. In contrast, CedV differs in its surface glycoproteins and immune evasion strategies. Although it uses ephrin-B2 for cell entry, it does not utilize ephrin-B3, is not neutralized by the broadly protective monoclonal antibody m102.4, and can engage alternative ephrin receptors (*Laing et al., 2019*). Additionally, CedV lacks RNA editing in the P gene and therefore does not express the V and W interferon-antagonist proteins, resulting in limited suppression of type I interferon responses.

Epidemiologically, CedV has been detected primarily in bats and can often be handled under BSL-2 conditions. Experimental infections in multiple animal models result in viral replication and antibody responses without disease (*Marsh et al, 2012*). Recombinant CedV platforms expressing reporter genes or NiV/HeV glycoproteins enable safe studies of viral entry, tropism, and antiviral interventions, particularly in immunodeficient mouse models (*Amaya et al, 2023*). However, recent serological evidence of CedV-like virus exposure in a small number of humans with febrile illness suggests possible zoonotic spillover, underscoring the need for continued surveillance (*Mittal et al, 2025*).

In summary, CedV is a safe and accessible experimental model for studying conserved *Henipavirus* biology and for preliminary antiviral evaluation. However, its attenuated immune evasion and lack of pathogenicity limit its ability to fully model NiV and HeV

disease, and findings should be validated using authentic pathogenic *Henipaviruses* where feasible.

3. Measles virus (*Morbillivirus, Orthoparamyxovirinae*)

Measles virus (MeV) is selected as a key prototype pathogen primarily to serve as the scientific model for extreme transmissibility and immunomodulation within the *Paramyxoviridae* family. As one of the most contagious human pathogens known, its highly efficient airborne transmission and high basic reproduction number (R_0 of 12-18) make it a crucial model for understanding the mechanisms of rapid respiratory spread (*Parums 2024*). In contrast to the zoonotic prototypes in the selected suite, the Measles virus is an exclusively human pathogen with no known animal reservoir, which allows for a focused investigation of human-specific transmission pathways. The study of its transmission characteristics is considered vital for preparing for potential future Paramyxoviruses that could emerge with a similar capacity for high contagion. A significant strategic advantage of selecting the Measles virus is its Biosafety Level 2 (BSL-2) classification, which renders it a safe and accessible system for high-throughput research and development in standard laboratory settings. This accessibility is critical for the rapid creation and validation of broadly applicable platform technologies, such as novel vaccine platforms or diagnostic assays, which can subsequently be adapted for high-containment (BSL-4) pathogens like Nipah virus.

From a countermeasure and platform perspective, Measles virus is uniquely attractive as a prototype because of the extensive global experience with safe, highly efficacious live-attenuated vaccines and the mature reverse-genetics toolkit built around these strains. Licensed Measles vaccines induce durable humoral and cellular immunity, with well-defined correlates of protection, and they have been repurposed as vectors to express heterologous antigens from a wide range of pathogens. Beyond its utility for platform development, the Measles virus also provides a unique model for studying the complex interactions between Paramyxoviruses and the host immune system. Its ability to induce a profound and long-lasting state of immunosuppression, commonly referred to as "immune amnesia," offers an invaluable opportunity to investigate the mechanisms of immune evasion and modulation (*Laksono et al, 2018*). A thorough understanding of this process is considered important for designing future vaccines that are both safe and effective. As the prototypic *Morbillivirus*, Measles virus has been dissected in detail at the levels of receptor usage cell and tissue tropism, immune modulation, and determinants

of transmission, providing a template for understanding related zoonotic *Morbilliviruses*.

4. Human Parainfluenza virus type 3 (Genus *Respirovirus,* subfamily*: Orthoparamyxovirinae)*

The genus *Respirovirus* constitutes a coherent group defined by a shared genomic organization, transcriptional strategy, and virion architecture, yet its members exhibit distinct, host-specific pathogenicity (*Rima et al, 2019*). Human Parainfluenza Virus 3 (HPIV-3) serves as the prototype for this genus due to its significant clinical impact and role as a foundational biological model. As a primary cause of global acute lower respiratory illness, HPIV-3 contributes to approximately 19 million cases annually in children under five (*Afroz et al, 2024; Linster et al, 2018*). Its entry dynamics, mediated by the HN and F glycoproteins, provide a structural template that is broadly representative of the genus (*Stearns et al, 2024; van Wyke Coelingh et al, 1990*).

HPIV-3 provides critical insights into host susceptibility and potential spillover dynamics. While it is closely related to bovine parainfluenza virus 3, both maintain marked host specificity in natural settings. Evidence of HPIV-3 in wild nonhuman primates in Zambia and in pangolins suggests susceptibility under natural or high-contact conditions, though these are currently categorized as incidental or spillover events. These instances are most plausibly explained by reverse zoonosis rather than sustained independent circulation (*Sasaki et al, 2013; Que et al, 2022*). Such findings emphasize the importance of monitoring HPIV-3 as a model for understanding cross-species transmission within the broader *Paramyxoviridae* family.

The translational value of HPIV-3 is substantial because, despite its high disease burden, no licensed vaccine currently exists. This gap has catalyzed the development of advanced medical countermeasures, including live-attenuated candidates using codon-pair deoptimization and chimeric bovine-human vectors (*Afroz et al, 2024; Saul et al, 2025*). The availability of robust reverse genetics, cryo-EM structural data, and established animal models such as hamsters and ferrets positions HPIV-3 as an essential platform for accelerating broad-spectrum vaccines and antivirals against emerging respiroviruses (*Danov et al*, 2025).

5. Parainfluenza virus 5 (*Orthorubulavirus, Rubulavirinae*)

Parainfluenza virus 5 (PIV5) is designated as the prototype for the genus *Orthorubulavirus* based on its extensive molecular characterization, exceptional safety profile, and its established role as a versatile platform for vaccine development. While other members of the subfamily *Rubulavirinae*, such as the Mumps virus, are significant human pathogens, PIV5 lacks any known association with human disease despite a global seroprevalence of up to 52% (*Chen et al, 2012*). This allows for rigorous structural and functional research under BSL-1 or BSL-2 conditions, facilitating global research equity and collaboration. The virus follows a canonical "rule of six" for efficient encapsidation, and its 15,246-nucleotide genome provides a clear model for rubulavirus organization, including the characterization of the small hydrophobic (SH) protein which modulates innate immunity by inhibiting TNF-α signalling (*Alayyoubi et al, 2015*).

The selection of PIV5 as a prototype is further justified by its laboratory tractability and the existence of a robust reverse genetics system established in 1997. This system allows for precise genomic manipulation, enabling PIV5 to serve as a structural blueprint for understanding paramyxovirus entry through its HN-F functional syncytia and receptor-induced conformational changes (*Parks et al, 2013*). Furthermore, PIV5 provides an essential model for studying viral persistence and immune evasion, particularly through V-protein mediated STAT1 degradation, which parallels the strategies used by more virulent relatives (*Contreras et al, 2021*). Its ability to replicate efficiently across diverse cell lines without inducing cytotoxicity makes it a unique surrogate for studying long-term host-virus co-evolution and the molecular determinants of paramyxovirus chronicity.

In terms of translational utility, PIV5 offers a highly stable and immunogenic vector platform for the rapid development of medical countermeasures. The virus accommodates the stable insertion of large foreign gene sequences at intergenic junctions without the risk of genomic integration or recombination common in other RNA viruses (*Chen et al, 2012*). This platform has been successfully utilized to express antigens for various respiratory pathogens, including influenza, Respiratory Syncitial Virus (RSV), and SARS-CoV-2, demonstrating robust protective efficacy in preclinical models (*Phan et al, 2014; Beavis et al, 2025*). The successful advancement of PIV5-vectored vaccines into Phase 1 clinical trials, confirming their ability to induce mucosal IgA and systemic T-cell responses solidifies its status as a premier model for accelerating the deployment of vaccines against emerging *Orthorubulaviruses* and other Pathogen X threats.

6. Menangle virus (*Pararubulavirus, Rubulavirinae*)

Pararubulaviruses, such as Menangle, Tioman, and Achimota viruses, have demonstrated the ability to spill over from bats to humans or livestock. They are genetically diverse and widely distributed among global bat populations, lacking specific medical countermeasures, which provides a more relevant focus for broad-spectrum preparedness platforms applicable to novel zoonotic outbreaks (*Kuzmin et al, 2011*). There is no well-established zoonotic *Orthorubulavirus* currently known to cause disease in humans. Human infections within the *Orthorubulavirus* genus are primarily represented by the Mumps virus and human parainfluenza viruses, which are human-adapted and not considered animal-to-human zoonoses.

Menangle virus (*Pararubulavirus, Rubulavirinae*) is recommended as the prototype for the *Rubulavirinae* subfamily because it represents an emerging zoonotic virus with proven cross-species transmission potential. First identified during an outbreak in pigs in Australia that was also associated with human infection presenting as a febrile, influenza-like illness, Menangle virus occupies a crucial intermediate position between well-known human *Rubulaviruses* (such as Mumps virus) and numerous, poorly studied animal *Rubulaviruses* (*Philbey et al, 1998*). Selecting Menangle instead of Mumps allows preparedness efforts to be directed at a less-studied but epidemiologically relevant virus, thus broadening the scope of research beyond traditional human pathogens. Its documented zoonotic spillover potential, the availability of viral isolates, and its amenability to laboratory work make it a rational choice to represent *Rubulaviruses* in the prototype framework.

While numerous other *Pararubulaviruses* have been identified in bat populations, such as Achimota virus, Tuhoko virus, Sosuga virus, and Tioman virus, Menangle is considered a superior prototype for several practical and scientific reasons. Critically, Menangle virus has caused documented zoonotic outbreaks with clear clinical disease in both pigs (resulting in major reproductive losses) and humans (*Rupprecht and Burgess, 2015*). This provides a tangible model of cross-species transmission, pathogenesis, and public health impact, which most other listed *Pararubulaviruses* lack, as they have not been definitively linked to disease outbreaks. Its association with significant livestock health events also makes it highly relevant for One Health research.

Furthermore, Menangle virus isolates from both pigs and bats have been fully characterized at the molecular and structural levels, supporting its use as a reliable

comparative prototype for genetic and immunological studies. Because it infects multiple host species and results in recognizable clinical signs, it provides a practical and reproducible model for understanding zoonotic emergence, host adaptation, and transmission dynamics. This combination of proven zoonotic potential, significant impact on livestock and humans, and extensive characterization makes Menangle virus a more informative prototype for *Rubulavirus* research and countermeasure development compared to other *Pararubulaviruses*, which are mostly known from bat surveillance and lack clear disease associations.

7. Newcastle Disease Virus (NDV): subfamily *Avulavirinae*

Newcastle Disease Virus (NDV; *Avian Orthoavulavirus 1*) is the designated prototype for the subfamily *Avulavirinae* due to its phylogenetic centrality and extensive research infrastructure. While a significant poultry pathogen, zoonotic infection in humans is typically limited to mild, self-limiting conjunctivitis. The virus possesses a 15,186-nucleotide negative-sense RNA genome organized into six units (3'-NP-P-M-F-HN-L-5') and utilizes "P gene editing" to generate structural P and non-structural V and W proteins. The V protein serves as a model for immune evasion by targeting STAT1 for degradation, a mechanism mirrored in pathogens like Nipah and Measles (*Steward et al, 1993*).

NDV virulence is governed by the Fusion (F) protein cleavage site. A monobasic motif in lentogenic strains acts as a biological safety lock, restricting replication to specific avian tissues and preventing systemic disease in humans while allowing for effective antigen expression (*Alexander 2000; Kim & Samal, 2016*). This safety profile, alongside efficient reverse genetics and a capacity for large transgenes (4.5 to 5 kb), supports its use as a versatile vaccine vector (*Choi 2017*).

The platform has successfully expressed priority antigens for SARS-CoV-2 and Ebola (*Bukreyev et al, 2006; Sun et al, 2020*). Intranasal delivery induces mucosal IgA and sterilizing immunity, while viral RNA acts as a PAMP to drive Th1-biased adaptive responses (*Tcheou et al, 2021*). Clinical validation of the NDV-HXP-S COVID-19 vaccine confirmed safety and immunogenicity comparable to mRNA platforms, verifying the pipeline from design to deployment (*Sun et al, 2021; Peixoto de Miranda et al, 2025*).

