World Health Organization

CORC-CoV – Coronavirus Research & Development Roadmap

12 JANUARY 2026

R&DBlueprint
Powering research to prevent epidemics

PREPARE

Content

Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
AI/ML	Artificial Intelligence/Machine Learning
APN	Aminopeptidase N
BSL	Biosafety Level
CEPI	Coalition for Epidemic Preparedness Innovations
COP	Correlates of Protection
CORC	Collaborative Open Research Consortium
CoV	Coronavirus
DPP4	Dipeptidyl Peptidase-4
GWAS	Genome-Wide Association Study
hCoV	Human Coronavirus
HR1/HR2	Heptad Repeat 1/Heptad Repeat 2
ICU	Intensive Care Unit
IP	Intellectual Property
LMICs	Low- and Middle-Income Countries
mAbs	Monoclonal Antibodies
ORF	Open Reading Frame
PABS	Pathogen Access and Benefit Sharing
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
PREPARE	Programme for Research in Epidemic Preparedness and REsponse
QA/QC	Quality Assurance/Quality Control
R&D	Research and Development
RBD	Receptor Binding Domain
RdRp	RNA-dependent-RNA-polymerase
WHO	World Health Organization

Preamble

To combat future pandemic threats, the WHO together with member states adopted the pandemic agreement in May 2025. One of the goals is to foster greater global collaboration for research. The WHO has identified twelve priority pathogen groups and established the Collaborative Open Research Consortium (CORC) for each group. The mode of operation of the CORCs are decentralized from the WHO with a main goal of focusing on research initiatives to advance each field. Designated by the WHO, each CORC is operated by autonomous institutes/agencies globally. The Programme for Research in Epidemic Preparedness and REsponse (PREPARE) in Singapore is designated to lead the coronavirus CORC (CORC-CoV). The first goal of the CORC-CoV is to create a research and development road map that accurately lists the research priorities that are necessary to advance the coronavirus field with the overarching goal of being prepared for a future coronavirus disease outbreak.

Scope

This coronavirus research & development roadmap outlines the primary challenges, key needs, knowledge gaps, strategic goals, and priority research activities required to bolster coronavirus pandemic response capabilities. It defines the boundaries of the required research, and the timelines for implementation. By establishing a shared understanding of direction and expectations, this roadmap provides a structured framework for coordinated execution and informed decision making. While the roadmap strives to prioritize key coronavirus research areas for funding and advancement of the field, the intent is to avoid policy pronouncements and/or manufacturing targets. This also includes supply chains and global accessibility to medical countermeasures, all of which are beyond the scope of the roadmap.

Executive Summary

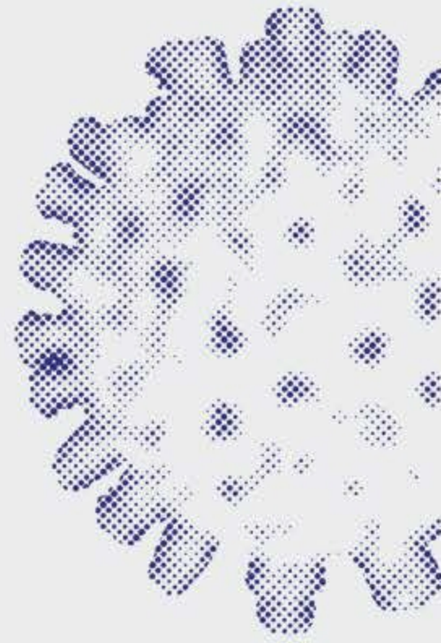
This research and development road map consists of six themes that systematically defines plans needed to advance coronavirus research. While there are unavoidable overlaps (e.g. diversity of coronaviruses, reference reagents, biorepositories, correlates of protection) in primary challenges/key needs between themes, we have established unique milestones for each theme to tackle the respective issues. However, there are additional cross-cutting challenges and priorities identified that are not applicable to a single theme. An important example is the overall lack of urgency and sustained funding that is likely due to a waning of public interest in coronaviruses with the perception that the COVID-19 pandemic has ended. Despite the crucial advances made through fundamental research into the COVID-19 response, the lack of investment significantly increases the global vulnerability to future coronavirus outbreaks.

There continues to be a persistent threat posed by coronaviruses with the more recent emergence of SARS-CoV, MERS-CoV, SARS-CoV-2 from animals and the identification of zoonotic canine coronavirus and porcine deltacoronavirus strains. Notably, merbecoviruses have been discovered capable of utilizing other known coronavirus receptors (ACE2 and APN) as entry portals, to an extent that human cells have shown to be susceptible.

We recognize that all coronavirus research initiatives will benefit significantly from a CORC-CoV coordinated global biobank of critical reagents and standard operating procedures. This will ensure that access and availability to reagents will not impede future response efforts. Importantly, all six themes need to be integrated as part of the pipeline for any coronavirus risk assessment. A challenge is to expand risk mitigation and responses for all themes. Pandemic preparedness is complex, requiring integrated cross-theme and One Health approaches.

Given that another coronavirus pandemic could occur precipitously, urgent global collaborative efforts are required including the ratification of the WHO Pandemic Agreement and establishment of the CORC-CoV. These initiatives have brought about this road map that will provide a viable and relevant framework for WHO and other agencies to combat future coronavirus pandemic threats.

Introduction



Coronaviruses are enveloped and positive-sense RNA viruses that belong in the order *Nidovirales*. They are further classified within the *Orthocoronavirinae* subfamily *into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus*, and *Deltacoronavirus*. Based on genomic organization and similarity of conserved genes, member species are further segregated into twenty-six subgenera. Notably, among the human-infecting zoonotic betacoronaviruses, SARS-CoV and SARS-CoV-2 are members of subgenus *Sarbecovirus*, while MERS-CoV is a member of the subgenus *Merbecovirus*.

To date, there are ten coronaviruses that are recognized to infect humans. There are the four common cold human coronaviruses (hCoVs): 229E, NL63, OC43, and HKU1. SARS-CoV, SARS-CoV-2, and MERS-CoV have been the main cause of epidemics/pandemics/outbreaks in the 21st century. SARS-CoV circulated during the 2002–2004 outbreak. Since emerging in 2012, MERS-CoV is still endemic in dromedary camels with sporadic infections of humans in the Arabian Peninsula. SARS-CoV-2 caused the ongoing COVID-19 pandemic and has resulted in an estimated seven million deaths. Lastly, there were four independent cases of human infection: Two canine coronaviruses, CCoV-HuPn-2018 and CCoV-Z19 (*Alphacoronavirus*) in Malaysia and Haiti, respectively; KUMC22-3 in South Korea (*Alphacoronavirus*); and Hu-PDCoV (*Deltacoronavirus*) in Haiti, albeit no known sustained human-to-human circulation.

Infections caused by coronaviruses typically present as an enteric or respiratory disease. Whilst an upper respiratory tract infection is commonly observed for infections with hCoVs and SARS-CoV-2, severe manifestations such as pneumonia can occur in selected populations, including elderly and immunocompromised people. Comparatively, SARS-CoV and MERS-CoV infections have been associated with higher pathogenicity and mortality rates. Despite the damage caused by COVID-19 disease, there are effective antivirals and vaccines against SARS-CoV-2 that significantly reduce disease severity.

01. Ecology and Transmission

Primary Challenges

- **Unknown coronavirus virosphere in animals:** Animal coronaviruses are associated with sporadic zoonotic spillovers, disease outbreaks, epidemics, and pandemics in humans. Yet little is known about the genomic and phylogenetic diversity of coronaviruses in most animal species, especially at the human-animal interface that drives disease emergence, and in many geographic locations.

- **Understanding the biological determinants essential for a spillover:** Lack of a detailed understanding of the biology, genomic and evolutionary determinants of successful human emergence and which of the myriads of animal coronaviruses are at the greatest risk of emergence.

- **Tools for emergence prediction and modelling:** Lack of experimental and computational tools that can accurately and rapidly predict the risk of an animal coronavirus emerging in humans and its potential for sustained transmission.

- **Availability of resources in LMICs:** Most coronaviruses emerge in LMICs that do not have the computational and laboratory resources necessary to generate genomic sequence data and track coronavirus evolution and spread.

- **Adoption of the One Health approach:** Insufficient long-term, systematic and targeted surveillance that adopts a One Health approach to understand coronavirus evolution and emergence.

- **Host species ecology:** Lack of information on the natural history of host species (e.g. location of roosting sites, migration patterns, host ranges) and how they are affected by ecosystem disturbances from human activities (e.g. deforestation, intensive farming, pesticide usage, seasonal food shortages). This information can inform surveillance and emergence risk mitigation.

Key Needs

- **Knowledge of coronavirus diversity:** Access the diversity of coronaviruses in nature, particularly at the human-animal interface where emergence is most likely to occur, including an understanding of the key drivers of coronavirus evolution and emergence.

- **Robust tools for risk assessment:** New tools to rapidly and accurately assess the zoonotic/emergence risk of animal coronaviruses and whether some coronavirus lineages, or particular virus genetic factors, are associated with an enhanced capacity to jump hosts. Wet-lab tools are also needed to measure the phenotypic effects of mutations in viral genomes, such as assessing and defining receptor binding usage for coronaviruses that frequently jump species boundaries.

- **Surveillance to mitigate emergence risk:** Continuous monitoring of animal reservoirs and likely intermediate hosts to screen for coronaviruses of elevated emergence risk. Waste water and air sampling surveillance can also provide crucial early-warning signals.

- **Universally aligned biosafety and biosecurity guidelines:** Development of safe work protocols for animal sampling to be undertaken with the minimum risk of human exposure.

- **Global collaboration:** A network of laboratories, especially in LMICs to rapidly analyze viral phenotypes through experimental assays. Implementation of a comprehensive coronavirus surveillance system using a quadripartite One Health approach that includes humans, animals, wildlife, and the environment, to mitigate risks at the community level.

- **Infrastructure improvement in LMICs:** Establishment of computational and laboratory facilities that require minimal technology for LMICs and with appropriate training in LMICs.

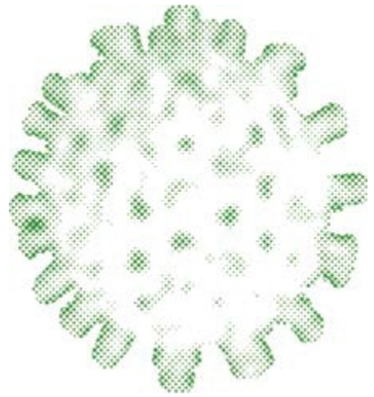
- **Data sharing:** Incentives for the routine and timely sharing of genomic data and associated metadata in open access and open-source databases.

- **Artificial intelligence-driven tools:** New computational tools, including those utilizing artificial intelligence (AI) approaches, should be developed that can forecast potential spillover risk to humans, should include pre-pandemic prediction together with One Health. Also, predict viral phenotypes and functional properties, and estimate key epidemiological parameters, improving the proactiveness of the surveillance network. AI-based models should be trained in solid, empirically derived laboratory results.

Knowledge Gaps

- **Surveillance in hotspot countries:** Research is needed to reveal the diversity and prevalence of coronaviruses in animal populations. This will require identification of the pathogens of diverse mammalian species (both natural reservoirs and likely "intermediate" hosts), including bats, wild fur, game, farmed and domestic animal species, particularly of animals that interact with human populations, as well as those from ecosystems in which animal coronaviruses have been previously identified. There should be a focus on geographic regions that have been poorly sampled to date, such as South America and Africa. Genomic and metagenomic sequencing should be applied to diverse sample types, via tissue, fecal, wastewater or air sampling, as well as targeted serological assays. The prevalence, seasonality and geographic distribution of any identified viruses of interest should be assessed using targeted PCR-based, pan-CoV PCR, genomic and/or serological studies. Species that harbor coronaviruses should be documented, with viral diversity mapped and hotspots of zoonotic risk identified.

- **Criteria for risk assessment of coronaviruses:** Animal coronaviruses with potentially increased risk of human emergence should be identified and continually monitored. Criteria for risk assessment may include viruses that (i) are closely related to known human pathogens (e.g. particularly betacoronaviruses from the subgenera Sarbecovirus, Merbecovirus, and Embecovirus), (ii) are able to infect different host species, genera, families, orders (i.e. host generalists), and (iii) are likely able to utilize human cell receptors and/or possess genetic traits associated with the capacity to infect new hosts. Genome-scale evolutionary relationships, patterns of recombination, history of host-jumping, and geographic spread should be assessed. Molecular clock dating can be used to determine the timescale of virus evolution and of host jumping events. The entry receptors used by many coronaviruses remain unknown. Experimental studies focusing on elucidating receptor usage across coronavirus diversity will fill in a wider knowledge gap and benefit the assessment of spillover risk. For coronaviruses considered to be of spillover risk, phenotypic characters such as cell receptor usage, transmissibility, immune evasion, mode of transmission, and virulence should be measured and their ongoing evolution assessed. The phenotypic impact of mutations (combination of mutations) should be determined. Mutations that define viral lineages that commonly jump host species should be defined.



- **Evolutionary parameters:** Research is needed to understand the evolutionary potential of coronaviruses. This will require the accurate measurement of the rates of viral mutation, evolution (i.e. nucleotide substitution) and recombination in animal reservoirs, as well as of the selection pressures acting on individual genes, and whether these parameters are associated with host jumping. Rates of virus spillover should be assessed by animal species, by geographic region, and by virus lineage. Research should determine whether different viruses occupy different geographic ranges and animal species, indicative of competitive exclusion or enhancement. Factors such as pregnancy, age, seasonality and immunity in animal reservoirs associated with virus amplification and shedding need to be identified to understand the spillover factors clearly.

- **LMIC-focused collaboration:** A network of laboratories should be established, including in LMICs, for ongoing surveillance and to measure biological traits associated with disease emergence in real-time. This will promote the early detection and characterization of novel coronavirus.

- **Streamlined data sharing:** An integrated coronavirus genomic database that incorporates genomic, experimental, epidemiological and environmental data should be developed, with data freely shared via open access and open-source tools. A comprehensive analytical pathway that can be used by researchers globally, including in LMICs, to analyze the spread of any newly emerged pathogens should be established. This should comprise appropriate bioinformatic tools, incorporating the latest developments in phylogenetic analysis, phylogeography and phylodynamics. Appropriate training in all methodologies should be provided.

- **Peacetime radar for active surveillance:** A global emerging coronavirus "radar" for the surveillance of emerging coronaviruses should be established. Data sharing governance and networks in which IP is guaranteed for researchers should be established. Sequencing and computational capacity and infrastructure in LMICs should be expanded, and standardized where possible, enabling the local identification of viral lineages of importance.

- **Adoption of One Health:** An integrated One Health framework should be developed for the surveillance and analysis of coronaviruses at the human-animal interface, linking ecology, veterinary medicine, public health and the social sciences, and promoting real-time data exchange. An integrated coronavirus surveillance system for human and animal health should be developed. Risk communication and community engagement strategies should be developed to co-design interventions with local populations. Interventions should be developed based on data from R&D to enhance community prevention and alertness. A behavioral and sociocultural assessment should be conducted to evaluate the effectiveness of public health measures in preventing virus transmission.

Strategic Goals and Aligned Milestones

STRATEGIC GOAL 1

Determine the diversity and prevalence of coronaviruses in animals and identify those with the greatest potential to emerge in human populations that can then be monitored

MILESTONES

YEAR 1–2

01 Establish a standard protocol for safe practices in animal sampling and the collection of associated biological and ecological data. This includes conducting coronavirus genomic and serological testing, as well as virus characterization through both experimental laboratory methods and computational analysis.

YEAR 3–5

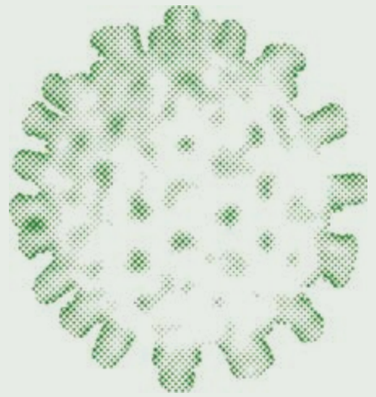
01 Provide comprehensive assessments of coronavirus diversity and prevalence in animals through the targeted surveillance of coronaviruses in farmed, captive, and free-living wildlife populations (natural reservoirs and intermediate hosts).

02 Identify novel coronaviruses, determine their phylogenetic relationships, history and pattern of recombination events, and track their evolution in animal hosts.

03 Conduct a risk assessment of all animal coronaviruses and identify those at the greatest risk of emerging in humans.

04 Reveal the viral and host factors associated with successful host emergence and ongoing virus evolution.

05 Characterize the phenotypic effect of virus variants on transmissibility, immune evasion, and disease severity.



STRATEGIC GOAL 2

Build global capacity to mitigate the risk of viruses with high potential to breach the animal-human interface

MILESTONES

YEAR 1–2

01 Develop tools that can combine multiple data sources to assess accurately the zoonotic risk of any coronavirus.

YEAR 3–5

01 Build tools and resources for the timely analysis of epidemiological and genomic data from any emerging coronavirus, as well as methodologies for evaluating the effectiveness of public health measures to prevent virus transmission.

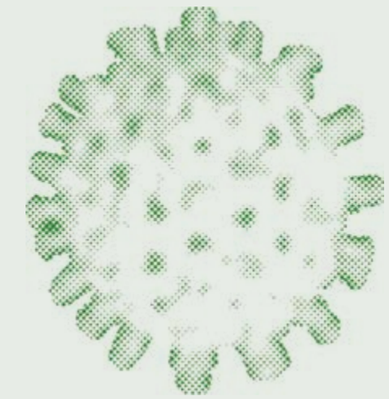
02 Build a global open access data-sharing platform for coronaviruses.

03 Establish capabilities to expand international (including in LMICs) surveillance networks and sequencing capabilities for identifying and characterizing variants of interest and concern for outbreak forecasting.

04 Strengthen cross-sectoral collaboration between veterinary medicine, public health, social sciences, and environmental health to develop One Health strategies to mitigate the emergence of zoonotic coronaviruses, particularly focusing on the community of high-risk groups.

Priority Areas/ Activities

- **Identify** new animal coronaviruses and determine their prevalence
- **Reveal** the key drivers of coronavirus evolution and emergence
- **Develop** new tools for coronavirus risk assessment
- **Predict** the risk of any animal coronavirus of emerging in humans
- **Conduct** ongoing surveillance for any high-risk coronavirus
- **Build** global capacity to generate genomic and epidemiological data for emerging coronaviruses
- **Establish** a global research infrastructure to track the spread of coronaviruses and assess their epidemiological and biological properties
- **Share** coronavirus genomic data freely through open access tools
- **Mitigate** the potential of high-risk viruses to breach the animal-human interfaces
- **Increase** community awareness of the risk of zoonotic coronavirus emergence in hotspots



02. Virus Biology

Primary Challenges

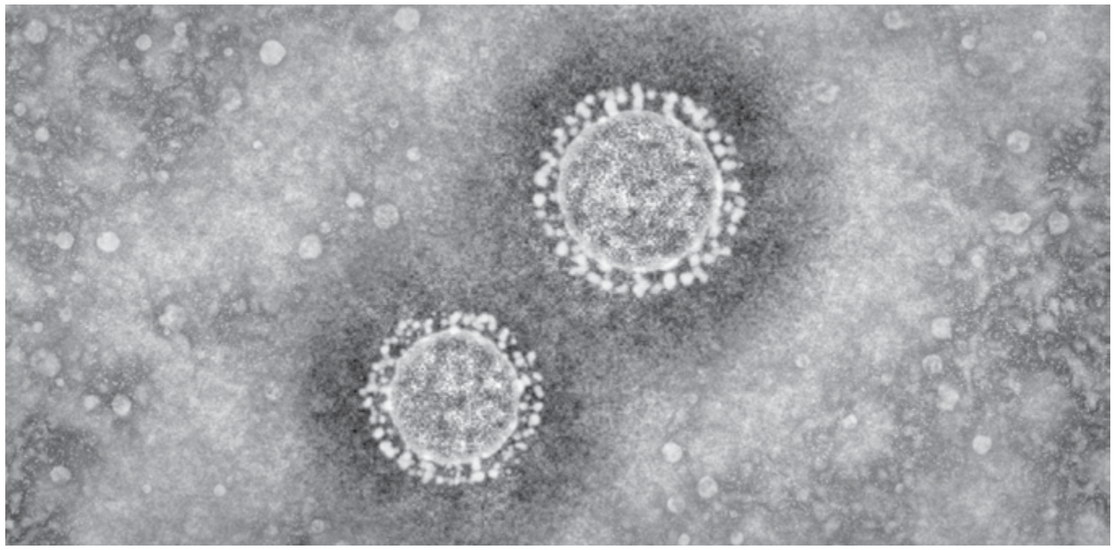
- **Universally available reference reagents and tools:** There is a lack of widely available, standardized reference reagents (cell lines, pseudoviruses, infectious clones, validated clinical specimens, positive/negative controls, viral gene libraries, receptor ortholog libraries) for each coronavirus subgenus.

- **Coronaviruses are highly diverse:** Coronaviruses are found in many animal species. They are highly diverse and rapidly evolving, leading to variants with altered host range, transmissibility, immune evasion, and pathogenicity. The situation is further complicated by our limited capacity to predict phenotypes from genotypes, as even minor genetic variations can lead to substantial phenotypic changes.

- **Virus propagation remains challenging:** Many subgenera have never been successfully isolated, and some can only be grown in primary cell cultures. Only a limited number can replicate in standard cell lines without first acquiring culture-adaptive mutations—changes that often arise because these models fail to accurately reproduce the virus' natural cellular environment. Such mutations can markedly alter important viral phenotypes and reduce the relevance of findings to natural infection.

- **Accurately modeling coronavirus pathogenesis and transmission:** Coronavirus pathogenesis is highly complex, with disease mechanisms that vary widely depending on the virus, host biology, and environmental influences, resulting in diverse clinical outcomes across affected population. Animal models often misrepresent key aspects of human infection, while *in vitro* models lack the required complexity, human challenge models do not model severe disease, and clinical studies generally miss the critical first stages of disease.

- **Assessing coronavirus spillover risk:** Predicting coronavirus spike–receptor interactions, virulence, host range, as well as regions and species where novel viruses are likely to emerge due to the vast genetic diversity, abundance of viruses with unknown receptor usage, and limited understanding of the molecular determinants governing virulence and host switching. While forecasts and predictions will likely involve a considerable degree of uncertainty, they play a vital role in guiding the prioritization of resources and actions.