Summary

The Collaborative Open Research Consortium (CORC) has identified seven prototype

pathogens to drive pandemic preparedness against the *Paramyxoviridae* family. This selection includes Nipah virus and Cedar virus (*Orthoparamyxovirinae*), Measles virus (*Orthoparamyxovirinae*), Human Parainfluenza virus type 3 (*Respirovirus*), Parainfluenza virus 5 and Menangle virus (*Rubulavirinae*), and Newcastle disease virus (*Avulavirinae*). This panel attempts a balance between high-consequence pathogens and laboratory-tractable surrogates. Nipah virus represents the high-lethality threat of zoonotic *Henipaviruses*, while the BSL-2 Cedar virus serves as a safe, accessible genetic platform for countermeasure development. Measles virus provides the model for extreme transmissibility and immune modulation. Within Respiroviruses, HPIV3 is a leading cause of lower respiratory tract infections and hospitalizations in infants and young children worldwide. Within the *Rubulavirinae*, Menangle virus captures the risk of emerging zoonoses, while Parainfluenza virus 5 (PIV5) offers a safe model for a proven viral vector platform. Finally, Newcastle disease virus (NDV) is included not only to represent the *Avulavirinae* but specifically for its validated utility as a scalable vaccine vector for human use. By focusing research and development on this diverse yet complementary suite of viruses, the consortium aims to establish the molecular tools, animal models, and immunological baselines necessary to rapidly respond to any future "Pathogen X" emerging from this viral family.

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CHAPTER 2: Epidemiology, Animal Reservoirs and Socio-behavioural Studies

Background

Paramyxoviruses are diverse, spanning human-adapted, endemic respiratory, and zoonotic spillover transmission systems. Epidemiology of a limited number of Paramyxoviruses, such as Measles virus with decades of global surveillance data, is well established but evolving (*World Health Organization, 2025; Moss, 2017*). Important advances have also been made in Nipah virus epidemiology, with outbreak investigations demonstrating repeated spillovers from bat reservoirs, amplification in caregiving and healthcare settings, and the influence of ecological and behavioral factors on transmission (*Luby et al, 2006; Gurley et al 2007; Luby et al, 2009; Plowright et al, 2015; Eby et al, 2023*). Studies of endemic respiratory viruses such as Human Parainfluenza virus-3 indicate its substantial role in pediatric respiratory disease, while Newcastle disease virus epidemiology is relatively well characterized within poultry production systems (*Henrickson et al, 2003; Ganar et al, 2014*).

Despite these advances, major uncertainties remain across the Paramyxovirus family. The true infection burden is poorly defined for many viruses due to surveillance programs biased toward severe disease and limited sero-epidemiological data. Surveillance systems remain fragmented across human, animal, and environmental sectors, constraining early detection of spillover events. Evidence linking reservoir ecology, environmental change, and transmission risk remains incomplete, and key transmission parameters including routes of spread, reproduction numbers, and transmission heterogeneity are insufficiently quantified for most zoonotic paramyxoviruses. Socio-behavioral determinants of exposure and transmission are under-studied, and the natural history and full disease spectrum remain inadequately characterized outside a few well-studied pathogens. Persistent gaps in data harmonization, longitudinal cohort infrastructure, and inter-epidemic preparedness further limit predictive capacity and rapid research activation during outbreaks. The global health impact of several priority paramyxoviruses thus remains incompletely quantified. This section of the roadmap establishes a strategic framework for coordinated epidemiological research and surveillance on this virus family.

Key Needs

1. **Integrated One Health surveillance and spillover detection:** Establish integrated One Health surveillance systems with standardized case definitions, sentinel/event-based platforms, and strengthened surveillance at zoonotic spillover interfaces. This should include community reporting, deployable high-biosafety mobile laboratories, and broad host-range point-of-care diagnostics to enable early detection of paramyxoviruses such as Nipah virus, Measles virus, and Human parainfluenza virus type 3.

2. **Harmonized data systems and genomic epidemiology:** Promote global harmonization of surveillance data through standardized reporting systems and shared epidemiological–clinical–genomic metadata, while integrating genomic sequencing into routine surveillance to track transmission, detect spillovers, monitor viral evolution, and support medical countermeasure development.

3. **Accurate disease burden estimation and natural history research:** Integrate surveillance data with sero-epidemiological studies, longitudinal cohorts, standardized specimen collection, and coordinated biobanking to accurately estimate disease burden and detect mild or asymptomatic infections. These efforts should define the full disease spectrum and natural history of Paramyxovirus infections, including transmission dynamics, immune responses, reinfection patterns, and determinants of disease severity, to identify immunity gaps and inform surveillance, therapeutics, and vaccine development for viruses such as Menangle virus and Human Parainfluenza virus type 3.

4. **Reservoir ecology and transmission dynamics research:** Systematically characterize reservoir hosts, intermediate hosts, and amplification interfaces driving paramyxovirus emergence, including longitudinal surveillance of bat reservoirs and livestock hosts for viruses such as Newcastle disease virus. Parallel studies should quantify transmission parameters including attack rates, reproduction numbers, and transmission heterogeneity across healthcare, household, and community settings.

5. **Integration of socio-behavioural and community determinants:** Embed socio-behavioural research within epidemiological investigations to identify high-risk behaviours, improve community engagement, build trust, and support culturally appropriate implementation of prevention measures and medical countermeasures during outbreaks.

6. **Predictive modelling and sustained preparedness capacity:** Integrate epidemiological, ecological, and environmental datasets to enable predictive spillover modelling and outbreak simulation exercises, while sustaining inter-epidemic preparedness through sentinel respiratory surveillance, trained rapid response teams, operational clinical trial sites, and strengthened laboratory capacity.

Key Challenges and Knowledge Gaps

1. **Poorly quantified disease burden:** The geographical distribution and true burden of paramyxoviruses remain poorly defined. Severe infections such as Nipah virus are more likely to be detected, whereas vaccine-preventable infections like Measles virus may be inadequately captured despite long-standing surveillance (*World Health Organization, 2025; Moss, 2017*). Respiratory viruses such as Human parainfluenza virus type 3 are often under-recognized (*Henrickson et al, 2003;Cunha et al, 2011*) due to non-specific symptoms, while zoonotic viruses including Newcastle disease virus and Menangle virus may go undetected due to mild or asymptomatic infections (*Philbey et al, 1998; World Organization for Animal Health*). Limited sero-epidemiological data further obscures the true burden, hindering accurate risk assessment and public health planning.

2. **Absence of inclusive and representative surveillance architecture:** Current surveillance systems often show weak linkage between syndromic and laboratory data and limited integration across human, animal, and environmental sectors. Surveillance at the animal–human interface is essential for detecting zoonotic spillover (*Gurley & Plowright, 2025*). For pathogens such as Measles virus and Human Parainfluenza virus type 3, fragmented programmes and poorly defined catchment populations further limit surveillance sensitivity (*German et al, 2001*).

Although environmental surveillance expanded after the COVID-19 pandemic, similar systems remain largely absent for most paramyxoviruses despite their potential for early outbreak detection (*Asghar et al, 2014; World Health Organization, 2022*).

3. **Limited surveillance capacity at spillover sites:** Zoonotic spillovers mostly take place at animal-human interfaces, which lack adequate health infrastructure. This delays diagnosis and facilitates the spread of infection.

- **Absence of standard case definitions:** Standard case definitions for suspected and confirmed infections may exist nationally for some zoonotic viruses (*National Centre for Disease Control, 2024*), but global harmonization is lacking (*Luby et al, 2006; World Health Organization, 2018*), delaying case notification and limiting cross-country comparability and coordinated outbreak response (*Chua et al, 2003; Playford et al, 2008*). Respiratory pathogens such as Human parainfluenza virus type 3 often present as non-specific ILI/SARI, while spillovers of viruses like Menangle virus and Parainfluenza virus 5 may be missed due to insensitive case definitions.

- **Impaired laboratory surveillance:** Delays in case notification can degrade samples, reducing diagnostic sensitivity and obscuring epidemiological links. There is also a lack of point-of-care diagnostics for use at the animal–human interface and broad-spectrum tests capable of detecting pathogens across animal, human, and environmental samples (*Mazzola et al, 2026*). In addition, the absence of standardized specimen collection, longitudinal sampling, and biobanking systems limits investigation of transmission, pathogen evolution, and long-term epidemiological patterns.

- **Limited use of newer surveillance tools:** Paramyxovirus surveillance lacks support of newer tools such as genomics and AI-based tests, which can complement field-based epidemiology, assist in outbreak management, and guide forecasting and control measures (*Grubaugh et al, 2019; Pybus et al, 2009; Kraemer et al, 2025*). Where such capacity exists, limited integration of genomic/modelling data with epidemiological investigations restricts real-time transmission inference, source attribution, and mitigation measures.

4. **Limited knowledge on risk factors for Paramyxovirus infection:** There is lack of adequate knowledge on risk factors for Paramyxovirus infections. Some of the key limitations are listed below:

- **Pathogen reservoir:** Though pathogens are varied, common reservoirs of zoonotic Paramyxoviruses, such as bats, pigs and shrews, have been studied in limited capacity. Information on reservoir virome, their behaviour, adaptation, habitat, food sources, habits, disease patterns and immunity across age groups, as well as their interaction with humans and livestock, are critical knowledge gaps. Several aspects of reservoirs' roles have been described with respect to bats and Nipah virus outbreaks in Bangladesh (*Plowright et al, 2015; Eby et al, 2023; Gurley et al, 2025; Peel et al, 2025; Drexler et al, 2012; Plowright et al, 2024*), but such granular data on other reservoirs and/or amplifiers of infection is missing. Additionally, bats are protected ecological reservoirs, and their capture and sampling are constrained by strict ethical and biosafety regulations.

- **Host range of Paramyxoviruses:** This spans a diverse host range, with currently limited evidence. This descriptive data is critical as Paramyxoviruses are known to infect farm animals and amplifiers such as pigs and poultry, and pets such as dogs and cats, posing considerable threat of zoonotic spillover into humans (*Negrete et al, 2005; Bonaparte et al, 2005; Rima et al, 2019; Aguilar et al, 2011*).

- **Transmission dynamics:** Knowledge of Paramyxovirus transmission remains limited. Although animal-to-human and human-to-human spread is documented, key details on transmission routes, infectious dose, and metrics such as attack rates and reproduction numbers are poorly defined, limiting evidence-based infection control. These parameters are well characterized for Measles virus (*Guerra et al, 2017*) and partially studied for Nipah virus (*Luby et al, 2013; Nikolay et al, 2019)*, but require validation across diverse settings, while sporadic zoonotic outbreaks further restrict robust data generation.

- **Seasonality and environmental factors:** Seasonality of Paramyxovirus infections remains poorly defined. Although seasonal patterns can provide early warning signals for outbreaks (*Henrickson et al, 2003; Ferrari et al, 2008; Pulliam et al, 2012*),

and insights into zoonotic spillovers influenced by climate, land use, and reservoir behaviour (*Eby et al, 2023; Plowright et al, 2024*), integration of ecological and epidemiological data remains limited, constraining predictive modelling.

- **Socio-behavioural aspects:** Region-specific social and behavioural factors play a critical role in paramyxovirus transmission and zoonotic spillovers, yet these drivers remain insufficiently studied. Practices such as consumption of bat-contaminated food, caregiving behaviours (*Nikolay et al, 2019*), livestock exposure, health-seeking patterns, and vaccination gaps influence transmission of viruses including Nipah virus, Measles virus, Human Parainfluenza virus type 3, Menangle virus, and Newcastle disease virus. Limited characterization of high-risk populations, exposure settings, and community risk perceptions hampers the design of culturally appropriate prevention strategies and reduces uptake of medical countermeasures, highlighting the need for stronger socio-behavioural research and adaptable outbreak research frameworks.

5. **Incomplete natural history of disease**: The natural history of Paramyxovirus infections remains incompletely defined. While pathogenesis is well characterized for Measles virus and partly described for Nipah virus, key aspects such as clinical variability, viral shedding, and host immune responses remain poorly understood (*Moss, 2017; Plowright et al, 2015; Aguilar et al, 2011; Griffin et al, 2020; Luby et al, 2013; Ang et al, 2018*), particularly for prototype viruses causing mild or asymptomatic infection. Limited longitudinal studies further hinder understanding of infectious periods, long-term sequelae, and correlates of protection needed to guide surveillance and medical countermeasure development.

6. **Inadequate knowledge on disease spectrum:** Data on severity, reinfections, and illness patterns in immune and non-immune populations remain limited for many prototype Paramyxoviruses, particularly zoonotic viruses causing mild disease. Sporadic and geographically restricted outbreaks further limit the ability to define age-specific severity, reinfection dynamics, and determinants of clinical variability across populations (*Plowright et al, 2015; Aguilar et al, 2011; Griffin et al, 2020; Luby et al, 2013; Ang et al, 2018).*

7. **Incomplete data sharing and lack of harmonized data standards:** Real-time cross-border data sharing on Paramyxovirus infections remains limited, and the lack of harmonized datasets and interoperable reporting frameworks hampers comparative analysis. Unlike pandemic-prone influenza surveillance systems such as Global Influenza Surveillance and Response System, similar global platforms are largely absent for Paramyxoviruses, with only Nipah virus and Measles virus widely notifiable in human surveillance systems.

8. **Challenges in sustaining outbreak preparedness:** A key challenge in paramyxovirus preparedness is maintaining surveillance and operational readiness during inter-epidemic periods, when declining cases often reduce surveillance sensitivity, workforce capacity, and coordination across sectors (*Moon et al, 2015; Kandel et al, 2020*).. Sporadic pathogens such as Nipah virus and Menangle virus illustrate how long intervals between outbreaks lead to loss of institutional memory, weakened diagnostics, and limited epidemiological data, undermining timely outbreak detection and evaluation of medical countermeasures.

Key Research Priorities

1. **Strengthen integrated One Health surveillance systems:** Develop integrated human–animal–environment surveillance platforms with standardized case definitions and sentinel/event-based systems to enable early detection and monitoring of Paramyxoviruses including Nipah virus, Measles virus, and Human Parainfluenza virus type 3, with particular focus on zoonotic spillover interfaces.
2. **Harmonize epidemiological data systems and global reporting frameworks:** Establish standardized case definitions, interoperable reporting systems, and shared epidemiological–clinical–genomic metadata frameworks to improve comparability of data across regions and support coordinated responses to paramyxovirus outbreaks.

3. **Integrate genomic epidemiology into routine surveillance:** Embed genomic sequencing within routine public health surveillance, linked with epidemiological metadata, to identify spillover events, reconstruct transmission chains, monitor viral evolution, and guide medical countermeasure development.

4. **Generate reliable estimates of disease burden and immunity gaps:** Conduct sero-epidemiological studies, longitudinal cohorts, and integrated surveillance analyses to quantify infection burden, detect mild or asymptomatic infections, and identify immunity gaps for viruses such as Menangle virus and Human Parainfluenza virus type 3.

5. **Characterize reservoir ecology and spillover pathways:** Undertake systematic research on reservoir hosts, intermediate hosts, and amplification interfaces, including longitudinal monitoring of wildlife and livestock reservoirs and ecological modelling to identify drivers of spillover and emergence.

6. **Establish longitudinal research and biobanking frameworks:** Develop longitudinal cohorts, standardized specimen collection protocols, and coordinated biobanking systems to study natural history, immune responses, and correlates of protection.

7. **Define transmission dynamics and epidemiological determinants:** Quantify transmission parameters, including secondary attack rates, reproduction numbers, and transmission heterogeneity across healthcare, household, and community settings, to inform infection prevention and control strategies.

8. **Integrate socio-behavioural determinants into outbreak investigations:** Strengthen socio-behavioural research within epidemiological investigations to understand exposure pathways, healthcare-seeking behaviour, and community risk perception, while promoting culturally appropriate prevention strategies and community engagement.

9. **Build predictive modelling capacity and sustain inter-epidemic preparedness:** Integrate epidemiological, ecological, and environmental data to develop predictive models for spillover and outbreaks, while maintaining long-term preparedness capacity through sentinel respiratory surveillance, trained response teams, operational clinical trial platforms, and strengthened laboratory networks.

Strategic Goals and Aligned Milestones

Strategic Goal	Milestones
Strategic Goal 1: Establish foundational epidemiological R&D infrastructure across prototype paramyxoviruses	• By Year 1, finalize Paramyxovirus case definitions with global consensus. • By Year 2, identify sentinel surveillance sites with defined catchment populations, map spillover hotspots using existing datasets, and standardize specimen collection. • By Year 3, finalize and adopt metadata templates for standardized case reporting.
Strategic Goal 2: Operationalize integrated One-Health surveillance	• By Year 1, finalize frameworks for integrated human–animal–environmental surveillance. • By Year 2, identify model sites for surveillance across species interface, and establish frameworks for deployment of resources and tools (such as mobile laboratories) in spillover sites. • By Year 3, pilot species-interface and environmental surveillance, and integrate genomic surveillance workflows into outbreak response.
Strategic Goal 3: Generate robust epidemiological evidence on disease burden, trends and transmission	• By Year 3, establish sentinel surveillance and multi-country longitudinal cohort studies on natural history of disease and spectrum of illness, and operationalize biobanks. • By Year 4, integrate socio-behavioural R&D components in sentinel surveillance and cohort studies, and initiate ecological studies on reservoirs and amplifiers of disease. • By Year 5, integrate genomic epidemiology and newer tools in surveillance, and operationalize regional data-sharing mechanism.
Strategic Goal 4: Develop predictive	• By Year 5, initiate triangulation of epidemiological, ecological, clinical and laboratory data for outbreak prediction.

algorithms for outbreak forecasting	• By Year 5, pilot AI-assisted surveillance tools and conduct outbreak simulation exercises in priority regions.
Strategic Goal 5: Achieve sustained inter-epidemic preparedness	• By Year 5, initiate community engagement to establish clinical trial-ready cohorts and sites, and institutionalize frameworks for continued training of workforce in critical scientific techniques.

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CHAPTER 3: Laboratory & Assays, Basic Research and Disease Models

Background

Paramyxoviruses are enveloped viruses with a conserved virion structure (*Enders G, 1996*). Viral entry is mediated by surface glycoproteins responsible for host receptor binding and membrane fusion, while the matrix (M) protein regulates virus assembly and budding. Despite this conserved architecture, Paramyxoviruses show substantial diversity in receptor usage and host range (*Drexler et al., 2012; Rima et al., 2019*). For example, *Morbilliviruses* such as measles virus bind SLAMF1/CD150 receptors, viruses such as Human Parainfluenza Virus-3, Parainfluenza Virus-5, and Newcastle Disease Virus bind sialic acid receptors, while *Henipaviruses* such as Nipah virus utilize Ephrin-B2/B3 receptors (*Tatsuo et al, 2000; Mühlebach et al, 2011; Yin et al, 2005; Yin et al, 2006; Welch et al, 2012; Eaton et al, 2006; Negrete et al, 2005; Wang et al, 2010; Chang et al., 2012; Navaratnarajah et al., 2020*). These structural differences influence host range, pathogenicity, tissue tropism, and transmission dynamics.

Standardized laboratory procedures and robust quality control systems are essential for effective surveillance, early outbreak detection, understanding viral biology, and developing medical countermeasures for viruses in the *Paramyxoviridae* family. Laboratory characterization relies on multiple assay platforms, including virus neutralization tests to measure functional antibodies, ELISA assays for large-scale antigen or antibody detection, PCR-based methods for viral RNA detection, and nucleic acid sequencing for genome characterization and pathogen discovery.

Infection and disease models are essential for understanding pathogenesis and evaluating vaccines and therapeutics for *Paramyxoviridae,* but many fail to replicate the natural course of human disease. In-vitro systems support viral replication studies but have limited physiological relevance (*Zhang et al., 2011*). For viruses such as PIV5, Cedar virus, and Newcastle Disease Virus, model selection is difficult due to minimal human pathogenicity (*Zhang et al, 2011, Marsh et al, 2012; Laing et al, 2018; Ganar et al, 2014*). Measles models rely on transgenic mice and inadequately capture complications like SSPE (*Laksono et al., 2020*). For Nipah virus, African green monkeys and Syrian golden hamsters are the most useful models (*de Wit et al, 2015*), while Menangle virus lacks a defined

disease model (*Philbey et al, 1998; Bowden et al, 2012*). Although HPIV-3 has been studied in several airway and animal models, no paramyxovirus disease model is fully standardized (*Lin Y, 2024; Porter et al, 1991; Garg et al, 2019*), and the absence of standardized protocols for model selection and challenge studies limits reproducibility and comparability of research data. In addition, biosafety requirements influence research capacity, as certain viruses such as Nipah virus require high-containment laboratory facilities (*Daniel et al, 2001*). Besides, there is no global consensus on the containment requirements of the Menangle virus (*Barr et al, 2012*).

Key Needs

1. **Comprehensive characterization of prototype Paramyxoviruses:** Expanded laboratory research is needed to characterize viral structural proteins, receptor-binding mechanisms, and host–virus interactions across prototype Paramyxoviruses. Improved understanding of glycoprotein structure, receptor usage, and immune responses will support the development of vaccines, therapeutics, and diagnostics.

2. **Standardized open-access laboratory protocols:** Develop global open-access Standard Operating Procedures (SoPs) for biosafety, sample collection, transport, processing, and testing, based on studies of disease kinetics and optimal specimen types for Paramyxovirus infections.

3. **Identification of targets for vaccines and antivirals:** Strengthen in-silico and laboratory studies on viral structure, replication mechanisms, and virus–host interactions to identify key targets for vaccine and antiviral development.

4. **Biorepositories and reference standards:** Establish biorepositories for clinical samples, pathogen strains, and environmental/animal specimens, supported by clear legal frameworks and MTAs. Develop regional reference standards calibrated to WHO International Standards and harmonize virus nomenclature across genomic databases.

5. **Well-characterized infection and disease models:** Develop and standardize both in-vitro (cell lines, organoids, VLPs, pseudoviruses, reverse genetics systems) and

in-vivo models to study viral replication, pathogenesis, and evaluate medical countermeasures. Infection models with appropriate endpoints (e.g., mucosal shedding) should also be established for prototype viruses that cause minimal disease in humans, such as Cedar virus, PIV-5, and Newcastle Disease Virus.

6. **Global network of harmonized laboratories and strengthened biosafety capacity:** Establish a coordinated global network of R&D laboratories with harmonized methods and robust QA/QC systems, while expanding access to appropriately equipped biosafety facilities, including BSL-3 laboratories for high-risk pathogens such as Nipah virus. Use of alternatives to live virus work (e.g., pseudoviruses) should also be promoted to expand research capacity and reduce reliance on high-containment laboratories.

7. **Development of accessible and validated diagnostic assays:** Define Target Product Profiles (TPPs) for Paramyxovirus diagnostics and develop accessible, field-deployable assays suitable for early detection in resource-limited and remote settings where zoonotic spillovers occur. This includes identifying optimal specimen types and sampling timelines, developing point-of-care and automated diagnostic platforms, and validating promising assays through multi-center international studies.

8. **Sustained R&D funding and market incentives:** Strengthen funding mechanisms, procurement commitments, and regulatory pathways to incentivize development, commercialization, and adoption of Paramyxovirus diagnostics and other medical countermeasures.

Key Challenges and Knowledge Gaps

1. **Virus diversity and research complexity:** The *Paramyxoviridae* family comprises of multiple genera with substantial structural and genetic diversity, which complicates laboratory research and development. Variations in viral proteins, receptor usage, and host range require virus-specific approaches for diagnostics, vaccines, and therapeutics and thereby creating a need for customised laboratory assays. Historically, research efforts have focused primarily on vaccine-preventable viruses

and high-impact zoonotic pathogens such as *Henipaviruses*, leaving several prototype pathogens comparatively under-characterized.

2. **Biocontainment requirements:** Paramyxovirus research requires different levels of biosafety containment depending on the pathogen. While many prototype viruses can be studied in Biosafety Level-2 laboratories (*Marsh et al, 2012; Henrickson et al., 2003; Chen et al., 2018*), highly pathogenic zoonotic viruses such as Nipah virus require maximum containment facilities with controlled access, specialized protective equipment, and stringent waste management systems (*Daniel et al, 2001*). Such facilities are limited globally, especially in regions that frequently experience outbreaks, creating logistical, financial, and operational barriers to research.

3. **Limited structural and pathogenesis data:** Although Paramyxoviruses share broadly conserved virion architecture (*Enders G, 1996*), significant variation exists in their glycoprotein structures, receptor binding domains, and fusion mechanisms. These structural differences influence host range, tissue tropism, pathogenicity, and transmission. For several prototype viruses, detailed information on viral protein structure, receptor interactions, and host immune responses remains incomplete, limiting the development of targeted vaccines, therapeutics, and diagnostics.

4. **Limitations of commonly used laboratory assays:** Despite their utility, these assays have important limitations. Neutralization tests are labor-intensive and difficult to standardize (*Cohen et al, 2008; Menangle virus Fact Sheet, 2021*), ELISA assays may not accurately reflect functional immunity (*Cohen et al, 2008*), PCR sensitivity can be affected by viral mutations (*McMillen et al, 2022*), and sequencing requires costly infrastructure and bioinformatics expertise (*Cheval et al, 2011*).

5. **Lack of well-characterized infection and disease models:** Many existing models do not adequately replicate the natural course of Paramyxovirus infections in humans (*Laksono et al., 2020*), and suitable models are difficult to establish for viruses with minimal human pathogenicity or limited clinical data (*Zhang et al, 2011, Marsh et al, 2012; Laing et al, 2018; Ganar et al, 2014*). In addition, there is a lack of standardized protocols for model selection and challenge studies, which limits

reproducibility and comparability of results across laboratories and slows the development of medical countermeasures.

6. **Quality control and standardization challenges**: Laboratory research on Paramyxoviruses is constrained by the lack of standardized, reproducible protocols and limited availability of proficiency testing programs across laboratories. Differences in assay design, reagents, and experimental conditions contribute to methodological variability, making it difficult to compare results across studies or laboratories and limiting the global acceptability of research findings.