Key Needs

- **Virus culture systems:** Cell lines and organoid platforms should be designed and validated to closely replicate key features of the virus's natural target cells, thereby minimizing the risk of adaptation during culture. Building shared, quality-controlled reagents and validated model systems across coronavirus subgenera will improve reproducibility and accelerate research.

- **Intelligence pipelines for risk prioritization:** AI/ML-enabled tools that can systematically prioritize coronaviruses with zoonotic or epizootic potential by predicting virus-host interactions (structural data on RBD interactions with known receptors). Such approaches would generate the intelligence needed to inform vaccine R&D and support global preparedness initiatives. While significant progress has been made in characterizing spike-receptor interactions, host range, and the phenotypic impact of mutations, further work is needed to integrate them into cohesive frameworks that move toward scalable decision tools, and to extend beyond receptor binding to other early determinants of infection/disease. The success of such computational pipelines depends largely on the availability of comprehensive, well-curated datasets to train the models. These include detailed host data for sampled coronaviruses, as well as spike-receptor co-structures to enable structure-based predictions.

- **Forecasting virus-host evolution:** Recognizing that viral diversity is constantly changing, cross-scale, uncertainty-aware models that forecast where (hosts, geographies) and under what conditions coronavirus evolution is most likely to generate novel, zoonotic, more pathogenic or more transmissible strains. These models would integrate within-host mechanisms (e.g. recombination) with ecological and environmental contexts, be parameterized and calibrated with experimental and surveillance data, and provide actionable risk factors and maps to support resource allocation and prioritization.

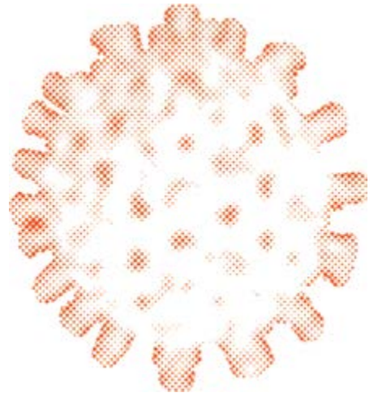
- **Broadening coronavirus research to other subgenera:** Current coronavirus research is heavily focused on subgenus *Sarbecovirus* and *Merbecovirus* and we lack preparedness for other coronavirus subgenera. Broader attention is needed for other human coronaviruses, as well as animal coronaviruses (e.g. those found in wild animal species that are in close contact with humans but also farmed and/or are companion animals). Expanding research beyond the well-studied lineages will provide a more comprehensive understanding of coronavirus diversity and better prepare for zoonotic spillovers.

- **Reference reagents:** There is a need for widely available, standardized reference reagents, including cell lines, pseudoviruses, infectious clones, validated clinical specimens and isolates, positive/negative controls, viral gene libraries, and receptor ortholog libraries

- **Experimental infection models:** There is a need for experimental systems that more faithfully represent coronavirus infection and transmission. Current models can misrepresent key aspects of human infection, while *in vitro* models lack physiological complexity. Human challenge studies do not capture severe disease, and clinical cohorts rarely capture the earliest stages of infection. We also lack models that capture infection dynamics in the natural reservoirs where these viruses evolve, to be able to identify key viral and host interactions that relate to innate immunity, virulence, tissue tropism, transmissibility, etc. Many bat coronaviruses have been evaluated in generic animal models, or even in bats of unrelated species, but seldom in the actual host species that maintains the virus in nature. This limits our understanding of how adaptation to natural hosts shapes viral traits.

- **Full, standardized pipelines for rapid pathogenesis assessment:** There is a need for standardized *in vitro* and *in vivo* models to rapidly risk assess viruses for their zoonotic, reverse zoonotic, and epizootic potential. These pipelines should be a collection of standardized models that assess host range, tropism, receptor usage, pathogenicity, and transmissibility.

Knowledge Gaps



- **Entry and tropism:** For many coronaviruses, the primary entry receptors are still unknown as is the evolution of receptor usage acquisition and receptor shift. While ACE2, DPP4, and APN are established receptors for many coronaviruses, other viruses may use these, ortholog variants, or entirely different host molecules. Defining the full range of receptors, co-receptors, and attachment factors, including glycans and proteases that act as entry cofactors, is necessary to understand tropism and anticipate cross-species transmission. In addition, the subcellular microenvironment of the receptor and localized host proteases may substantially affect virus entry. The key protein-protein interactions, including spike–receptor interactions, are incompletely defined. Progress will require systematic experimental mapping across broad panels of coronaviruses and host species, using binding and functional assays complemented by high-resolution structural studies, to capture the diversity of possible interactions. These datasets could then be used to develop AI/ML tools trained to predict spike interactions across large numbers of host receptors and orthologs, supporting risk assessment of host range and cross-species transmission potential.

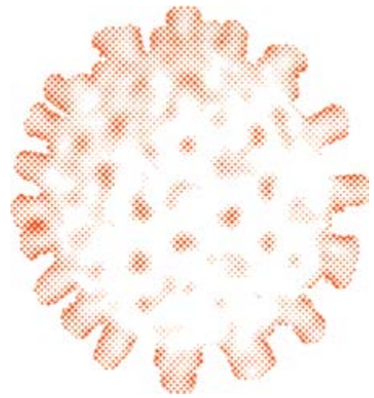
- **Replication machinery:** Many aspects of the coronavirus replicase complex are incompletely understood, particularly the detailed molecular mechanisms that govern viral RNA synthesis and the intricate coordination of the replicase complex with both viral and host co-factors during replication. The diverse functions and multifaceted roles of coronavirus non-structural proteins are only partially elucidated, because many of these proteins are large and only their individual domains have been investigated. Furthermore, the precise mechanisms by which coronaviruses induce and utilize specialized replication compartments like double-membrane vesicles remain unclear. A significant knowledge gap also persists regarding the molecular mechanisms and viral and host factors that drive recombination in coronaviruses, including template switching by the RNA polymerase.

- **Virus-host interactions beyond entry:** It is thought that uncontrolled inflammation ultimately leads to severe immunopathology, characteristic of COVID-19, but how this inflammatory state is induced and progresses remains uncertain. The multifaceted roles of non-structural proteins, structural proteins and accessory open reading frame (ORF) gene products, and their interactions and how they affect pathogenesis, host range, and tropism, remains incompletely understood. This knowledge gap limits our understanding of their contributions to host range and pathogenesis—and whether they present viable targets for antiviral therapies. Viral restriction factors play a crucial role in determining the host range and tropism of many viruses. Many of the antiviral host factors that limit coronavirus replication across various tissues and species are still largely uncharacterized. Likewise, there may be unrecognized viral evasion strategies. Uncovering these virus-host interactions may lead to new targets for antiviral therapies.

- **Human-to-human transmission:** For most coronaviruses, modes of transmission (e.g. droplet versus aerosol, fecal-oral) are not well understood. It is unclear whether spread is driven by cell-free virions, virus–mucus aggregates, infected cells, or cell-associated material (infected cells, extracellular vesicles), cell-cell transmission, and how these contributions vary by site, stage of infection, and environment. The concept/role of superspreaders in human transmission of coronaviruses is documented but poorly understood, as is the impact of viral transmission route, dose, and host factors on zoonotic spillover and infection and disease outcome in humans. These uncertainties make it difficult to translate experimental findings to human populations. Factors such as spike cleavage and activation, viral stability, proteolytic activity of the extracellular space, mucous type and composition, mucociliary clearance, and host antiviral responses are not well resolved, yet they likely influence interspecies and human-to-human transmission.

- **Virus evolution and drivers of emergence:** The extent to which specific hosts—and particular sites of viral replication within these hosts—drive the selection of coronaviruses with increased host range, zoonotic/pandemic potential remains poorly understood. Identifying how host species and cellular microenvironments shape viral evolution and emergence is a critical but largely unexplored area in coronavirus biology. Exploring this may also help identify mutational signatures that could be biomarkers related to interspecies transmission. Additionally, immunocompromised hosts and secondary animal hosts have been suggested as drivers behind the emergence of viral variants, but this has yet to be confirmed. Moreover, the pathways (e.g. gradual adaptive mutations or recombination events) through which coronaviruses acquire novel receptor specificities or shift between distinct receptor families remain poorly defined. Defining the fundamental rules by which viral and host factors shape coronavirus adaptation and emergence will be essential for improving forecasts of future host jumps and for proactively identifying potential zoonotic threats. The rates, constraints, and immunologic drivers of evolution in hCoVs, 229E, NL63, OC43, and HKU1 remain poorly defined. We lack continuous, multi-year genomic and antigenic datasets to quantify substitution, co-infection, and recombination rates, and map how population immunity shapes viral change.

- **Mechanisms and constraints of recombination:** Coronavirus recombination has been proposed to be a pathway of discrete conditional events that unfold across biological scales. A key gap is understanding the biological mechanisms that drive this process, from molecular to ecological. This includes clarifying the mechanistic and genetic limits of template switching, and other steps that govern: (i) the opportunity for recombination, (ii) the production of recombinant genomes, and (iii) the selective pressures and competitive interactions that novel recombinants must overcome before establishing in nature.



Strategic Goals and Aligned Milestones

STRATEGIC GOAL 1

Develop and disseminate universally accessible research and diagnostic tools

MILESTONES

YEAR 1–2

01 Establish a virtual (physically separate collaborative entities) biorepository of standardized reference reagents (cell lines, pseudoviruses, infectious clones, validated clinical specimens and isolates, positive/negative controls, viral gene libraries, receptor ortholog libraries) and associated validated assay protocols for all coronavirus subgenera.

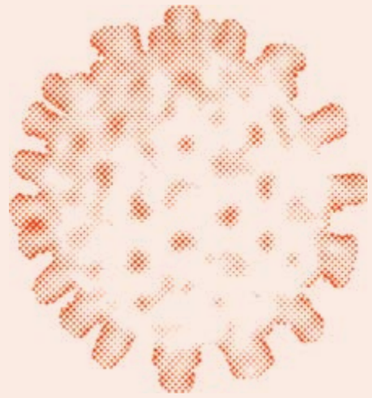
02 Create a collaborative virtual, interactive specialized center for tissue engineering of *in vitro* models to study coronavirus pathogenesis, transmission, and host range.

03 Create a collaborative virtual, interactive specialized center for reverse genetics and virus propagation/isolation.

YEAR 3–5

01 Develop a shareable, universal cell line(s) for coronavirus isolation and propagation that expresses a wide range of known entry factors (or allows receptor-independent entry), and can also be used for isolation of coronaviruses that do not use currently known receptors.

02 Establish an organoid biobank containing key experimental animal organoid models, including mice, non-human primates, ferrets, Roborovski hamsters, and golden Syrian hamsters, which can be used for rapid animal model selection, and isolation/propagation of a wide range of coronaviruses. Respiratory and intestinal organoids are of the highest priority. The repository should include detailed protocols for organoid expansion, differentiation, and quality control. Models should be validated for their relevance through extensive comparisons with the animal tissues that they model.



STRATEGIC GOAL 2

Improve the understanding of the replication cycle of coronaviruses including breadth of host cell receptors, attachment factors, and proteases for coronaviruses

MILESTONES

YEAR 3–5

01 Continue the identification of entry receptors for a wide range of coronaviruses.

02 Improve the understanding of glycan receptors or attachment factors in determining coronavirus entry, tropism and host range.

03 Improve the understanding of spike-priming protease usage and the underlying molecular mechanisms.

04 Improve the understanding of the detailed molecular mechanisms underlying coronavirus RNA synthesis, the coordinated action of the replicase complex with viral and host factors, the precise functions of nonstructural proteins, the formation and use of replication organelles, and the processes driving recombination.

STRATEGIC GOAL 3

Improve the understanding of animal-to-human, human-to-human and human to animal transmission for a wide range of coronavirus subgenera

MILESTONES

YEAR 1–3

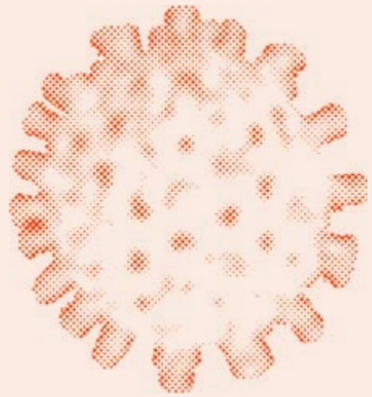
01 Improve physiologically relevant models that cover the entire respiratory and intestinal tracts as well as differentiation conditions to accurately model the respective human tissues.

YEAR 3–5

01 Develop ready-to-use or adaptable animals and controlled human infection models to quickly assess airborne and fecal-oral transmission, improve quantitation of transmissibility, and understand the determinants of transmission efficiency, identify the factors that drive spread.

02 Investigate the aerobiological, biological, and physical mechanisms behind superspreading events to understand better their impact on transmission dynamics.

03 Develop tissue-engineered, human respiratory tract cell models quantify airborne transmission rapidly.



STRATEGIC GOAL 4

Improve the understanding of coronavirus pathogenesis across coronavirus subgenera

MILESTONES

YEAR 3–5

01 Develop ready-to-use or adaptable animal models to study coronavirus pathogenesis, including the late-stage inflammatory phase. Enhance the capacity to elucidate host factors (e.g. genetic polymorphisms, comorbidities, or other predisposing factors) that protect from or contribute to susceptibility to infection or severe disease in humans and animals. This includes models that capture infection dynamics in the natural reservoirs.

02 Establish scalable, cost-effective organoid and organ-on-chip platforms to study coronavirus pathogenesis in humans. Efforts should be focused on tissue engineering approaches to model immunopathogenesis (e.g. by incorporating specific immune cell subsets) and late-stage inflammatory disease in the lungs, and the addition of host microbiota to model their impact.

03 Enhance the experimental toolkit to be able to screen for host factors (e.g. dependency and restriction factors), validate screening hits (e.g. from GWAS or CRISPR screens), and confirm therapeutic targets in relevant *in vitro* and *in vivo* models.

04 Improve the understanding of innate immune evasion and virulence factors.

STRATEGIC GOAL 5

Develop comprehensive pipelines for rapid virus risk assessment

MILESTONES

YEAR 3–5

01 Use the organoid models developed in strategic goal 4 to rapidly risk assess potentially zoonotic coronaviruses for pathogenicity, transmissibility and host range.

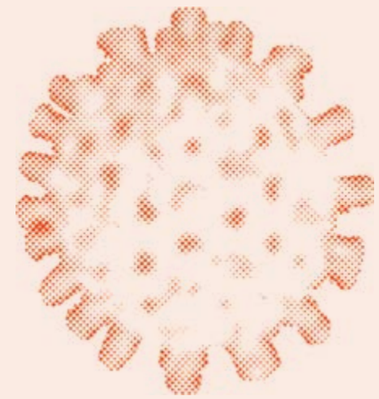
02 Develop animal organoid models to isolate/propagate diverse coronaviruses, facilitate rapid assessment of coronavirus host range/tropism, and provide platforms for dissecting the underlying molecular mechanisms. This includes organoid banking of a wide range of (potential) host species, including, but not limited to, bats, rodents, civet cats, pangolins, raccoon dogs, mink, cats, dogs, pigs, cows, and camelids. Respiratory and intestinal organoids are of the highest priority. The repository should include detailed protocols for organoid expansion, differentiation, and quality control. Models should be validated for their relevance through extensive comparisons with the human/animal tissues that they model.

03 Develop new and improve existing animal models to assess zoonotic, reverse zoonotic and epizootic risk, and assess pathogenicity, transmissibility and host range.

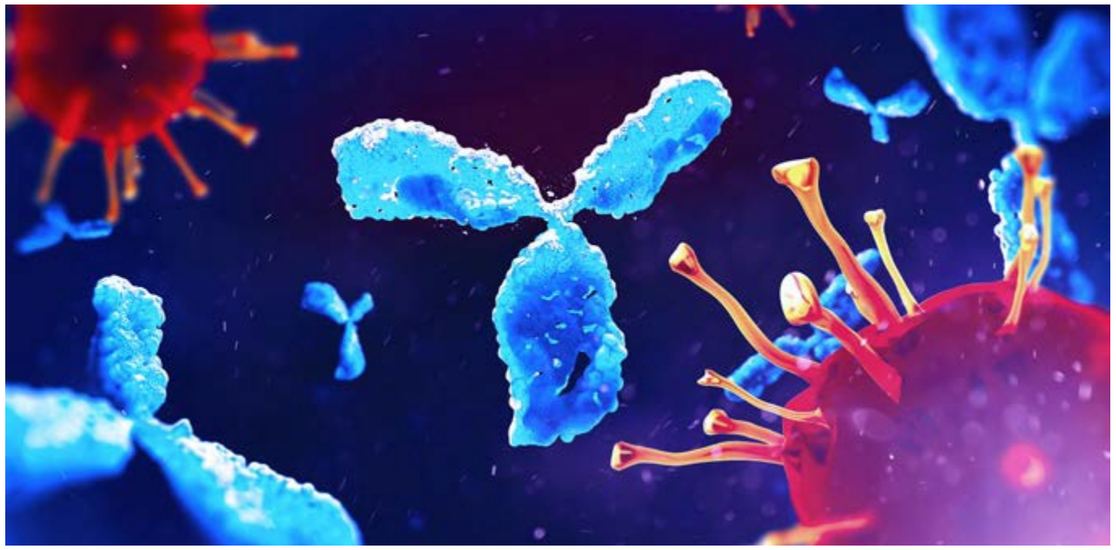
04 Develop uncertainty-aware AI/ML pipelines for risk prioritization. (i) This includes tools that can systematically prioritize coronaviruses with zoonotic or epizootic potential by predicting virus-host interactions and (ii) Tools that can forecast where (hosts, geographies) and under what conditions coronavirus evolution is most likely to generate novel and zoonotic strains. These models should provide actionable risk factors and maps to support resource allocation and prioritization.

Priority Areas/ Activities

- **Generate** standardized reference reagents and tools
- **Enhance** the understanding of the mechanisms that govern virus entry, replication, tropism, host range, pathogenesis, and transmissibility
- **Advance** experimental models to study transmission and pathogenesis
- **Identify** drivers behind the emergence of coronaviruses, coronavirus variants, and coronavirus recombinants
- **Develop** improved cell lines and realistic organoid models for coronavirus isolation and propagation
- **Develop** improved experimental infection models to study host range, transmission, pathogenesis, and test interventions
- **Build** and maintain large-scale, accessible online biorepositories for coronavirus-related reagents
- **Create** specialized virtual collaborative research centers (i) on reverse genetics and virus propagation and (ii) on tissue engineering



03. Immune Responses



Primary Challenges

- **Accessing high-quality and diverse coronavirus clinical samples for immune studies in a timely and standardized manner:** Rapid access to high quality biological samples is essential for understanding immune responses and developing countermeasures for coronavirus research. Many clinical studies lack access to well-characterized, geographically diverse specimens collected at defined time points post-infection or vaccination. Without such samples, analyses of immunity across age groups, comorbidities, and viral variants are incomplete.

- **Characterisation and standardization of immune assays:** Previous efforts to standardize coronavirus assays were initiated by the WHO/CEPI and have involved the identification of sites of antibody testing worldwide. Unknown samples along with standards have been provided to these regional laboratories and results compared by a central laboratory. As immune assays against coronaviruses are developed and refined, it will be critical to standardize these assays.

- **Pre-clinical models replicating human disease or immune protection patterns:** Existing pre-clinical models for coronaviruses can reproduce certain aspects of infection but often fail to mirror aspects such as human mucosal immune responses, immune imprinting, or disease severity profiles. This limits predictive value for vaccine and therapeutic testing.

- **Influence of pre-existing immunity (including immune imprinting) on future coronavirus infections or vaccinations:** Pre-existing immunity from prior exposures to human common cold coronaviruses like 229E, NL63, OC43, and HKU1, as well as to emerging ones such as MERS-CoV, SARS-CoV, and SARS-CoV-2, may significantly influence the immune response to future coronavirus infections and vaccinations, through mechanisms such as cross-reactive antibodies and memory T/B cells, which may enhance or hinder protection.

Key Needs

- **Coordinated, global (virtual) biobanking systems for accessing clinical samples and immune reagents:** A global virtual biobanking network is needed to facilitate access to diverse clinical samples and immune reagents from various populations and coronavirus exposures. This sustainable country-based network must operate under standardized protocols and adhere to ethical data-sharing frameworks, such as the WHO's Pathogen Access and Benefit Sharing (PABS) system, to ensure equitable global access. A central digital platform would integrate sample inventories with clinical and genomic data, enabling researchers to conduct vital comparative analyses across different viral variants and populations while upholding strict biosafety and data privacy standards.

- **Standardisation of immune assays and reagents:** To ensure globally comparable data, it's essential to standardize novel immune assays, particularly those for Fc-dependent antibody, mucosal antibody, and T-cell testing. A central testing laboratory should lead this effort by harmonizing methods and distributing reference materials to regional centres. This, combined with a centralized database for performance monitoring, will allow for reliable conclusions about immune responses to various coronaviruses across diverse populations.

- **Comprehensive methods to assess both systemic and mucosal immunity:** Blood-based antibody tests measure SARS-CoV-2 responses but miss respiratory mucosal immunity, which is key to preventing infection. Mucosal IgG/IgA assays exist but require specific sampling procedures. Standardized, robust methods for mucosal fluid and immune cell sampling are needed. New assays for mucosal T cells and memory B cells require further development. Simplifying T-cell tests by using whole blood directly would aid field use. Overall, standardizing T and B cell assays is crucial.

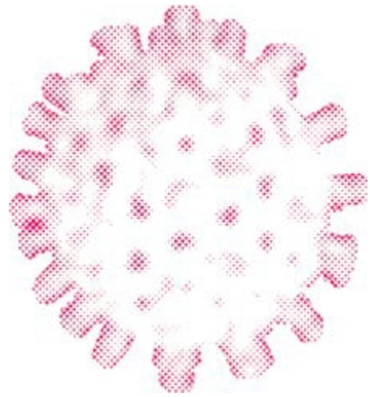
- **Improved preclinical and translational models that better mimic human immunity and immune pathology:** Current preclinical models inadequately replicate key aspects of human coronavirus immunity, such as mucosal responses and immune imprinting, limiting their translational value. Therefore, advanced models—including genetically engineered mice, humanized mice, and human organoids are essential for dissecting the precise immune mechanisms of protection and pathology. Future efforts must focus on standardizing these models and validating them with human challenge study data to improve their predictive power for new vaccines and therapeutics.