7. **Limited availability of clinical samples, viral strains, and reference reagents:** Access to well-characterized clinical samples, viral isolates, and standardized reference reagents remains a major challenge for Paramyxovirus research (*World health Organization - WHO Catalogue, 2024*). These materials are particularly scarce for viruses that cause sporadic outbreaks, such as Nipah virus, or for viruses that produce mild or asymptomatic infections in humans. In addition, the absence of clear international frameworks for sharing biological resources, fragmented genomic databases, and limited availability of WHO international standards further hinder collaborative research and assay development.

8. **Challenges in diagnostic product development and commercialization**: Most existing laboratory diagnostic assays for Paramyxoviruses require sophisticated equipment and highly trained personnel, limiting their use in remote or resource-limited settings where zoonotic spillovers often occur. There is also limited evidence on optimal specimen types, timing of sample collection, and sample transport conditions for several Paramyxovirus infections. Lack of target product profiles also compromises product development. Furthermore, the sporadic nature and relatively low incidence of many zoonotic paramyxoviruses reduce commercial incentives for companies to invest in the development and sustained production of validated diagnostic tests (*Mazzola et al, 2025, Gómez Román et al, 2020; Mishra et al, 2024*).

Key Research Priorities

1. **Structural, molecular, and functional characterization of prototype paramyxoviruses:** Conduct detailed structural and functional studies of viral proteins (e.g., attachment glycoproteins, fusion proteins, and matrix proteins) to understand receptor usage, host–virus interactions, and determinants of host range, pathogenicity, and transmission. Integrate genomic sequencing and bioinformatics approaches to improve understanding of viral evolution and transmission dynamics.

2. **Identification of molecular targets for vaccines and therapeutics:** Use integrated structural biology, in-silico modelling, and experimental approaches to identify and validate viral and host targets involved in virus entry, replication, transcription, and immune evasion, enabling the development of vaccines, monoclonal antibodies, and antiviral therapeutics.

3. **Development and standardization of laboratory assays:** Develop robust, scalable, and standardized diagnostic and immunological assays, including improved neutralization assays, multiplex serology platforms, mutation-resilient molecular diagnostics, and cost-effective sequencing approaches. Harmonize assays across laboratory networks through validated reagents, proficiency testing, and development of reference standards.

4. **Establishment of standardized infection and disease models:** Develop and validate physiologically relevant in-vitro systems (e.g., cell lines, organoids, virus-like particles, pseudoviruses, and reverse genetics systems) and appropriate in-vivo models to study viral replication, pathogenesis, immune responses, and evaluation of medical countermeasures. Infection models should also be established for minimally pathogenic prototype viruses.

5. **Characterization of disease kinetics and optimal sampling strategies:** Conduct studies to describe disease progression, viral shedding dynamics, optimal specimen types, and timing of sample collection across Paramyxovirus infections to inform surveillance, diagnostics, and therapeutic evaluation.

6. **Development and validation of accessible diagnostic technologies:** Develop and evaluate point-of-care and near-point-of-care diagnostic platforms suitable for

outbreak settings and resource-limited regions. This includes defining target product profiles (TPPs), exploring innovative detection technologies, and validating promising assays through multicentre international studies.

7. **Establishment of biorepositories and harmonized reference standards:** Create global and regional repositories of well-characterized clinical samples, viral isolates, and animal/environmental specimens to support assay development, validation, and comparative research. Develop calibrated regional reference standards to ensure reproducibility and comparability of laboratory results.

8. **Strengthening laboratory networks and biosafety capacity:** Develop a coordinated global network of laboratories with harmonized protocols, strong quality assurance systems, and expanded biosafety infrastructure, including BSL-3 capacity where required, to enable safe research and outbreak investigation.

9. **Capacity building, collaboration, and translational pathways:** Promote global research collaboration, open resource sharing, and training in Paramyxovirus diagnostics and laboratory methods. Engage regulatory authorities to define pathways for evaluation and licensure of diagnostics and develop implementation guidelines to support deployment during outbreaks.

Strategic Goals and Aligned Milestones

Strategic Goal	Milestones
Strategic Goal 1: To standardize and harmonize laboratory assays for prototype/priority Paramyxoviruses and ensure open-resource data sharing	• Identify laboratories with in-house Paramyxovirus assays and standardize protocols through collaborative multi-centric reproducibility studies. • Harmonize assays across a network of quality-assured laboratories covering all WHO regions. • Initiate development of a WHO international antibody standard/reference animal sera standard for calibration of diagnostic assays for each prototype Paramyxovirus.

Strategic Goal	Milestones
	• Prepare a global open-resource compendium of validated Standard Operating Procedures for Paramyxovirus laboratory techniques.
Strategic Goal 2: To generate knowledge on Paramyxovirus structure, biology and infection kinetics	• Initiate imaging/in-silico studies on each prototype virus structure, conformational dynamics of viral proteins including their interactions with host cell, and disease pathogenesis. • Generate evidence on molecular mechanisms governing the replication and transcription of Paramyxoviruses, including promoter recognition, gene expression gradients, and RNA editing; identify essential steps in the replication cycle that can be targeted by therapeutics. • Initiate studies to define in-vitro and in-vivo models of infection. • Establish protocols for virus challenge studies and define correlates of protection.
Strategic Goal 3: To establish biorepositories for Paramyxovirus specimens	• Identify existing biorepositories of Paramyxovirus clinical samples. • Develop an international legal framework and Material Transfer Agreements (MTAs) for sample sharing. • Launch a global network of strengthened biorepositories containing human, animal and environmental samples.
Strategic Goal 4: To develop Target Product Profiles for Paramyxovirus diagnostics	• Chart a competitive landscape of existing Paramyxovirus diagnostics. • Develop Target Product Profile for prototype Paramyxovirus laboratory-based assay, including point-of-care/ near-patient diagnostic assay by 2028.
Strategic Goal 5: To validate Paramyxovirus diagnostics	• Engage regulatory agencies to establish licensure pathways for high-risk Paramyxovirus assays with limited clinical samples for evaluation.

Strategic Goal	Milestones
	• Identify promising assays/ technologies, conduct analytical performance evaluation and field performance evaluation exercises. • Commercialize at least one affordable point-of-care/ near-patient prototype Paramyxovirus assay with acceptable performance and turnaround time.
Strategic Goal 6: To guide funding bodies on Paramyxovirus R&D	• Identify focus public health research areas to guide global funding bodies on Paramyxovirus R&D.

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CHAPTER 4: Development of Medical Countermeasures

A. Accelerating Vaccine development for Paramyxoviruses

1. Vaccine development for disease causing Paramyxoviridae prototypes:

i. Nipah Virus Disease:

Nipah virus encodes surface glycoproteins (G and F) that mediate host entry via ephrin-B2/B3 receptors and are the primary targets of protective neutralizing antibodies, while non-structural proteins (V, W, C) antagonize innate immunity and drive pathogenesis, supporting antibody-focused vaccine strategies (*Negrete et al, 2005, 2006; Yoneda et al, 2010*). Consistent evidence, including monoclonal antibody m102.4 studies, shows that G- and F-specific neutralizing antibodies correlate strongly with protection (*Mire et al, 2020; Zhou et al, 2026*). However, sporadic outbreaks limit feasibility of phase III trials, positioning NiV vaccines as epidemic preparedness tools reliant on immune correlates, animal models (*Lv et al, 2025*), and regulatory pathways like the FDA animal rule (*Beasley et al, 2016*). Despite progress and a few vaccines under development, no licensed vaccine is yet available (*Kim et al, 2025*).

Nipah virus subunit vaccines target the G glycoprotein, with recombinant soluble G (including Hendra-derived) showing strong cross-protective immunity in animal models and early clinical promise (*Salleh et al, 2025; Bossart et al, 2012; Frenck et al, 2025*). Emerging immunoinformatics-driven G-based multi-epitope vaccine designs further highlight next-generation potential, though they require experimental validation (*Kim et al., 2025*). Recombinant viral-vectored vaccines are leading Nipah virus candidates, with rVSVΔG-EBOV GP/NiV G and ChAdOx1 NipahB demonstrating strong protection and immunogenicity, primarily through induction of neutralizing antibodies (*DeBuysscher et al, 2016; van Doremalen et al, 2022*). Both have shown efficacy in non-human primates and are progressing through early-phase clinical trials, underscoring their potential as outbreak-ready vaccines (*Kim et al, 2025*). RNA-based Nipah virus vaccines encoding G and/or F glycoproteins, including nanoparticle formulations, have demonstrated strong immunogenicity and protection in preclinical models, offering advantages of rapid manufacturing and adaptability for outbreak response (*Brandys et al, 2025; Chen et al,*

2024). Complementary nanoparticle platforms that present G in a multivalent format further enhance neutralizing antibody responses by mimicking native viral structure, supporting their promise as next-generation vaccine strategies (*Sun et al, 2026*).

ii. Measles:

Current measles vaccines are live-attenuated (Edmonston strain), delivered as monovalent or combination (MR/MMR) formulations, provide ~93% protection after one dose and ~97% after two doses, with strong, long-lasting immunity and a well-established safety profile that has enabled near-elimination in several regions (*Gastañaduy et al., 2021; Plans-Rubió, 2021*). Future efforts should focus on vaccines effective in early infancy despite maternal antibodies, improved thermostability, needle-free delivery (e.g., microneedle or aerosol), enhanced mucosal immunity, and safer alternatives for immunocompromised populations to improve coverage and sustain elimination (*Sathiyanarayanan et al, 2020; Joyce et al, 2021*).

iii. Human Para-influenza Virus 3 (HPIV3):

HPIV3 reinfections are common because natural infection induces incomplete, short-lived mucosal immunity, primarily dependent on secretory IgA and airway-resident T cells that wane rapidly and are poorly recalled (*Noone et al, 2008*). This is further compounded by viral inhibition of T-cell responses (*Schaap-Nutt et al, 2010*) and limited maintenance of memory immunity, leading to non-sterilizing protection despite minimal antigenic variation (*Branche & Falsey, 2016*).

Developing an effective HPIV3 vaccine is challenging due to its primary impact on young infants, where immunologic immaturity and maternal antibodies limit vaccine responses (*Lee et al, 2001*). Protective immunity targets the HN and F glycoproteins, but as a mucosal respiratory pathogen, HPIV3 requires strong local IgA and cellular responses that are poorly induced by parenteral vaccines (*Suryadevara et al, 2024; Baker et al, 2022*). Live-attenuated intranasal vaccines are preferred but face challenges in balancing safety and immunogenicity, compounded by viral sensitivity to innate immune responses and lack of durable natural immunity. Progress is further hindered by undefined immune correlates and non-predictive animal models, highlighting the need for optimized strategies tailored to infant mucosal immunity (*Vacher et al, 2025*).

No HPIV3 vaccine is currently licensed, although multiple platforms including live-attenuated intranasal, vectored, subunit, and mRNA vaccines are in preclinical or early clinical development, with progress particularly in pediatric and combination vaccine approaches (*Vacher et al, 2025*). Live-attenuated intranasal vaccines are the most

advanced, showing acceptable safety and moderate immunogenicity in infants, but are limited by challenges in balancing attenuation and replication, delaying phase III trials. Vectored and chimeric vaccines have shown promise in early trials but remain underdeveloped, while subunit and nucleic acid platforms are largely preclinical, constrained by poor induction of mucosal immunity. Overall, progress across all platforms is hindered by gaps in immune correlates, infant immunology, and predictive models, preventing advancement to licensure.

Key Needs

1. **Establishment of validated immune correlates of protection:** Define quantitative and mechanistic correlates (including mucosal, humoral, and cellular immunity) supported by standardized assays to enable immunobridging and regulatory approval.

2. **Development of predictive and harmonized translational models:** Improve animal models and develop standardized frameworks that reliably link preclinical immunogenicity to human protection, including support for regulatory pathways such as the animal rule.

3. **Advancement of platform-optimized vaccine strategies:** Design vaccine platforms that balance safety, immunogenicity, and durability, particularly enabling strong mucosal immunity and effectiveness in challenging populations (e.g., infants for HPIV3, rapid response for NiV).

4. **Strengthening manufacturing, scalability, and deployment readiness:** Integrate manufacturability, thermostability, and stockpiling strategies early to ensure rapid scale-up and equitable deployment, especially for outbreak-prone or low-resource settings.

5. **Enhancement of regulatory, clinical, and surveillance frameworks:** Develop clear regulatory pathways, innovative trial designs, and strengthened epidemiological and genomic surveillance systems to support vaccine evaluation, licensure, and implementation.

6. **Development of vaccines effective in early infancy despite maternal antibodies:** Advance strategies (e.g., higher immunogenicity platforms or alternative delivery routes) to ensure robust protection in young infants.

7. **Innovation in needle-free and thermostable vaccine delivery systems:** Enable simplified administration (e.g., microneedle patches, aerosolized vaccines) and reduced cold-chain dependence to improve coverage and programmatic feasibility.

Key Challenges and Knowledge Gaps

Overlapping challenges and knowledge gaps in vaccine development for Paramyxoviruses pathogenic to humans

- Lack of clearly defined immune correlates of protection, uncertainty in protective immune thresholds, incomplete understanding of role of cellular immunity, contribution of non-neutralizing immune responses (*Griffin, 2016*).
- Absence of fully predictive animal models, weak linkage between animal immunogenicity and human protection and challenges in translating preclinical findings into clinical efficacy (*Lv et al, 2025*).
- Uncertainty regarding long-term protection, limited data on immune waning kinetics and inadequate evidence to guide boosting strategies pose challenges (*Kennedy et al, 2019*).
- Significant challenges exist in balancing safety vs immunogenicity (especially for live-attenuated vaccines), non-replicating platforms have reduced ability to induce robust mucosal immunity (*Russel et al, 2018*).
- Manufacturing and deployment constraints are related to challenges in scalability, vaccine stability, cold-chain requirements and need for better integration of manufacturability early in development (*Mukherjee et al, 2023*).
- Limited understanding of antigenic variability and cross-protective immunity across strains (*de Vries et al, 2020*).
- Lack of clearly defined regulatory pathways due to lack of validated endpoints for licensure and dependence on non-traditional approval pathways (*Orenstein et al, Plotkin's Vaccines*).

Vaccine development for NiV has the following additional challenges and knowledge gaps

- Outbreak and trial feasibility is constrained due to sporadic, unpredictable outbreaks limiting Phase III trials, insufficient case accrual for efficacy endpoints and reliance on animal rule and immunobridging strategies (Kim et al, 2025).

- Dependence on BSL-4 facilities for Nipah virus related studies which restricts global research capacity and creates high operational and regulatory burden (van den Hurk et al, 2025).
- Poor understanding of the role of mucosal immunity in reducing viral shedding post-vaccination, impact on transmission dynamics and indirect protection (Park et al, 2024).
- Lack of clear strategy on the need to stockpile and deploy the vaccine in public health emergencies, limiting commercial incentives (Gopinathan et al, 2020).

Vaccine development for HPIV3 has the following additional challenges and knowledge gaps

- HPIV3 predominantly affects infants, where immunologic immaturity, maternal antibody interference, and stringent safety requirements complicate vaccine development and deployment (*Crofts et al, 2020*).
- Protection relies heavily on transient mucosal responses due to the respiratory route of infection (*Song et al, 2024*).
- High sensitivity to type I interferon restricts replication of live-attenuated vaccine candidates (*Childs et al, 2012*).
- Absence of standardised human challenge models, variable performance of intranasal vaccines, and poorly defined clinical endpoints hinder evaluation (*Lambkin et al, 2018; Deng et al, 2025*).
- Limited genomic surveillance and incomplete disease burden data constrain prioritisation and trial design (*Martyn et al, 2026*).
- Sparse data in high-risk groups, uncertainty around co-administration, limited combination vaccine development, and lower mortality relative to RSV reduce industry prioritisation (*Vacher et al, 2025*).

Additional challenges and knowledge gaps in next-generation Measles vaccine development

- Reduced vaccine effectiveness in early infancy, with limited clarity on strategies to overcome maternal antibody interference and define protective immune thresholds (Voysey et al, 2017; Plotkin 2010).
- Insufficient long-term durability data for non-live platforms, creating uncertainty about sustained immune protection (Bianchi et al, 2021).

- Limited evidence supporting safe and effective non-replicating vaccine options for immunocompromised individuals (Papaevangelou, 2021).
- Challenges in maintaining vaccine potency outside strict cold-chain conditions (Juan-Giner et al, 2020).
- Dependence on injectable formats requiring trained personnel, while immune correlates for needle-free approaches (e.g., microneedle, aerosol) remain poorly defined (Goodson & Rota, 2022).
- Lack of harmonised assays and comparability frameworks to benchmark next-generation candidates against existing vaccines (Woudenberg et al, 2019).
- Limited data on co-administration, real-world effectiveness, and scalability in low-resource settings (Endalamaw et al, 2024; Restrepo-Méndez et al, 2016).
- Uncertainty regarding effects on transmission dynamics and herd immunity (Plans-Rubió, 2020).

Key Research Priorities

1. **Laboratory preparedness:** Harmonize and standardize immunological assays, develop reference standards to enable cross-study comparability, strengthen genomic and antigenic surveillance and evaluate cross-lineage or cross-strain protection, validate BSL-2 surrogate assays against BSL-4 pathogens (particularly important for NiV).

2. **Animal models:** Robust animal models for defining quantitative immune correlates of protection, identify mucosal, humoral, and cellular immune markers and develop validated surrogate endpoints for licensure, characterization of mucosal immune responses (e.g., nasal IgA, tissue-resident T cells) and immunobridging frameworks.

3. **Immunological assessment:** Evaluate durability of immunity and booster strategies by defining kinetics of immune waning, need for booster regimens and long-term immunogenicity data.

4. **Vaccine platform optimization:** Improve antigen design and breadth, enhance immunogenicity and safety balance, advance next-generation platforms (mRNA, subunit, vectors), safety of use in paediatric population. For Measles and PIV3, additional considerations include reduction in interference by maternal antibodies,

suitability of non-injectable routes of vaccination or use of painless delivery devices; use of combination vaccines, improved suitability for immunocompromised populations, preterm and malnourished children.

5. **Integrate early manufacturing and enabling regulatory frameworks:** strengthen global manufacturing capacity for scalable deployment, improve thermostability to reduce cold-chain dependence, define licensure criteria and validated endpoints, develop harmonized regulatory guidance and enable alternative approval pathways where needed

6. **Develop outbreak deployment plans:** For NiV, it is critical to define use cases, develop target product profiles, regulatory pathways for compassionate use, develop protocols for innovative trials (described in section C).

583 ## Strategic Goals and Milestones

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Strategic Goal 1 (short-term): *Milestones to be achieved in 0-3 years* *Establish foundation and bridge the gaps in Immunology, laboratory assays and animal models; initiate R&D of novel vaccine platforms, optimize doses and new delivery devices; initiate clinical trials with advanced candidates and lay out strategies for resolution of operational constraints*	1. Immunology • Establish immune correlates of protection, including mucosal immune markers (e.g., sIgA, tissue-resident T cells). • Systems immunology approaches to identify predictive immune signatures and biomarkers. • Early safety and immunogenicity data in infants, accounting for maternal antibody interference (particularly for PIV3 and Measles). 2. Laboratory: • Develop standardized assays for neutralization, mucosal immunity and immune profiling. • Strengthen genomic and antigenic surveillance of circulating HPIV3 strains. • Establish and standardize BSL-2 surrogate assays for Nipah virus. 3. Vaccine platforms: • Optimize vaccine platforms: balance attenuation vs replication. • Improve genetic stability and safety in infants (particularly for PIV3 and Measles). • Further develop promising platforms (e.g., viral vectors, mRNA, subunit). • Optimize antigen constructs (G and F glycoproteins). • Evaluate adjuvants and formulations to enhance immunogenicity. 4. Animal models: • Harmonize animal challenge models (strain, dose, route). • Initiate comparative studies across small animals and NHPs.

	• Define standardized endpoints (survival, viral load, neurological outcomes). 5. **Vaccine trials:** • Advance leading candidates into Phase 1/2 trials. • Generate initial safety and immunogenicity datasets in humans. • Begin development of immunobridging frameworks. 6. **Operational:** • Address thermolability, formulation and delivery challenges for intranasal and live attenuated vaccines including stability, dosing, needle free delivery devices (particularly for PIV3 and Measles).
Strategic Goal 2 (medium-term) *Milestones to be achieved in 3-5 years* *Validation of proof of concept and laboratory assays, advance clinical development, develop regulatory frameworks and manufacturing capacity*	1. **Immune correlates and regulatory readiness:** • Validate immune correlates across animal models and recapitulate infant disease and immunity (particularly for HPIV3 and Measles). • Establish standardized human challenge models for early efficacy evaluation, establish accepted surrogate endpoints for regulatory use. • Strengthen immunobridging strategies linking animal and human data. **2. Advanced clinical development:** • Conduct Phase 2/expanded trials in at-risk populations. • Conduct clinical trials in high risk populations including preterm infants, malnourished children and immunocompromised individuals. • Generate robust immunogenicity, safety, and dose-optimization data. • Evaluate booster strategies (homologous and heterologous).

	3. Durability and vaccination strategies: • Generate longitudinal data on immune persistence (≥12–24 months). • Define duration of protection and need for boosters. • Evaluate single-dose regimens for outbreak use. • Evaluate mucosal vaccine strategies like intranasal/inhaled vaccines inducing IgA responses. **4. Transmission and mucosal immunity:** • Quantify viral shedding and transmission in animal models. • Characterize mucosal immune responses (e.g., nasal IgA). • Incorporate transmission endpoints into advanced studies. **5. Vaccine platforms and delivery approaches: (Justify text alignment)** • Advance next-generation platforms, improve mucosal immunogenicity of subunit and nucleic acid vaccines. • For HPIV3 and Measles, generate evidence on co-administration with routine childhood vaccines, initiate development of multivalent/combination vaccines. • Scaled development of delivery devices like microneedle patches, optimized aerosol/inhaled vaccines. • Advance development of vaccines effective in early infancy by overcoming maternal antibody interference. **6. Manufacturing and deployment:**

	• Scale up manufacturing processes to industrial level. • Optimize thermostability and cold-chain requirements. • Develop stockpiling and distribution strategies. **7. Regulatory pathways:** • Engage regulators for alignment on animal rule/EUL pathways. • Prepare dossiers using immune-bridging and animal efficacy data.
Strategic Goal 3 (long-term) *Milestones to be achieved in 6-10 years* *(Licensure, deployment, and sustained preparedness)*	**1. New vaccines and novel vaccine platforms:** • Develop non-replicating, safer alternatives to live vaccines for use in immunocompromised individuals and next generation mRNA or nucleic acid vaccines. • Develop pan-paramyxovirus or multivalent respiratory vaccines by targeting multiple pathogens (e.g., Measles + RSV + HPIV or Human Metapneumovirus Virus (HMPV + RSV + HPIV). • Develop vaccines inducing sterilizing immunity by blocking infection and transmission. • Establish AI-driven antigen design and precision vaccinology. • Optimize immunogen design for durability and breadth. **2. Regulatory pathways, licensure and policy integration: (Justify text alignment)** • Establish regulatory pathways for pediatric mucosal vaccines, including harmonized global guidance. • Define licensure criteria and validated clinical endpoints.

	• Achieve regulatory approval via, EUL, or equivalent pathways. • Establish global policy recommendations and WHO prequalification. **3. Sustainable manufacturing and access: (Justify text alignment)** • Address market shaping and financing mechanisms to overcome low commercial incentives. • Establish regional manufacturing capacity in endemic areas. • Ensure equitable access and long-term stockpile sustainability. • Implement lifecycle management (reformulations, strain updates if needed). **4. Deployment and outbreak use:** • Operationalize stockpiles and rapid deployment mechanisms. • Implement vaccination strategies (e.g., ring vaccination, targeted immunization). • Integrate vaccines into national and regional preparedness plans. **5. Real-world effectiveness:** • Generate post-licensure effectiveness data during outbreaks. • Assess impact on transmission, morbidity, and mortality.

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2. Vaccine development for Paramyxoviridae prototypes not known to cause significant human disease:

Cedar virus, Menangle virus, Parainfluenza virus 5 (PIV5) and New Castle Disease virus

Background and Rationale

Developing vaccines using non-pathogenic paramyxovirus prototypes such as Cedar virus, Menangle virus, Parainfluenza virus 5, and Newcastle disease virus provides a safe, proactive platform for pandemic preparedness (*Marsh et al, 2012; Naveed et al, 2025; Kondakova et al, 2025; Wang et al, 2023*). These models enable optimization of vaccine design, immune correlates, and regulatory pathways before emergence of pathogenic strains. Antigen strategy should prioritize prefusion-stabilised Fusion (F) protein (*Krarup et al, 2015*), complemented by attachment glycoproteins (G) (*Zhou et al, 2024*) and conserved internal proteins, while attenuation relies on multi-layered engineering to ensure stable, mucosa-restricted replication with preserved immunogenicity. A tiered preclinical framework integrating airway-relevant in vitro systems, multi-species small animal models, and biologically relevant hosts should assess attenuation, durability, and transmission-blocking immunity (*Lv et al, 2025*). Integrated evaluation of neutralising antibodies, mucosal IgA, and tissue-resident T cells, alongside regulatory-ready safety datasets and a One Health approach, enables rapid bridging to emerging Paramyxoviruses while reducing zoonotic and animal health risks (*Mettelman et al, 2022; Vera-Peralta et al, 2024*).