- **Characterisation of vaccine-induced and infection-derived immunity against coronavirus:** Longitudinal cohorts should follow diverse populations exposed to SARS-CoV-2, MERS-CoV and endemic coronaviruses, measuring neutralizing titers, cross-variant protection, Fc-dependent functions, T-cell functionality, and memory B-cell persistence after infection or vaccination. Analyses should quantify long-term durability and waning kinetics. Trials of broad-spectrum vaccines (e.g. CEPI programs) should coordinate and share samples to enable head-to-head comparisons. Detailed donor metadata—prior infections, health status, age, comorbidities, and vaccine history—are essential to explain cross-variant protection and durability. Mathematical models should project immunity trajectories (rapid early waning followed by stabilization) and guide booster strategies as variants evolve.

- **Study the influence of pre-existing immunity on future coronavirus vaccines and infections:** Research should prioritize serologic and cellular assays to map cross-reactivity, leveraging large epidemiologic datasets from regions with different hCoV prevalence. This includes evaluating how pre-existing immunity affects systemic and mucosal responses, which are critical for reducing transmission/severity, and incorporating findings into vaccine design, such as through mosaic or chimeric or de novo designed antigens that mitigate imprinting while leveraging beneficial cross-protection, as well as establishing animal models that can accurately recapitulate human immune imprinting for better vaccine performance evaluation. Collaborative efforts with global networks could extend these investigations.

- **Identify correlates of protection against coronavirus infections:** Early in the pandemic, systemic neutralizing antibody responses were shown to correlate well with vaccine efficacy. However, with time and the emergence of SARS-CoV-2 variants, it became clear that vaccinated or previously infected individuals were protected against hospitalization, ICU admission and death but not re-infection when neutralizing antibody levels were diminished or virtually absent. These results indicated that other arms of the anti-viral immune response must have afforded protection. These include virus-specific T cells, memory B cells, Fc-dependent antibody responses, mucosal immunity and trained innate immunity, which need to be investigated further for delineating associated COP. Standard modelling and AI-based methods should be used to analyse these data to identify COP, which may involve integration of several components of the humoral and cellular immune responses. COP against infection, severe disease and transmission should be established. Once these models are established, they will need to be extended to infection with evolving SARS-CoV-2 variants, and to infections of different populations (aging, geographical variation, sex differences, etc). These efforts would also benefit from the development of an internationally based database as described above.

Knowledge Gaps



- **Defining the hallmarks of a protective immune response:** Studies from COVID-19 patients and from experimental animal studies show that a coordinated immune response, involving both the innate and adaptive immune responses, is required for virus clearance and good clinical outcomes. How is this immune response characterized? Are there differences in protective immune responses elicited against various coronaviruses? A major challenge is the lack of standardized assays to compare these responses directly. To fully characterize them, it is critical to standardize assays for mucosal, T-cell, and B-cell immunity, which provide a more complete picture than systemic antibody measurements alone. Developing reproducible methods for collecting mucosal samples is particularly important, as these local responses are crucial for preventing initial infection but are often overlooked in standard blood-based analyses.

- **Dissecting differences between natural and vaccine-induced immunity:** Are there differences between immune responses to natural infection and vaccine-induced immune responses? A key distinction lies in the location and breadth of immunity; natural infection induces robust mucosal immunity in the respiratory tract, a response that is critical for preventing infection and transmission but is not efficiently induced by current systemic vaccines. Longitudinal cohort studies are needed to systematically track and compare metrics like antibody titers, T-cell functionality, and memory B-cell persistence between these two scenarios. Understanding these differences is essential for designing next-generation vaccines that can mimic the most protective aspects of immunity derived from infection.

- **Understanding global variations in vaccine efficacy:** Is there different vaccine immunogenicity/protection in low versus high-income countries? These disparities are likely driven by regional differences in pre-existing immunity shaped by prior pathogen exposure, alongside the impacts of co-infections and malnutrition on the immune system. Exposure to a diverse range of endemic coronaviruses may shape their baseline immunity in ways that either enhance the vaccine response through cross-protective effects or hinder it through mechanisms like immune imprinting.

- **Identifying the drivers of coronavirus-induced immunopathology:** Immunopathological disease has not been demonstrated after SARS-CoV-2 vaccination but is a component of the natural infection caused by all coronaviruses. It would be important to identify aspects of the coronavirus-specific immune response that led to immunopathological disease for better design of medical countermeasures. This requires improved preclinical models that can accurately replicate human immune pathology, as existing models often fail to mirror disease severity profiles. The use of humanized mice or human organoid systems could help bridge this gap, allowing for mechanistic studies to pinpoint the specific immune components that drive pathology versus protection.

- **Determining the persistence and significance of circulating antigens:** Some studies suggest that variants containing certain spike proteins circulate for variable times after infection or vaccination. This should be investigated and the biological significance, if any, determined. Addressing this requires longitudinal cohort studies that can track antigen levels, clinical disease and immune responses in diverse populations. Accessing high-quality, serial biological samples through a global biobanking network is essential to correlate the persistence of antigens with long-term standardized immune outcomes, such as the quality of memory B-cell responses and T-cell durability. This would clarify whether prolonged antigen presence is beneficial for memory development or potentially detrimental.

Strategic Goals and Aligned Milestones

STRATEGIC GOAL 1

Build and sustain virtual biobanks for coronavirus clinical samples and immune reagents

MILESTONES

YEAR 1–3

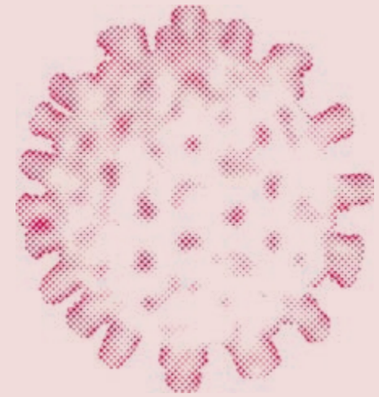
01 Initiate virtual biobanks for clinical samples associated with various coronaviruses and for immune reagents.

02 Expand sample collections to encompass disease severity, reinfections, breakthrough cases, and diverse populations.

03 Establish protocols for sharing metadata and for distributing validated sample panels and reference reagents to global partners.

YEAR 3–5

01 Maintain sustainable, open-access virtual repositories with QA/QC systems for rapid deployment in future outbreaks.



STRATEGIC GOAL 2

Elucidate mechanisms of mucosal and systemic immunity relevant to coronavirus infection, including broadly protective immune responses

MILESTONES

YEAR 1–3

01 Establish and standardise immune assays and reagents for determining systemic and mucosal immunity against coronaviruses.

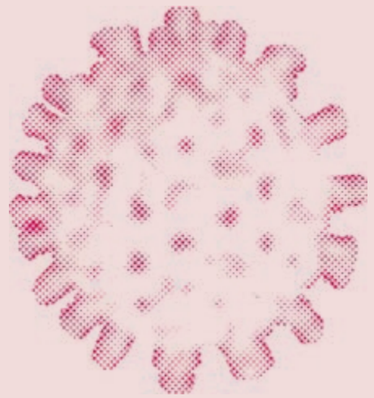
02 Establish relevant pre-clinical models (animal models, organoids, etc) for investigating coronavirus induced immunity and pre-existing immunity.

03 Identify immune cell subsets and effector mechanisms contributing to protection in mucosa/systemic compartments.

04 Identify broadly protective epitopes recognized by B and T cells that may provide broad cross-protection against SARS-CoV-2 variants, sarbecoviruses, other betacoronaviruses and all coronaviruses in that order.

YEAR 3–5

01 Identify correlates of cross-protection, such as broadly neutralizing antibodies and other immune factors.



STRATEGIC GOAL 3

Conduct immunological studies to quantify vaccine-induced and infection-derived immunity, including its durability and waning over time

MILESTONES

YEAR 1–3

01 Establish protocols for conducting clinical trials in populations infected with or vaccinated against coronaviruses (best for vaccine with non-SARS-CoV-2 antigen).

YEAR 3–5

01 Conduct longitudinal cohort studies to track immune responses by assessing metrics such as neutralizing antibody titers, T-cell functionality and memory B-cell persistence.

STRATEGIC GOAL 4

Investigate the impact of pre-existing immunity to circulating coronaviruses on the development of future coronavirus vaccines

MILESTONES

YEAR 1–3

01 Assess how pre-existing immunity affects immune imprinting and vaccine efficacy against novel coronavirus variants.

YEAR 3–5

01 Translate findings into immunization strategies that leverage or circumvent preexisting immunity.

Priority Areas/ Activities

- **Establish** global (virtual) biobanking to ensure access to reference clinical samples and immune reagents
- **Improve** methods for mucosal sample collection and assay systems for different immune responses
- **Standardise** immune assays and reagents for characterising mucosal antibody and T-cell responses
- **Determine** mechanisms of mucosal and systemic immunity
- **Conduct** immunological studies to quantify vaccine-induced / infection-derived immunity, including its durability and waning over time and any associated immunopathology
- **Investigate** the impact of pre-existing immunity to circulating coronaviruses
- **Identify** immune correlates of protection using biomarkers for T and B cell responses

04. Detection Technologies

Primary Challenges

- **Developing detection assays encompassing great viral diversity:** Detection assays, including molecular and serological methods, are generally designed to be specific to particular viral lineages. However, the considerable genetic diversity among coronaviruses poses significant challenges in developing assays capable of detecting all lineages.
- **Lack of tests to determine infectious virus:** Current PCR and antigen-based tests quantify both infectious and non-infectious viral products. Assays that determine infectivity of patient samples are needed to inform clinical and public health management. Additionally, there is a lack of data on infectious particles versus nucleic acid levels and on thresholds of infectiousness. Assays that determine infectivity of patient samples are needed to inform clinical and public health management; focusing on coronavirus biology is paramount to enable rapid detection of infectious samples.
- **Lack of well-validated standardized tests for detecting novel coronaviruses:** Despite the availability of the universal, rapid detection technologies capable of identifying novel coronaviruses, there are no standardized tests/methods available (or routinely used) for the detection of zoonotic/novel coronaviruses in humans. Surveillance efforts to detect spillover events are insufficient, especially in regions with common human-animal interactions, and it remains limited in resources constrained areas with high biodiversity, dense human-animal interactions and inadequate healthcare infrastructure. Rapid, well-validated tests are either not available or not routinely used in coronavirus surveillance, and there is a lack of a harmonized/standardized system to validate diagnostic tests for emerging coronaviruses. Countries at highest risk of spillover, particularly LMICs, often lack surveillance infrastructure, resulting in large blind spots.

Key Needs

- **Genomic surveillance and data integration:** Virus sequencing platforms and bioinformatics pipelines for effective genomic surveillance need to be enhanced and standardised. Specifically, it is essential to implement standardized sampling strategies, including clearly defined sample types, frequencies, and quantities, to ensure robust detection capabilities. Moreover, integrating genomic data with ecological and epidemiological information is crucial to move beyond simple sequence description toward meaningful risk assessment, focusing on the relationship between genotype and phenotype. Establishing a comprehensive CoV genomic surveillance platform that combines viral genome, epidemiological, and clinical data, along with strong governance for data sharing and use, aligned with the WHO genomic surveillance strategy, is also a vital requirement.

- **Early warning and monitoring system:** Early warning systems need to be strengthened by integrating hospital-based monitoring, cross-sector data sharing, advanced AI and machine learning analytics, and environmental surveillance to enable rapid detection of emerging threats. Establishing a global early-warning network that combines hospital, veterinary, and environmental surveillance with public health linkages, standardized clinical indicators, and multi-sector data streams is essential for the timely identification of emerging coronaviruses. Additionally, developing a harmonized clinical and laboratory algorithm for diagnosing pneumonia of unknown origin is crucial to improve diagnostic accuracy and response.

- **Diagnostic and assay development/ standardization:** Reliable pan-coronavirus (or pan-genus/subgenus) detection assays (virus, antibody or T cell-based), along with protocols, reference reagents, internal controls, and proficiency panels should be harmonised and developed. There is also a need to improve point-of-care test for antigen, antibody and T-cell detection for early detection to aid effective contract-chasing and early public health intervention during the coronavirus outbreak situation.

Knowledge Gaps

- **Conduct further research on the sensitivity and specificity of various diagnostic platforms:** This work entails evaluating existing and novel assays—antigen, genomic, serological and T-cell based assays—across diverse coronaviruses. Standardized panels of well-characterized positive and negative specimens and reference standards to benchmark inter-laboratory performance need to be established. Outputs will include sensitivity, specificity, and positive / negative predictive value, each reported with confidence intervals for every assay. An appropriate balance between sensitivity and specificity must be achieved and should be adaptable to context. For example, during a pandemic when large-scale population testing is needed to curb transmission, prioritizing high sensitivity (to minimize false negatives) may be warranted, even if this entails some reduction in specificity (and thus more false positives).

- **Limited availability of multiplex, rapid, point-of-care diagnostic platforms:** There is a critical need to develop integrated proof-of-concept devices capable of detecting both acute coronavirus infection (via antigen or RNA) and past coronavirus exposure (via antibody or T-cell response) within a single cartridge or combined workflow.

- **Insufficient genomic surveillance to detect spillover events:** Current surveillance systems lack systematic sampling across wildlife, livestock, companion animals, and high-risk interfaces (e.g. wet markets, farms, abattoirs), which is essential for early detection of spillover events and emerging threats.

- **Fragmented integration of clinical, genomic, and health system data for early phenotypic characterization:** There is a gap in standardized platforms that allow clinicians and researchers to input and analyse clinical and genomic data together. Such integration is necessary to identify early phenotypic signatures—such as pathogenicity, virulence, immune evasion, and receptor usage—either observed through clinical presentation or *in vitro* characterization.

Strategic Goals and Aligned Milestones

STRATEGIC GOAL 1

Design and validate low-cost, high-performance multiplex nucleic acid/antigen point-of-care diagnostics to enable rapid detection of coronavirus infections

MILESTONES

YEAR 1–3

01 Develop and validate high-resolution multiplex rapid antigen / nucleic acid detection lateral flow assays for coronaviruses with high risk of pandemic.

02 Develop and standardize rapid nucleic acid detection platforms for coronaviruses.

03 Determine the correlate of infectiousness.

STRATEGIC GOAL 2

Build next-generation serological and T-cell based detection platforms

MILESTONES

YEAR 1–3

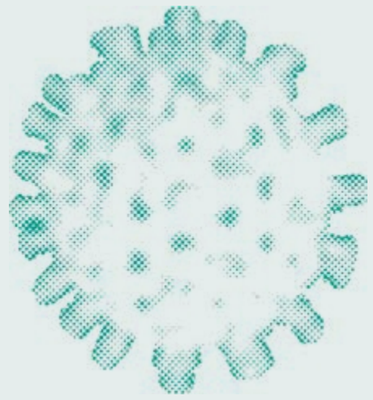
01 Validate antigen/antibody and T-cell based assays for detection of both known and novel coronaviruses across human and animal samples.

YEAR 3–5

01 Develop high resolution lab-based serological and T-cell based platforms for specific coronavirus functional antibody / T-cell detection.

02 Develop and harmonise protocols for multiplex antibody detection / T-cell based detection assays for rapid detection of coronavirus infection.

03 Generate & distribute harmonized standards for coronaviruses using hyperimmunized animal sera or humanized monoclonal antibody cocktails.



STRATEGIC GOAL 3

Establish harmonized sequencing protocols to facilitate global genomic surveillance

MILESTONES

YEAR 1–3

01 Publish and adopt global standards for coronavirus sequencing and metadata.

02 Ensure at least 80% of submitted coronavirus sequences include a complete metadata set, uploaded via a platform that enables researchers to submit CoV sequences and returns linked virus phenotype information.

03 Launch automated risk-scoring pipelines that combine genomic and ecological indicators.

YEAR 3–5

01 Establish a coordinated network of test validation and tap in virtual network of biobanking.

Priority Areas/ Activities

- **Explore** new pan-coronavirus diagnostic platforms, preferably in multiplex and point-of-care (portable) format, capable of detecting existing known and unknown coronaviruses
- **Develop** harmonized protocols and guidelines for diagnosis of existing or novel coronavirus infection
- **Establish** enhanced and standardized sequencing protocols and bioinformatics pipeline for detection and metadata reporting
- **Deploy** a real-time global surveillance platform integrating coronavirus genome repositories, antigenic characterization pipelines, and standardized clinical phenotypes
- **Develop** affordable, highly sensitive and specific prototype for multiplex point-of care or near-patient rapid diagnostic tests for coronavirus infections
- **Generate** international reference or standard for calibration of diagnostic tests for coronavirus

05. Medical Countermeasures

Primary Challenges

- **Limited breadth of vaccines and antivirals:** Current coronavirus vaccines and antivirals are largely strain-specific, with limited cross-protection against divergent or emerging lineages. The rapid antigenic evolution of coronaviruses, particularly within the spike protein, continues to undermine the durability and breadth of immune protection. Developing broad-spectrum vaccines and therapeutics that remain effective despite viral mutation and immune escape remains one of the most pressing challenges in pandemic preparedness.

- **Inadequate pre-clinical models:** Existing pre-clinical models do not accurately replicate the complexity of human coronavirus disease, spectrum of clinical manifestations, transmission dynamics, or immune protection. Small-animal models often fail to mimic the human upper-airway environment, leading to discrepancies in correlates of protection such as neutralizing antibody levels, mucosal IgA, and T-cell responses. Moreover, these models seldom incorporate comorbidities common in human populations, limiting their predictive value. There is also a lack of validated animal models for assessing mucosal and transmission endpoints, which are critical for evaluating next-generation vaccines.

- **Incomplete understanding of mucosal immunity:** A comprehensive understanding of mucosal immunity in coronavirus infection and vaccination remains elusive. The mucosa is the primary site of viral entry, yet the correlates of mucosal protection—such as the roles of secretory IgA, tissue-resident memory T cells, and local cytokine responses—are poorly defined. The ability to induce strong and durable mucosal immunity through vaccination is not well understood, constraining the development of vaccines capable of preventing infection and transmission at the portal of entry.

- **Global health inequities:** Persistent global inequities in access to diagnostics, therapeutics, and vaccines continue to undermine pandemic response efforts. LMICs often experience significant delays in obtaining countermeasures due to limited manufacturing capacity, logistical constraints, and economic barriers. These inequities exacerbate the impact of emerging coronavirus threats and highlight the urgent need for equitable distribution mechanisms, regional manufacturing hubs, and affordable countermeasure platforms that can be rapidly deployed worldwide.

- **Delays in countermeasure availability:** There remains a substantial lag between the identification of novel coronavirus threats and the availability of safe and effective vaccines or therapeutics. These delays are magnified when new variants exhibit antigenic profiles distinct from known lineages, requiring extensive reformulation and testing. Supply chain and manufacturing bottlenecks, particularly for biologics requiring cold-chain storage, further hinder timely deployment. The absence of agile manufacturing systems and harmonized regulatory pathways compounds these challenges, slowing global response readiness.

Key Needs

- **Broadly protective vaccines and antivirals:** There is a pressing need to develop next-generation vaccines and antivirals that provide broad and durable protection across coronavirus genera, (including alphacoronaviruses). Future vaccine platforms should incorporate additional viral proteins beyond the spike antigen to expand immune breadth and target conserved regions less prone to mutation. Low-cost versions suitable for LMICs and formulations enhanced for older adults, such as single-cycle RNA replicons expressing immunomodulators should be explored to promote both equity and efficacy in pandemic response.

- **Monitoring for antiviral and antibody resistance:** Continuous surveillance of emerging variants and zoonotic coronaviruses for resistance to existing antivirals and monoclonal antibodies is critical. Incorporating resistance monitoring into global genomic surveillance systems would improve preparedness and allow rapid adaptation of treatment strategies.

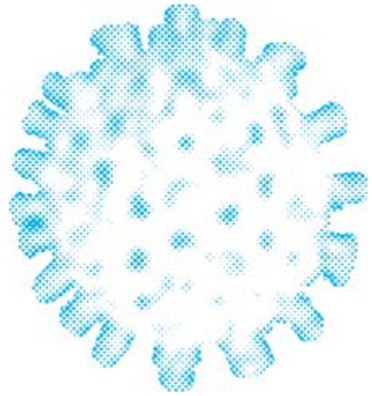
- **Enhancing mucosal immunity and local protection:** Strategies that effectively elicit mucosal immunity, particularly within the nasal and upper respiratory tissues, are vital for preventing infection and transmission. Innovative delivery approaches, such as intranasal vaccines or mucosal adjuvants could help generate localized IgA and tissue-resident T-cell responses. Establishing standardized methods to measure mucosal immune responses in pre-clinical and clinical trials would accelerate progress in this field.

- **Stage-specific therapeutic targeting:** Therapeutic development should account for the distinct immunopathological phases of coronavirus infection. Early interventions may focus on inhibiting viral replication, whereas later phases may benefit from immunomodulators that temper excessive inflammation and tissue injury. Tailoring therapeutics to these stages could enhance efficacy and minimize adverse outcomes, particularly in severe or chronic cases.

- **Standardization of clinical endpoints and reference reagents:** Harmonizing clinical endpoints, platforms, and standardizing reagents used in vaccine and therapeutic evaluation is essential for comparability and regulatory efficiency. Consistent definitions of efficacy and clinical outcomes across studies will enable more accurate cross-trial assessments. Building global infrastructure for standardized reagents, assays, and biobanks will strengthen the collective capacity to evaluate medical countermeasures during outbreaks.

- **Shared reference panels and collaborative frameworks:** Developing open-access virus and cell line panels, along with reference monoclonal antibody sets, would facilitate benchmarking of vaccine and antiviral breadth. Public–private partnerships and international collaborations can accelerate the development pipeline and promote transparent data sharing. Establishing such shared frameworks will be crucial for rapid and coordinated responses to future coronavirus threats.

Knowledge Gaps



- **Broaden research focus beyond betacoronaviruses:** Coronavirus research remains heavily concentrated on betacoronaviruses, leaving other genera understudied. Expanding research to less-studied lineages is necessary to anticipate and mitigate future spillover risks.

- **Limited understanding of durable mucosal immunity:** The mechanisms required to reliably and safely induce durable mucosal immunity remain poorly understood. The persistence and quality of mucosal memory B- and T-cell responses, and their correlation with long-term protection, are not well characterized. This gap limits the development of vaccines that can effectively block viral entry and transmission.

- **Lack of mechanistic correlates of protection:** There is currently no well-defined set of mechanistic correlates of protection for either transmission prevention or severe disease. T-cell–based correlates, particularly those relevant to mucosal immunity, remain underexplored. The absence of reliable markers hinders the evaluation of vaccine efficacy and complicates the comparison of candidate platforms.