Key Needs

1. **A validated cross-genus vaccine platform:** There is a critical need for modular, replication-competent (and alternative) vaccine platforms that are validated across Paramyxovirus genera, with harmonised attenuation strategies, optimised antigen design (e.g., prefusion F stabilisation), and platform-comparability datasets to enable rapid regulatory adaptation during outbreaks.

2. **Defined and quantifiable correlates of protection:** Regulatory acceleration depends on establishing validated immune correlates of protection including neutralising

antibody thresholds, mucosal IgA, and $CD4^+$/$CD8^+$ (including tissue-resident) T-cell responses supported by systems immunology and statistically defined immunobridging thresholds.

3. **Standardised translational and preclinical evaluation frameworks:** A harmonised, multi-species evaluation framework integrating small animals, natural hosts, and human-relevant respiratory models is needed to improve reproducibility, cross-model comparability, and predictive translation from preclinical to clinical stages.

4. **Alternative and accelerated efficacy pathways:** Given the infeasibility of traditional Phase III trials for low-incidence zoonotic viruses, there is a need to operationalise immunobridging, animal rule–like pathways, and species-bridging statistical models linking animal efficacy with human immunogenicity.

5. **Integrated safety, shedding, and regulatory preparedness systems:** Comprehensive characterisation of shedding, biodistribution, environmental risk, and durability combined with GMP-ready manufacturing platforms and pre-aligned regulatory dossiers is essential for outbreak-ready deployment.

6. **One-health driven spillover prevention strategy:** An integrated human–animal vaccination framework, supported by surveillance and reservoir-focused studies, is required to demonstrate that vaccination reduces viral circulation and spillover risk while strengthening epidemic preparedness.

Key Challenges and Knowledge Gaps

1. **Vaccine platforms and antigen design:** There is currently no validated, generalisable vaccine platform that can be readily applied across multiple Paramyxovirus genera, limiting rapid response to emerging threats. Harmonised attenuation strategies, such as reverse genetics based modifications and codon de-optimisation, remain insufficiently validated across diverse viruses. In addition, antigen design approaches, including prefusion stabilisation and multivalent constructs, require further optimisation to reliably induce broad, durable, and cross-protective immunity (*Moon et al, 2026; Duprex & Dutch, 2023*).

2. **Correlates of protection (CoP):** Validated correlates of protection are lacking for most Paramyxoviruses, creating uncertainty in defining protective immunity. The relative contributions of serum neutralising antibodies, mucosal IgA, and cellular immune responses remain poorly delineated. Moreover, quantitative immune thresholds needed to support immunobridging and accelerated regulatory pathways have not been established (*Escudero-Pérez et al, 2023; Plotkin, 2010*).

3. **Mucosal and cellular immunity:** Understanding of mucosal immune responses, particularly the durability and protective role of IgA at respiratory surfaces, remains incomplete. Data on tissue-resident memory T-cell responses and their contribution to preventing infection and transmission are limited. The mechanistic links between immune responses and reductions in viral shedding and onward transmission are also poorly defined (*Duprex & Dutch, 2023*).

4. **Preclinical models and translational relevance:** No single animal model adequately recapitulates human disease across the spectrum of Paramyxoviruses, complicating translational interpretation. Standardised, multi-species evaluation frameworks integrating small animals, natural hosts, and human-relevant systems are lacking. As a result, preclinical efficacy data often show limited comparability and reproducibility across models (*Sabir et al, 2024*).

5. **Clinical development pathways:** Standardised clinical endpoints tailored to respiratory Paramyxoviruses, including mucosal and cellular immune readouts, are not well established. Durability and breadth of immune responses beyond early timepoints (≥3–6 months) are insufficiently validated as endpoints. Early-phase trials also rarely incorporate viral shedding and transmission metrics, limiting assessment of population-level impact (*Peng et al, 2024*).

6. **Alternative efficacy pathways:** For low-incidence zoonotic viruses, conventional Phase III efficacy trials are often infeasible. Frameworks for immunobridging using correlates of protection and animal rule like licensure pathways remain underdeveloped. There is also no standardised approach to systematically link animal efficacy data with human immunogenicity outcomes (*Finch et al, 2022*).

7. **Controlled Human Infection Models (CHIM):** Human challenge models are not established for most Paramyxoviruses, restricting direct evaluation of vaccine efficacy. Ethical and biosafety constraints further limit their development for emerging or zoonotic viruses. Consequently, developers rely heavily on indirect immunological or surrogate endpoints (*Dayananda et al, 2024*).

8. **Safety, shedding, and biodistribution:** Data on viral shedding kinetics and transmission potential of live-attenuated and vectored vaccines remain limited. There is no clear consensus on acceptable shedding thresholds or harmonised monitoring strategies. Biodistribution and environmental risk assessments are also insufficiently characterised, particularly for replication-competent platforms (*Pitisuttithum et al, 2022; Duc Dang et al, 2022)*.

9. **Manufacturing and regulatory preparedness:** Pre-established GMP manufacturing processes for prototype Paramyxoviruses are lacking, slowing outbreak response. Platform-based regulatory dossiers that enable rapid adaptation to newly emerging viruses are not yet standardised. Regulatory experience with replication-competent respiratory vaccines also remains limited in many jurisdictions (*Kim et al, 2025; Leyva-Grado et al, 2024*).
10. **One-Health integration:** Integration of animal and human vaccine strategies remains insufficient, despite the zoonotic nature of many Paramyxoviruses. Evidence directly linking vaccination in animal reservoirs to reduced spillover risk is limited. Coordinated cross-sectoral frameworks for surveillance, vaccination, and intervention are underdeveloped (*Clifford et al, 2023*).

11. **Durability and cross-protection:** Longitudinal data on durability of immune responses beyond early clinical timepoints are sparse. The extent and mechanisms of cross-protection across Paramyxovirus species and variants are not well understood. These uncertainties limit rational design of broadly protective and longer-lasting vaccines (*Duprex & Dutch, 2023; de Vries et al, 2020*).

Key Research Priorities

1. **Development of cross-genus vaccine platforms:** Develop and validate modular, replication-competent and alternative vaccine platforms that can be applied across

Paramyxovirus genera. Standardise reverse genetics based attenuation strategies, including interferon antagonism modification and codon de-optimisation, and generate platform comparability datasets to support regulatory reliance and rapid adaptation during outbreaks.

2. **Definition and validation of correlates of protection:** Identify and quantify immune correlates of protection, including neutralising antibody thresholds, mucosal IgA responses, and $CD4^+$/$CD8^+$ T-cell immunity with tissue-resident memory responses. Establish statistically validated thresholds for immunobridging and licensure, integrate systems immunology and modelling approaches to define predictive immune signatures.

3. **Characterisation of mucosal and transmission-blocking immunity:** Elucidate the magnitude, durability, and protective role of mucosal immune responses, particularly IgA, in preventing infection and transmission. Define immune mechanisms linked to reduced viral shedding and standardise assays for mucosal and tissue-resident T-cell responses.

4. **Harmonisation of preclinical models and translational frameworks:** Establish standardised, multi-species preclinical frameworks integrating small animal models, natural hosts, and human-relevant respiratory systems. Define objective criteria for candidate advancement and generate cross-model datasets to enhance translational predictability.

5. **Optimisation of clinical trial design and endpoints:** Develop harmonised clinical endpoints incorporating neutralising antibody magnitude and breadth, mucosal IgA, and cellular immune responses. Integrate viral shedding and transmission metrics into early-phase trials and define durability benchmarks of at least 3–6 months.

6. **Advancement of alternative efficacy pathways:** Operationalise immunobridging frameworks that link human immune responses to animal-derived correlates of protection. Develop animal rule like regulatory pathways and establish statistical methodologies to bridge efficacy data across species and populations.

7. **Exploration of Controlled Human Infection Models (CHIM):** Assess the feasibility, ethics, and biosafety of CHIM for selected low-risk Paramyxoviruses. Develop standardised protocols and endpoints to use CHIM data for accelerating early efficacy assessment and candidate prioritisation.

8. **Evaluation of safety, shedding, and biodistribution:** Characterise shedding kinetics and transmission potential of live or vectored vaccines to define acceptable thresholds and monitoring strategies. Conduct comprehensive biodistribution and environmental risk assessments to inform regulatory decision-making.

9. **Strengthening manufacturing and regulatory preparedness:** Develop GMP-compliant manufacturing processes for prototype Paramyxoviruses and establish platform-based CMC packages with master seed systems. Create pre-aligned regulatory frameworks to enable rapid deployment during outbreaks.

10. **Integration of One-Health approaches:** Generate evidence that vaccination in animal reservoirs reduces viral circulation and spillover risk. Develop coordinated human–animal vaccination strategies and strengthen cross-sectoral surveillance and response systems.

11. **Evaluation of durability and cross-protective immunity:** Conduct longitudinal studies to define durability of immune responses beyond early timepoints. Evaluate cross-protection across paramyxovirus species and variants, and identify strategies to enhance breadth and longevity of protection.

Strategic Goals and Milestones

Strategic Goal 1 (short-term): *Milestones to be achieved in 0-3 years* *Establish foundation and bridge the gaps*	**1. Correlates, immunology, and assays:** • Identify and quantify immune correlates (neutralising antibodies, mucosal IgA, $CD4^+$/$CD8^+$ T cells). • Establish statistically validated thresholds for immunobridging and licensure.

in immunology, laboratory assays and animal models; initiate R&D of novel vaccine platforms, initiate clinical trials with advanced candidates and lay out strategies for manufacturing readiness and regulatory approvals	• Integrate systems immunology and modelling approaches. • Elucidate mucosal immunity (especially IgA) and its durability. • Define mechanisms of reduced viral shedding and transmission. • Develop and standardise mucosal and tissue-resident T-cell assays. **2. Clinical and translational acceleration** • Standardise endpoints (humoral, mucosal, cellular immunity). • Incorporate viral shedding and transmission metrics. • Define durability benchmarks (≥3–6 months). • Characterise shedding kinetics and transmission potential. • Define acceptable thresholds and monitoring strategies. • Conduct biodistribution and environmental risk assessments. **3. Platform and manufacturing readiness:** • Develop modular, replication-competent and alternative platforms. • Standardise reverse genetics attenuation strategies. • Establish platform comparability datasets. • Develop GMP-compliant manufacturing processes. • Establish platform-based CMC packages and master seed systems.

	• Create pre-approved regulatory frameworks for outbreak response.
Strategic Goal 2 (medium-term) *Milestones to be achieved in 3-5 years* *Validation of preclinical models, establishment of innovative clinical pathways and evaluation of durability and cross protective potential of immune response to various vaccine candidates*	**1. Harmonisation of preclinical models and translational frameworks:** • Establish multi-species evaluation frameworks (small animal + natural host + human-relevant systems). • Define advancement criteria from preclinical to clinical stages. • Generate cross-model comparative datasets. **2. Innovative clinical pathways** • **Advancement of alternative efficacy pathways** o Operationalise immunobridging frameworks. o Develop animal rule like regulatory pathways. o Establish statistical bridging methodologies. • **Exploration of Controlled Human Infection Models (CHIM)** o Evaluate feasibility, ethics, and safety. o Develop standardised protocols and endpoints. o Use CHIM to accelerate candidate selection. **3. Immunity breadth and durability** • **Evaluation of durability and cross-protective immunity** o Conduct longitudinal immune durability studies. o Evaluate cross-protection across species/variants. o Identify strategies to enhance breadth and longevity.

	○ Manufacturing and regulatory preparedness.
Strategic Goal 3 (long-term) *Milestones to be achieved in 6-10 years* *(Licensure, deployment, and sustained preparedness)*	1. Well established plug and play vaccine platforms to enable quick development of a new vaccine for a novel virus of the same genera. 2. Regulatory frameworks to consider the vaccine platform data and accord expedited approvals to new vaccines developed using the same platform. 3. Integration of One Health Approaches: Generate evidence linking animal vaccination to reduced spillover, develop integrated human–animal vaccination strategies and strengthen cross-sectoral surveillance and response frameworks

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B. Development of Broad-Spectrum Therapeutics for Paramyxoviruses

Background:

Therapeutic options for high-consequence Paramyxoviruses such as Nipah virus remain limited, with no widely approved antivirals despite high epidemic potential. Current strategies focus on monoclonal antibodies, small-molecule antivirals, and repurposed drugs, though most evidence remains preclinical (*Chan et al, 2025*). Neutralising antibodies are the most advanced modality, m102.4 has demonstrated strong protection in animal models and progressed to Phase 1 evaluation, while next-generation antibodies targeting viral entry glycoproteins show improved breadth (*Johnson et al, 2021*).

Among antivirals, Remdesivir has shown significant efficacy in non-human primates, with other agents such as Ribavirin and Favipiravir demonstrating variable results (*Lo MK et al, 2019; Madhukalya, 2025, Bhate et al, 2025*). Combination approaches may enhance potency and reduce resistance, but clinical validation remains sparse. Progress is constrained by limited outbreak opportunities for randomized trials, absence of validated therapeutic correlates, underdeveloped translational frameworks, and operational barriers including BSL-4 capacity, manufacturing scale-up, and stockpiling gaps (*Chan et al, 2025*). Viral diversity and resistance risks further complicate development of broad-spectrum agents. These challenges underscore the need for integrated, platform-based strategies that combine antibodies and antivirals with adaptive evaluation frameworks to accelerate regulatory readiness and equitable deployment during outbreaks (*Duprex & Dutch, 2023; Contreras et al, 2021*).

Key Needs

1. **Validated broad-spectrum targets and therapeutic platforms:** A coordinated effort is needed to validate conserved viral (e.g., F and L proteins) and host-directed targets across Paramyxoviruses, enabling development of cross-protective monoclonal antibodies, antivirals, and combination regimens supported by platform-based design strategies.

2. **Defined correlates and translational pathways for efficacy:** There is a critical need to establish quantitative correlates of therapeutic efficacy and harmonised PK/PD frameworks that link animal model outcomes to human clinical benefit, enabling immunobridging and regulatory reliance on surrogate endpoints.

3. **Standardised preclinical and adaptive clinical evaluation frameworks:** Harmonised multi-species animal models, validated assays, and adaptive outbreak-ready clinical trial designs are required to overcome the infeasibility of traditional phase III trials for sporadic, high-consequence pathogens.

4. **Scalable, equitable manufacturing and deployment systems:** Development of cost-effective, LMIC-suitable manufacturing platforms, thermostable formulations, and stockpiling strategies is essential to ensure rapid and equitable access during outbreaks.

5. **Strengthened high-containment, regulatory, and regional infrastructure:** Expanded BSL-4 capacity, trial-ready sites in endemic regions, and harmonised global regulatory pathways are needed to accelerate candidate evaluation and emergency authorization.

6. **An integrated end-to-end preparedness framework:** A coordinated development roadmap linking target discovery, modality selection, regulatory strategy, manufacturing readiness, and deployment planning is required to shift from reactive outbreak response to proactive therapeutic preparedness.

Key Challenges and Knowledge Gaps

1. **Scientific and biological gaps:** Therapeutic target validation remains incomplete across Paramyxoviruses, despite promising candidates such as the F and L proteins, and host-directed pathways are insufficiently explored. Clear correlates of therapeutic efficacy are lacking, and viral diversity including differences between Nipah virus and Human Parainfluenza virus lineages creates uncertainty for broad-spectrum strategies (*Contreras et al, 2021*).

2. **Preclinical and translational challenges:** Animal models (hamsters, ferrets, NHPs) lack full validation for predicting human outcomes, and access to BSL-4 facilities for high-risk pathogens is limited. In addition, non-harmonized neutralization, viral inhibition, and PK/PD assays reduce comparability and translational confidence (*Lv et al, 2025; Woudenberg et al, 2019; Broder et al, 2013*).

3. **Clinical development constraints:** Sporadic outbreaks make traditional Phase III trials infeasible, increasing reliance on animal rule like and immunobridging pathways with uncertain regulatory acceptance. Limited trial-ready infrastructure in endemic regions further delays rapid outbreak response (*Bossart et al, 2009; Geisbert et al, 2010; Plotkin, 2010*).

4. **Therapeutic-specific limitations:** Monoclonal antibodies face cost, cold-chain, and escape mutation challenges; small-molecule antivirals have limited pipelines and resistance risks. RNA-based and host-directed therapies face delivery, scalability, safety, and validation constraints (*Conteras et al, 2022; Marcink et al, 2024*).

5. **Manufacturing and access gaps:** There is insufficient scalable, LMIC-suitable manufacturing capacity, limited commercial incentives, and inadequate stockpiling strategies. Cold-chain and distribution barriers further restrict equitable deployment in endemic settings (*Malhotra et al, 2024*).

6. **Regulatory and policy barriers:** Global regulatory pathways for rare or emerging pathogens remain unharmonized, with inconsistent acceptance of surrogate endpoints and limited precedent for approvals under animal rule like frameworks outside biodefense contexts (*Beasley et al, 2016*).

7. **Preparedness and coordination gaps:** Therapeutic R&D is fragmented across pathogens and regions, with weak integration of platform technologies and poor alignment between research, manufacturing, and deployment planning (*Mishra et al, 2024*).

8. **Cross-cutting gap:** An overarching gap is the absence of a integrated and well-coordinated, end-to-end development roadmap linking target discovery, modality

selection, preclinical standardization, clinical pathways, regulatory strategy, manufacturing, and deployment.

Key Research Priorities

1. **Validation of broad-spectrum therapeutic targets:** Systematically validate conserved viral targets (e.g., F and L proteins) and prioritized host-directed pathways across multiple paramyxoviruses, including lineage variation to enable rational design of cross-species antivirals and antibodies.

2. **Definition of correlates of therapeutic efficacy:** Establish quantitative correlates and surrogate markers of treatment response (virological, immunological, and PK/PD parameters) to support translational decision-making, immunobridging, and regulatory approval under non-traditional pathways.

3. **Harmonisation of preclinical models and assays:** Develop standardized, multi-model preclinical evaluation frameworks integrating small animals and non-human primates, alongside harmonised neutralisation, viral inhibition, and PK/PD assays to improve cross-study comparability and predictive validity.

4. **Development of combination and resistance-mitigation strategies:** Advance rational combination therapies (e.g., monoclonal antibodies plus polymerase inhibitors) and implement resistance surveillance models to enhance therapeutic breadth and durability against viral escape.

5. **Adaptive and alternative clinical evaluation pathways:** Operationalise animal rule like frameworks, immunobridging strategies, and adaptive outbreak trial designs to overcome infeasibility of conventional Phase III trials for sporadic pathogens.

6. **Platform-based and LMIC-suitable manufacturing innovations:** Develop scalable, cost-effective manufacturing platforms, including thermostable formulations and alternative delivery systems to reduce cold-chain dependence and enable equitable access in endemic regions.

7. **Expansion of high-containment and regional clinical capacity:** Strengthen BSL-4 access, regional laboratory networks, and trial-ready infrastructure in endemic settings to accelerate candidate testing and outbreak responsiveness.

8. **Establishment of an integrated end-to-end development framework:** Create a coordinated therapeutic development roadmap linking target discovery, modality selection, preclinical validation, regulatory strategy, manufacturing readiness, and stockpiling to ensure rapid deployment during outbreaks.

Strategic Goals and Milestones

Strategic Goal 1 (short-term): *Milestones to be achieved in 0-3 years* *Establish foundation and bridge the gaps in discovery, assay & model standardization, therapeutic pipelines, enabling platforms and develop regulatory and clinical strategies*	i. **Target validation and discovery:** • Validate conserved viral targets (F, G/HN, L proteins) across priority paramyxoviruses. • Identify host factors suitable for broad-spectrum, host-directed therapies. • Establish structural and functional datasets to guide therapeutic design. ii. **Assay and model standardization:** • Develop and harmonize in vitro antiviral screening assays. • Standardize animal models (including NHP models for Nipah) with agreed endpoints. • Establish reference reagents and viral strains for cross-laboratory comparability. iii. **Early therapeutic pipeline development:** • Advance lead candidates across modalities (mAbs, small molecules, RNA-based). • Generate proof-of-concept efficacy data in relevant animal models. • Initiate PK/PD and safety profiling. iv. **Enabling platforms and infrastructure:** • Expand access to BSL-3/4 research capacity.

	• Establish platform technologies (e.g., antibody discovery, antiviral screening pipelines). • Build clinical trial networks in endemic regions. v. **Regulatory and clinical strategy development:** • Define immunobridging and surrogate endpoints. • Initiate early engagement with regulators. • Develop master protocols for adaptive/platform trials.
Strategic Goal 2 (medium-term) *Milestones to be achieved in 3-5 years*	i. **Advanced preclinical and translational studies:** • Conduct comparative efficacy studies across animal models. • Validate translational biomarkers and correlates of therapeutic effect. • Strengthen immunobridging frameworks linking animal and human data. ii. **Clinical development:** • Initiate and complete Phase 1/2 clinical trials for priority candidates. • Evaluate safety, dosing, and preliminary efficacy. • Test multiple candidates using adaptive/platform trial designs. iii. **Manufacturing and formulation optimization:** • Scale up production for lead therapeutic candidates. • Optimize thermostability, shelf life, and delivery formats. • Develop cost-effective manufacturing processes suitable for LMICs. iv. **Regulatory pathway advancement:** • Develop regulatory dossiers using animal rule and surrogate endpoints. • Align with WHO Emergency Use Listing (EUL) requirement.

	• Establish global consensus on data requirements for licensure. v. **Resistance and breadth:** Evaluate cross-Paramyxovirus activity of candidates. • Assess potential for viral escape and resistance. • Advance combination therapies where appropriate.
Strategic Goal 3 (long-term) *Milestones to be achieved in 6-10 years* *(Licensure, deployment, and sustained preparedness)*	i. **Licensure and policy integration:** • Achieve regulatory approval or WHO EUL/prequalification. • Develop global treatment guidelines and policy recommendations. ii. **Deployment and outbreak response:** • Establish stockpiles of priority therapeutics. • Implement rapid deployment strategies in outbreak settings. • Integrate therapeutics into national and global preparedness plans. iii. **Real-world effectiveness and impact evaluation:** • Generate post-licensure effectiveness data. • Assess impact on mortality, transmission, and outbreak control. • Conduct operational and implementation research. iv. **Next-generation therapeutics:** • Develop second-generation therapeutics with improved breadth (pan-Paramyxovirus activity), durability and ease of administration (e.g., oral, single-dose). v. **Sustainable manufacturing and access:** • Establish regional manufacturing hubs, especially in LMICs. • Ensure equitable access and long-term supply security.

	• Implement lifecycle management and product improvements.

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C. Clinical Trial Designs for Paramyxoviruses

Background

Trial designs for Paramyxovirus vaccines are driven by epidemiology, feasibility of efficacy evaluation, and regulatory expectations, resulting in two broad paradigms. For high-fatality, low-incidence zoonotic viruses such as Nipah and Menangle, traditional Phase III trials are impractical due to sporadic outbreaks; development therefore relies on animal rule like pathways, with efficacy demonstrated in animal models and bridged to humans through validated immune correlates, particularly neutralising antibodies (*Bossart et al, 2009; Geisbert et al, 2010; Plotkin, 2010*). In this setting, immunobridging is central to licensure, supported by standardised assays and, where feasible, platform or limited outbreak-based designs (*Henao-Restrepo et al, 2017; Dean et al, 2019*).

In contrast, endemic respiratory viruses such as HPIV3 and PIV5 allow more conventional clinical evaluation, though reinfection, partial immunity, and pediatric target populations require adaptive, cluster-randomised, and age-bridging approaches; controlled human infection models may accelerate early evaluation in select cases (*Carone et al, 2025; Wagstaffe et al, 2025*). For well-controlled pathogens like measles and veterinary targets such as Newcastle disease virus, where correlates are established, the focus shifts from efficacy demonstration to optimisation of delivery, population impact, and implementation through cluster trials and large observational studies (*Moss, 2017; Uzicanin and Zimmerman, 2011; Miller and Koch, 2013*). Overall, immunobridging is the unifying element across pathogens, essential for zoonotic viruses and supportive in endemic settings, while adaptive and platform designs are increasingly critical for preparedness and efficient vaccine development (*Bethe et al. 2024*).