- **Limited bridging of correlates across species:** Existing data from animal models do not reliably predict outcomes in humans, particularly regarding mucosal protection and transmission. Establishing preclinical correlates that can be translated from small animals to nonhuman primates, and eventually to humans, would greatly enhance predictive modelling and reduce clinical development timelines.

- **Poorly characterized non-RBD targets:** Conserved non-RBD regions of the Spike protein, such as the S2 fusion peptide and HR1–HR2 domains, are potential targets for broad protection. However, their immunogenicity, structural dynamics, and ability to elicit protective responses are insufficiently understood. Better characterization of these targets could open avenues for universal coronavirus vaccine design.

- **Sparse data on antiviral resistance evolution:** Data on how coronaviruses develop resistance to drugs targeting conserved enzymes such as RNA-dependent RNA polymerase (RdRp) and key proteases (e.g. 3CLpro) are limited. Systematic long-term studies and integrated genomic surveillance are needed to anticipate resistance pathways and inform the rational design of next-generation antivirals.

Strategic Goals and Aligned Milestones

STRATEGIC GOAL 1

Identify strategy for new generation antivirals and vaccines

MILESTONES

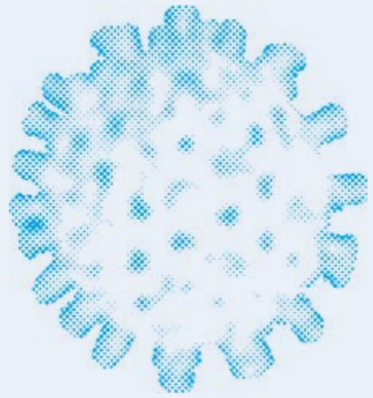
YEAR 1–3

01 Develop new direct acting antivirals against conserved viral proteins or host proteins required for their lifecycles.

YEAR 3–5

01 Develop pan-sarbecovirus/merbecovirus vaccines. Advance S2-focused antigens (fusion peptide/stem helix/HR1-HR2, etc.) or non-spike protein-based antigens into clinical trials with preclinical broad neutralization panels. Measure antibody protection through non-neutralizing mechanisms.

02 Develop pan-coronavirus vaccines.



STRATEGIC GOAL 2

Develop and validate mucosal vaccines

MILESTONES

YEAR 3–5

01 Measure vaccine-induced mucosal immune responses (IgA, IgG, memory B cells, memory T cells) in humans, by mucosal vaccine candidates as well as conventional vaccine candidates.

02 Measure and define the durability of mucosal vaccine immune responses in mucosal tissues in humans.

03 Model-to-human bridge trial – Conduct prospective study correlating animal mucosal endpoints with human nasal viral load and shedding in a paired intranasal trial.

04 Develop mucosal vaccines - Validate ≥1 mucosal correlates of protection and perform at least one head-to-head intranasal booster trial powered on shedding/upper-airway viral load.

Priority Areas/ Activities

- **Extend** research to other coronaviruses including alphacoronavirus and deltacoronavirus
- **Define** roles for mucosal vaccines in prime/boost strategies and for preparedness for novel coronaviruses
- **Identify** new direct acting antiviral targets
- **Investigate** conserved drug targets among coronaviruses
- **Develop** vaccine and antibodies with broad anti-coronavirus activity
- **Develop** intranasal vaccines to induce mucosal immunity
- **Develop** targeted product profiles for broad vaccines, small molecule therapeutics, and large molecule therapeutics
- **Compile** a biorepository for standardized reagents that include test reagents and benchmark controls
- **Design** mucosal assay trials. Run a blinded, multi-site validation of nasal IgA/IgG and neutralization outcomes with standardized reference materials
- **Develop** physiological-relevant *in vitro* platforms, such as primary cells or organoid models, for medical countermeasures evaluations

06. Biosafety and Biosecurity

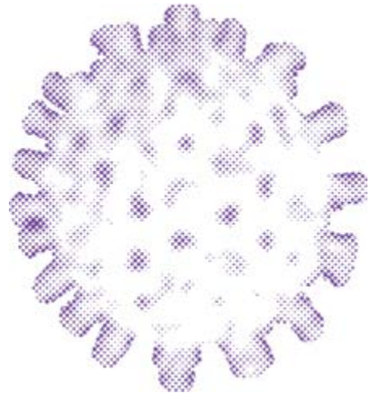
Primary Challenges

- **Harmonize equivocal guidelines across countries on handling coronaviruses:** Globally, many research groups are performing surveillance for novel zoonotic coronaviruses based on the hypothesis that some are at risk for emerging and causing disease in humans. Nations (and even institutions within one nation) may require different containment levels for working with human and zoonotic coronaviruses leading to difficulties in sharing samples, protocols, and replicating results.
  The research community needs harmonized recommendations for safe sample collection, storage, and handling including:
  1) Best practices in safely performing surveillance for novel zoonotic coronaviruses, 2) Safe collection recommendations for storage and tracking of samples, 3) PPE usage by surveillance groups, including sharing, outreach and education for locals who are primarily non-scientists participating in these efforts.
- **Sequence-based risk assessment:** Many novel coronaviruses are identified through sequencing only. How can we assess the risk of these coronaviruses based solely on metagenomic data? (i.e. What are the best practices for risk determination in the absence of virus isolate?).
- **Criteria for risk assessment:** Determining the risk of zoonotic coronaviruses infecting and causing pathogenesis in humans. There are multiple criteria that need to be accounted for when assessing risk: 1) Samples may come from humans, in which case we have some basis for determining human risk. How to assess the risk of novel viruses (or virus sequences) found in animals? 2) If starting at BSL2, what prompts a move to BSL3? And if starting at BSL3, what prompts a move to BSL2? 3) Recognition that very small genomic changes may have very large phenotypic effects and can impact pathogenicity.
- **Genetic manipulation of coronaviruses:** Awareness of the need to consider both local and national regulations for any genetic manipulation of replicating coronaviruses. The need to assess change-of-function concerns and ability to perform these experiments based on national policy as well as international policies.

Key Needs

- **Practical and safe guidelines:** Practical guidelines for biosafe surveillance sample collection and other field work.
- **Robust tools to assess risk:** Reliable and biosafe models and standards for assessing the ability of CoVs to infect human cells. Development of more robust surrogate systems to safely advance science without always requiring live viruses.
- **Appropriate protection for researchers:** Recommendations for guidelines and safety / mitigation plans for live virus and recombinant virus work, including health monitoring suggestions for CoV researchers, possibly including standard vaccinations.
- **Global coronavirus expertise panel:** Geographically diverse experts/ researchers/laboratories capable of providing advice and/or laboratory space to safely isolate novel human and/or zoonotic CoVs. CoV expert suggestions for safe handling and sharing of existing and future human and zoonotic CoVs to provide groundwork for countries developing rules and requirements for CoV research.

Knowledge Gaps



- **Risk to humans:** The risk of future zoonoses into the human population is unknown. Active surveillance in wild animals revealed a wide diversity of CoVs that includes close relatives to known human seasonal CoVs as well as to known high pathogenic CoVs. However, species, organ, and cell tropism are unknown, making it difficult to assess the risk of transmission to humans or intermediate hosts.
- **Viral factor-based risk assessment:** The spike protein is the major determinant of species, organ, and cell tropism. However, we know for only very few CoVs if the spike protein can facilitate infection of human cells.
- **Bats and other intermediate reservoir host species:** Zoonotic transmission of CoVs can happen directly from the reservoir species or through intermediate hosts. To reduce the risk of zoonotic transmission, we need to know about reservoir species and potential intermediate host species. Bats are known as an important reservoir to harbour many diverse CoVs. However, our knowledge concerning other CoV reservoir species and which animal species are likely candidates for intermediate hosts is limited. This knowledge is important for biosafe field work, surveillance, sample handling and sample transportation.
- **Tissue tropism and translation towards pathogenicity:** The organ, tissue and cell tropism are major determinants of pathogenicity and transmissibility of coronaviruses. There's a knowledge gap concerning the pathogenicity in humans and transmissibility between humans for almost all animal CoVs. This information is particularly of importance concerning CoVs in the bat reservoir and for advising about biosafety when handling animal samples or working with virus isolates.
- **Other factors beyond spike protein:** Viral replication, transmission, and pathogenicity are impacted by host factors beyond the spike protein. Our knowledge of species/ host restriction factors is limited as well as our knowledge concerning dependency factors and their expression in relevant target tissues and cells in humans.

- **Standardized global biorepository:** Sample materials and virus isolates are frequently exchanged between laboratories. To ensure biosafe exchange of materials, including virus isolates, we need to be able to assess associated risks and provide guidelines. Virus isolates that are shared between laboratories may not be fully characterized concerning the genome sequence and basic replication phenotypes. Repositories could fill this gap and ensure biosafe sharing of materials.

- **Harmonized global biosafety guidelines:** Internationally, legislation, regulations, and the role of biosafety committees differ. In order to ensure international adherence to biosafety guidelines and to identify best practices, regulations that are implemented in different countries should be analyzed and harmonized as far as possible.

Strategic Goals and Aligned Milestones

STRATEGIC GOAL 1

Establish a coronavirus biosafety working group to recommend safe handling guidelines

MILESTONES

YEAR 1–2

01 Review and obtain an overview of biosafety and biosecurity regulations in different countries pertaining to coronaviruses. Identify best practices and formulate recommendations.

02 Formulate recommendations for (i) field work/surveillance safety, (ii) safe handling of novel virus isolates, (iii) safe handling of animal and human samples, (iv) health monitoring guidelines for laboratory staff, field workers, and local citizens involved with CoV surveillance efforts.

STRATEGIC GOAL 2

Establish a risk assessment panel of coronavirus experts

MILESTONES

YEAR 1–2

01 Develop guidelines for how to perform risk assessments of zoonotic CoVs including emphasizing the importance of assays that do not require live virus replication to improve: 1) global access, and 2) safe handling.

02 Estimate the risk of current and novel CoVs, including recommendations for BSL2, BSL2+ or BSL3 handling for consideration by the CoV biosafety working group.