Innovative Vaccine Trial Designs and Use Cases

Trial Design	Primary Use Case
Immunobridging (Correlates of Protection)	When efficacy trials are infeasible; bridging across age groups or populations; low-incidence diseases

Controlled Human Infection Model (CHIM)	Pathogens with controlled risk and available treatment; early efficacy and immune correlate identification
Ring Vaccination Trials	Outbreak settings with clustered transmission (e.g., Ebola-like diseases)
Cluster Randomized Trials (CRT)	When individual randomization is impractical; evaluation of herd effects
Stepped-Wedge Design	Phased rollout where withholding vaccine is unethical; program evaluation
Adaptive Trial Designs	Efficient evaluation under uncertainty; modifying sample size/dose arms mid-trial
Observational Studies (TND, Cohort, Case-Control)	Post-licensure effectiveness; real-world performance; rare outcomes
Historical / External Controls	Rare diseases; when concurrent control group not feasible
Platform Trials	Simultaneous evaluation of multiple candidates; outbreak preparedness
Animal Rule (Translational Models)	When human efficacy trials are unethical/impossible (e.g., high-fatality pathogens)

Cross-Cutting Trial Design Applicability Matrix

Trial Design	Nipah	Cedar	Menangle	HPIV3	PIV5	Measles	NDV
Immunobridging	⭐⭐⭐ Essential	⭐ Limited	⭐⭐	⭐⭐⭐	⭐⭐	⭐⭐⭐	⭐⭐
CHIM	❌ Not ethical	❌	❌	⭐ (limited)	⭐ (theoretical)	❌	❌
Ring Vaccination	⭐⭐ Limited	❌	❌	⭐	❌	❌	❌
CRT	❌	❌	❌	⭐⭐	⭐	⭐⭐⭐	⭐⭐⭐
Stepped-Wedge	❌	❌	❌	⭐⭐	⭐	⭐⭐⭐	⭐⭐⭐

Trial Design	Nipah	Cedar	Menangle	HPIV3	PIV5	Measles	NDV
Adaptive Trials	⭐ ⭐	⭐	⭐	⭐ ⭐ ⭐	⭐ ⭐ ⭐	⭐ ⭐	⭐ ⭐
Observational Studies	⭐ ⭐	⭐	⭐	⭐ ⭐ ⭐	⭐ ⭐	⭐ ⭐ ⭐	⭐ ⭐ ⭐
Historical Controls	⭐ ⭐	⭐	⭐ ⭐	⭐	⭐	✕	✕
Platform Trials	⭐ ⭐ ⭐	⭐ ⭐	⭐ ⭐	⭐ ⭐	⭐ ⭐	⭐	⭐
Animal Rule	⭐ ⭐ ⭐ Core	⭐	⭐ ⭐ ⭐	✕	✕	✕	✕

⭐ = relevance (more stars = higher importance)

Key Needs

1. **Validated immunobridging frameworks:** Robust and standardised immunobridging approaches are needed to enable licensure where traditional efficacy trials are infeasible, particularly for high-fatality zoonotic viruses such as Nipah and Menangle. This requires harmonised neutralisation assays, defined correlates of protection, and regulatory alignment across jurisdictions.

2. **Translationally relevant animal models:** Well-characterised animal models that faithfully predict human protection are essential for animal rule based pathways. Comparative efficacy datasets and validated immune biomarkers linking animal protection to human immunogenicity are critical.

3. **Standardised clinical endpoints for respiratory viruses:** For endemic pathogens such as HPIV3, trials require harmonised endpoints that incorporate mucosal immunity, viral shedding, reinfection dynamics, and durability of protection, particularly in pediatric populations.

4. **Adaptive and platform trial infrastructure:** Preparedness-oriented trial networks capable of implementing adaptive, platform, and outbreak-responsive designs are

needed to accelerate candidate evaluation under uncertain epidemiological conditions.

5. **Regulatory harmonisation and preparedness:** Clear, globally aligned regulatory guidance for animal rule like pathways, surrogate endpoints, and emergency use frameworks is required to streamline development and ensure rapid response during outbreaks.

Key Challenges and Knowledge Gaps

1. **Infeasibility of conventional efficacy trials for zoonotic viruses:** For low-incidence, high-fatality viruses such as Nipah and Menangle, traditional phase III efficacy trials are impractical due to sporadic and unpredictable outbreaks (*Dean et al, 2019; Henao-Restrepo AM, 2017*). Small outbreak sizes further limit ring vaccination or cluster-randomized approaches, creating heavy reliance on indirect and surrogate evidence pathways.

2. **Limited validation of correlates of protection:** Validated immune correlates of protection are lacking for most Paramyxoviruses, particularly emerging zoonotic species (*Plotkin SA, 2010*). The absence of quantitative immune thresholds undermines the reliability of immunobridging and accelerated regulatory pathways.

3. **Translational uncertainty between animal and human data:** Animal rule based development depends on well-characterized models, yet there is insufficient evidence demonstrating how protective immune responses in animals translate quantitatively to human protection. Standardised frameworks linking animal efficacy, immune biomarkers, and human immunogenicity remain underdeveloped (*Finch et al, 2022*).

4. **Ethical and biosafety constraints on human challenge models:** Controlled human infection models are largely infeasible for high-fatality or emerging Paramyxoviruses due to ethical and safety concerns. This restricts early efficacy evaluation and forces reliance on indirect immune endpoints *(Bambery et al, 2016; Lv C et al, 2025).*

5. **Inadequate clinical endpoints for respiratory viruses:** For endemic pathogens such as HPIV3, reinfection and partial immunity complicate endpoint definition *(Schmidt ME et al, 2018).* Standardised endpoints incorporating mucosal immunity, viral shedding, transmission reduction, durability, and cross-protection are not well established.

6. **Heterogeneity across Paramyxoviruses:** Paramyxoviruses span zoonotic spillover threats, endemic pediatric respiratory viruses, and well-controlled vaccine-preventable diseases *(Thibault PA et al, 2017).* This epidemiological diversity necessitates distinct trial paradigms, complicating harmonisation and cross-platform development strategies.

7. **Operational gaps in innovative trial designs:** Although adaptive, platform, stepped-wedge, and historical control designs are conceptually relevant, practical implementation frameworks, preparedness infrastructure, and regulatory precedent remain limited across many Paramyxoviruses (*Dean et al, 2019)*.

Key Research Priorities:

1. **Establish and validate correlates of protection:** Defining robust correlates of protection is essential to enable immunobridging and alternative licensure pathways, particularly for low-incidence zoonotic Paramyxoviruses. Research should focus on identifying quantitative immune thresholds, including neutralising antibodies, mucosal IgA, and cellular responses that reliably predict protection. Standardised and harmonised immunological assays across laboratories and trial networks will be critical to ensure comparability and regulatory acceptance.

2. **Strengthen animal–human translational frameworks:** Well-characterised animal models must be systematically evaluated to ensure they faithfully predict human protection. Comparative efficacy studies and identification of translational biomarkers are needed to quantitatively link animal protection to human immune responses. Such frameworks will underpin animal rule like pathways and improve confidence in surrogate endpoint based approvals.

3. **Develop fit-for-purpose clinical endpoints:** Clinical trials for respiratory Paramyxoviruses should incorporate endpoints beyond symptomatic disease, including viral shedding, transmission metrics, and mucosal immunity. Validation of durability (≥3–6 months) and breadth of immune responses as regulatory-relevant endpoints is also required. Harmonised endpoint definitions will improve cross-trial comparability and support policy decision-making.

4. **Advance innovative and adaptive trial designs:** Adaptive, platform, and outbreak-responsive trial designs should be operationalised to enable efficient candidate evaluation under epidemiological uncertainty. Preparedness-ready master protocols can accelerate trial initiation during outbreaks. Evaluating the applicability of ring vaccination, cluster-randomised, and stepped-wedge designs in appropriate settings will further enhance flexibility.

5. **Enable immunobridging and alternative licensure pathways:** Structured immunobridging frameworks must be developed to support approval where conventional efficacy trials are infeasible. Clear regulatory alignment on surrogate endpoints, emergency use pathways, and evidentiary standards is essential. Standardised methodologies linking animal efficacy data, human immunogenicity, and real-world evidence will strengthen alternative licensure approaches.

6. **Build trial infrastructure for preparedness:** Sustainable multicentre clinical trial networks should be established in endemic and spillover-prone regions to ensure rapid study activation. Laboratory capacity for high-containment virology and advanced immunological assays must be strengthened. Data-sharing platforms and harmonised protocols will facilitate cross-pathogen learning and accelerate evidence generation across the paramyxovirus spectrum.

Strategic Goals and Milestones

Strategic Goal 1 (short-term): *Milestones to be achieved in 0-3 years* *(Foundation and Framework Development)*	**Establish scientific and regulatory groundwork for alternative and adaptive trial pathways** • Define preliminary correlates of protection and harmonise neutralisation and cellular immunity assays across laboratories. • Standardise animal models and initiate comparative translational studies linking animal protection to human immunogenicity. • Develop preparedness-ready master protocols for adaptive, platform, and outbreak-responsive trials. • Engage regulators to clarify evidentiary requirements for immunobridging, animal rule–like pathways, and surrogate endpoints. • Strengthen clinical trial infrastructure and laboratory capacity in endemic and spillover-prone regions.
Strategic Goal 2 (medium-term) *Milestones to be achieved in 3-5 years* *(Validation and Early Implementation)*	**Operationalise immunobridging and innovative trial designs in active development programs** • Validate quantitative immune thresholds predictive of protection using integrated animal and early-phase human datasets. • Incorporate mucosal immunity, viral shedding, and durability endpoints into Phase 1/2 trials. • Launch adaptive or platform trials evaluating multiple candidates where epidemiologically feasible. • Generate regulatory-ready translational datasets to support alternative licensure pathways for zoonotic viruses. • Expand multicentre trial networks and establish interoperable data-sharing platforms.
Strategic Goal 3 (long-term)	**Achieve mature, regulatory-accepted alternative evidence paradigms and sustained outbreak preparedness**

Milestones to be achieved in 6-10 years *(Regulatory Integration and Preparedness Readiness)*	• Establish fully validated correlates of protection enabling routine immunobridging across age groups and populations. • Secure licensure or emergency authorisation of candidates using animal rule like or surrogate endpoint frameworks where required. • Institutionalise adaptive and platform trial infrastructure as standing preparedness mechanisms. • Generate long-term durability and cross-protection data to refine booster and policy strategies. • Embed harmonised global regulatory standards to enable rapid activation and evaluation of vaccines for newly emerging Paramyxoviruses.

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Strategic Prioritization of Paramyxovirus MCM Development

Strategic categorization of resources will be critical to ensure that medical countermeasure (MCM) development for various Paramyxoviruses is aligned with the specific nature of unmet needs across pathogens. By distinguishing between areas requiring de novo innovation (e.g., Nipah virus, HPIV3), optimization of existing interventions (e.g., Measles), and platform development and preparedness (e.g., Cedar, NDV, PIV5, Menangle), this framework will enable efficient allocation of resources, reduce duplication of efforts, and support tailored regulatory and clinical pathways. The structured, portfolio-based approach will help maximize both near-term public health impact and long-term innovation, thereby enhancing the overall effectiveness and sustainability of R&D investments.

Category	Strategic Objective	Viruses	Key Focus
Create	Develop new MCMs where none exist	Nipah, HPIV3	Vaccine discovery, antivirals, monoclonal antibodies
Optimize	Improve impact of existing MCMs	Measles	Coverage, delivery (thermostability, needle-free), equity
Enable	Advance platforms & surrogate systems	Cedar, NDV, PIV5	Vaccine vectors, BSL-2 models, manufacturing scalability
Prepare	Build readiness for emerging threats	Menangle	Surveillance, diagnostics, early R&D

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ACKNOWLEDGEMENTS

The Collaborative Open Research Consortium for *Paramyxoviridae* family has been co-ordinated by the Indian Council of Medical Research, India, with valuable support and overarching guidance from the World Health Organization, especially Dr. Ana Maria Henao-Restrepo, Dr. Patrick Lydon, Dr. Regine Bonnand Coste, Dr. Ximena Riveros, & Ms. Neddy Mafunga. We are also grateful for the technical guidance on roadmap development received from experts Dr. Cesar Munoz-Fontela, Dr. Cristina Cassetti, Dr. Ira M Longini, Dr. Peter Horby, Dr. Phil Krause, Dr. Thomas R Fleming, and Dr. Richard Jarman. We would like to acknowledge the unwavering leadership support from ICMR, especially Dr. Rajiv Bahl, Secretary, Department of Health Research & Director General, Indian Council of Medical Research (ICMR), Dr. Manoj V Murhekar, Director, ICMR National Institute of Epidemiology (NIE), Chennai, and Dr. Naveen Kumar, Director, ICMR National Institute of Virology (NIV), Pune. This R&D roadmap is the culmination of the extensive efforts of 88 members across nine different working groups which convened regularly between April 2025 and November 2025, and we would like to thank each and every member who contributed their knowledge, ideas and data to the extensive discussions.

We would also like to acknowledge the valuable contribution of ICMR members who offered key support especially to Dr. Brindha S, Dr. Apoorva Choubey, Dr. Archana Upadhyay, and Dr. Kumar Vikram for contributing to targeted review of literature; to Dr. Nishtha Malhotra for contributing write-up to the section on Clinical Studies; and to Dr. Tarun Bhatnagar for participating in the discussions on epidemiological studies.

ANNEXURE-1: DOCUMENT REVIEW FORMAT

A. GENERAL INFORMATION

1. Name:
2. Designation and Affiliation:
3. Have you engaged with the Paramyxoviridae CORC before?
4. Please select the CORC working groups you have engaged with:

i. Prototype Virus Selection
ii. Epidemiological Research
iii. Socio-behavioural studies
iv. Reservoir (including bat) Studies
v. Basic Research
vi. Laboratory Studies
vii. Models of Disease
viii. Medical Countermeasures
ix. Clinical Studies

B. REVIEW SECTION *(Please add rows as needed)*

S.N.	Chapter No. (1/2/3/4)	Name of the chapter	Page No.	Line/Table No.	Current Text	Comment from the Reviewer	Suggested Text

Any other comment:

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