Priority Areas/ Activities

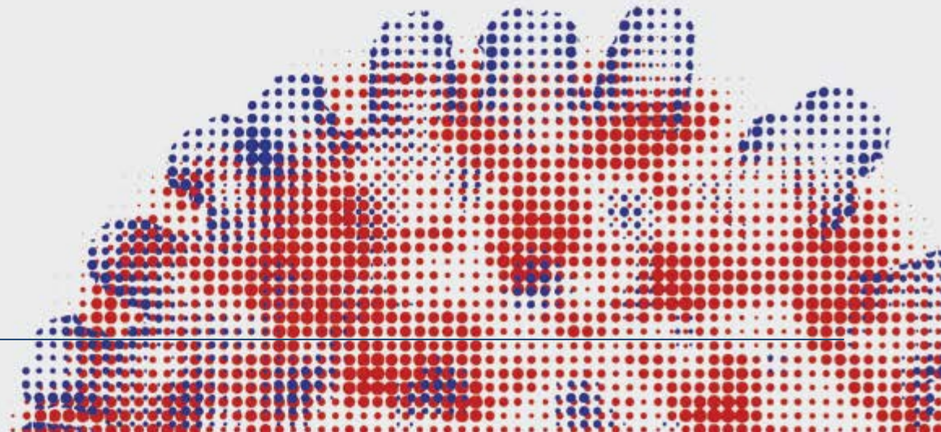
- **Establish** biosafety guidelines for sampling materials in the field taking into consideration the most common routes of transmission
- **Assess** risk based on the susceptibility of human cells to animal coronavirus infection as an important parameter for risk assessment
- **Assess** risk based on species specificity of animal coronaviruses
- **Harmonize** biosafety and biosecurity practices
- **Account** for all at-risk coronaviruses. Recommendations for sample handling and working with coronaviruses under conditions of specific biosafety levels are missing for most coronaviruses

Acknowledgements

The production of this roadmap has been coordinated by the Singapore PREPARE CORC-CoV working group. The CORC-CoV is led by Linfa Wang, team members include Marcus Mah, Neha Dikshit, Ramona Gutierrez, and David Lye. The consultation process to gather input was conducted with all CORC-CoV members (>150). Each of the six themes has been directed by two global theme leaders, Ecology & Transmission: Edward Holmes and Supaporn Wacharapluesadee; Virus Biology: Linda Saif and Mart Lamers; Immune Responses: Stanley Perlman and Yunlong Cao; Detection Technologies: Alessio Lorusso and Chee Wah Tan; Medical Countermeasures: Pamela Bjorkman and Hin Chu; Biosafety & Biosecurity: Volker Thiel and Lisa Gralinski.

The Programme for Research in Epidemic Preparedness and REsponse (PREPARE) aims to support and strengthen Singapore's key essential research capabilities, translational platforms, and expertise to develop tools, methods and products that can be tapped on to detect, respond to, and contain future infectious disease threats. PREPARE is a national programme under the Communicable Diseases Agency (CDA), and is supported by the Singapore Ministry of Health through the NMRC Office, MOH Holdings Pte Ltd under the National Epidemic Preparedness and Response R&D Programme Funding Initiative (MOH-001041/MOH-001073/MOH-001446).

Visit www.prepare.gov.sg for more information.



References

Mah MG, Dikshit N, Gutierrez RA, Lye DC, Wang LF. The threat of another coronavirus pandemic: How are we preparing for it? *Lancet Microbe*. 2025. 101308.

Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and sources of endemic human coronaviruses. *Adv Virus Res*. 2018. 100:163-88.

Global genomic surveillance strategy for pathogens with pandemic and epidemic potential, 2022–2032. Geneva: World Health Organization. 2022. License: CC BY-NC-SA 3.0 IGO.

Global framework to define and guide studies into the origins of emerging and re-emerging pathogens with epidemic and pandemic potential. Geneva: World Health Organization. 2024. License: CC BY-NC-SA 3.0 IGO.

Holmes EC. COVID-19 - Lessons for zoonotic disease. *Science*. 2022. 375:1114-1115.

Kawasaki J, Suzuki T, Hamada M. Hidden challenges in evaluating spillover risk of zoonotic viruses using machine learning models. *Commun Med*. 2025. 5(1):187.

Koopmans M, Csabai I, Remondini D, Snary E, Aarestrup F. Artificial intelligence and One Health: potential for spillover prediction? *Lancet Infect Dis*. 2025. S1473-3099(25)00498-0.

Liu D, Young F, Lamb KD, Robertson DL, Yuan K. Prediction of virus-host associations using protein language models and multiple instance learning. *PLoS Comput Biol*. 2024. 20(11):e1012597.

Peel AJ, Ruiz-Aravena M, Kim K, Scherting B, Falvo CA, Crowley DE, et al. Synchronized seasonal excretion of multiple coronaviruses coincides with high rates of coinfection in immature bats. *Nat Commun*. 2025. 16(1):6579.

Pekar JE, Lytras S, Ghafari M, Magee AF, Parker E, Wang Y, et al. The recency and geographical origins of the bat viruses ancestral to SARS-CoV and SARS-CoV-2. *Cell*. 2025. 188(12):3167-3183.e18.

Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, Lloyd-Smith JO. Pathways to zoonotic spillover. *Nat Rev Microbiol*. 2017. 15(8):502-510.

Anthony SJ, Johnson CK, Greig DJ, Kramer S, Che X, et al. Global patterns in coronavirus diversity. *Virus Evol*. 2017. 3(1): p. vex012.

Wells, HL, Bonavita CM, Navarrete-Macias I, Vilchez B, Rasmussen AL, et al. The coronavirus recombination pathway. *Cell Host Microbe*. 2023. 31(6): p. 874-889.

Pyrc K, Sims AC, Dijkman R, Jebbink M, Long C, et al. Culturing the unculturable: human coronavirus HKU1 infects, replicates, and produces progeny virions in human ciliated airway epithelial cell cultures. *J Virol*. 2010. 84(21): p. 11255-63.

Johnson BA, Xie X, Bailey AL, Kalveram B, Lokugamage KG, et al. Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis. *Nature*. 2021. 591(7849): p. 293-299.

Hoffmann M, Kleine-Weber H, Pohlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. *Mol Cell*. 2020. 78(4): p. 779-784 e5.

Mykytyn AZ, Breugem TI, Riesebosch S, Schipper D, van den Doel PB, et al. SARS-CoV-2 entry into human airway organoids is serine protease-mediated and facilitated by the multibasic cleavage site. *Elife*. 2021. 10.

Lamers MM, Mykytyn AZ, Breugem TI, Wang Y, Wu DC, et al. Human airway cells prevent SARS-CoV-2 multibasic cleavage site cell culture adaptation. *Elife*. 2021. 10.

Ogando NS, Dalebout TJ, Zevenhoven-Dobbe JC, Limpens R, van der Meer Y, et al. SARS-coronavirus-2 replication in Vero E6 cells: replication kinetics, rapid adaptation and cytopathology. *J Gen Virol*, 2020. 101(9)925-940.

Klimstra WB, Tilston-Lunel NL, Nambulli S, Boslett J, McMillen CM, et al. SARS-CoV-2 growth, furin-cleavage-site adaptation and neutralization using serum from acutely infected, hospitalized COVID-19 patients. *J Gen Virol*, 2020. 101(11)1156-1169.

Otieno, J.R., J.L. Cherry, D.J. Spiro, M.I. Nelson, and N.S. Trovao, Origins and Evolution of Seasonal Human Coronaviruses. *Viruses*. 2022. 14(7).

Matharoo-Ball B, Diop M, Kozlakidis Z. Harmonizing the COVID-19 sample biobanks: Barriers and opportunities for standards, best practices and networks. *Biosaf. Health*. 2022. 4, 280–282.

Azizi A, Manak M, Bernasconi V. The CEPI centralized laboratory network for COVID-19 will help prepare for future outbreaks. *Nat. Med*. 2023. 29, 2684–2685.

Azizi A, Kamuyu G, Spencer P, Bernasconi V. Future directions in combating outbreaks at CEPI Centralized Laboratory Network. Hum. *Vaccines Immunother*. 2025. 21, 2561458.

Jian F, Wang J, Yisimayi A, Song W, Xu W, et al. Evolving antibody response to SARS-CoV-2 antigenic shift from XBB to JN.1. *Nature*. 2025. 637, 921–929.

Bestion E, Halfon P, Mezouar S, Mège JL. Cell and Animal Models for SARS-CoV-2 Research. *Viruses*. 2022. 14, 1507.

Lee CY, Lowen AC. Animal models for SARS-CoV-2. *Curr Opin Virol*. 2021. 48, 73–81.

Hu C, Wang Z, Li R, Hao Y, Zhu M, et al. Pre-existing anti-HCoV-OC43 immunity influences the durability and cross-reactivity of humoral response to SARS-CoV-2 vaccination. *Front Cell Infect Microbiol* 2022. 12.

Hasan Z, Masood KQ, Veldhoen M, Qaiser S, Alenquer M, et al. Pre-existing IgG antibodies to HCoVs NL63 and OC43 Spike increased during the pandemic and after COVID-19 vaccination. *Heliyon*. 2025. 11, e42171.

Ortega N, Ribes M, Vidal M, Rubio R, Aguilar R, et al. Seven-month kinetics of SARS-CoV-2 antibodies and role of pre-existing antibodies to human coronaviruses. *Nat. Commun*. 2021. 12, 4740.

Cao Y, Jian F, Wang J, Yu Y, Song W, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. *Nature*. 2023. 614, 521–529.

Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019. 17(3): 181-92.

Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020. 382(8): 727-33.

Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020. 395(10224): 565-74.

Cho SY, Kang JM, Ha YE, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. *Lancet*. 2016. 388(10048): 994-1001.

Xiu L, Binder RA, Alarja NA, et al. A RT-PCR assay for the detection of coronaviruses from four genera. *J Clin Virol*. 2020. 128: 104391.

Vlasova AN, Diaz A, Damtie D, et al. Novel Canine Coronavirus Isolated from a Hospitalized Patient With Pneumonia in East Malaysia. *Clin Infect Dis*. 2022. 74(3): 446-54.

Lednicky JA, Tagliamonte MS, White SK, et al. Independent infections of porcine deltacoronavirus among Haitian children. *Nature*. 2021. 600(7887): 133-7.

Tang G, Liu Z, Chen D. Human coronaviruses: Origin, host and receptor. *J Clin Virol*. 2022. 155: 105246.

Vijgen L, Keyaerts E, Moes E, et al. Complete genomic sequence of human coronavirus OC43: molecular clock analysis suggests a relatively recent zoonotic coronavirus transmission event. *J Virol*. 2005. 79(3): 1595-604.

Shehata AA, Attia YA, Rahman MT, et al. Diversity of Coronaviruses with particular attention to the Interspecies Transmission of SARS-CoV-2. *Animals (Basel)*. 2022. 12(3).

Mura M, Trignol A, Le Dault E, Tournier JN. Lessons for medical countermeasure development from unforeseen outbreaks. *Emerg Microbes Infect*. 2025. 14, 2471035.

Sharma K, Syeda S, Shah SM, Kori SA, Shetty P, et al. Overcoming barriers to medical countermeasures: Strengthening global biosecurity. *Hum Vaccin Immunother*. 2025. 21, 2483043.

Kumar M, Baig MS, Bhardwaj K. Advancements in the development of antivirals against SARS-Coronavirus. *Front Cell Infect Microbiol*. 2025. 15, 1520811.

Menezes Pinto N, das Chagas Mendonca MR, da Silva Santos J, Dos Santos Ferraz CM, Santos Oliveira D, et al. Lessons learned from the COVID-19 pandemic: the intranasal administration as a route for treatment - a patent review. *Pharm Dev Technol*. 2025. 30, 400–416.

Kiyono H, Ernst PB. Nasal vaccines for respiratory infections. *Nature*. 2025. 641, 321–330.

Jin G, Wang R, Jin Y, Song Y, Wang T. From intramuscular to nasal: unleashing the potential of nasal spray vaccines against coronavirus disease 2019. *Clin Transl Immunology*. 2024. 13, e1514.

Lau KTK, Xiong X, Wong CKH, Au ICH, Lui AYC, et al. Comparative Effectiveness of Antivirals and Monoclonal Antibodies for Treating COVID-19 Patients Infected With Omicron Variant: A Systematic Review and Network Meta-Analysis. *Influenza Other Respir Viruses*. 2024. 18, e70065.

Chen Y, Zhao X, Zhou H, Zhu H, Jiang S, et al. Broadly neutralizing antibodies to SARS-CoV-2 and other human coronaviruses. *Nat Rev Immunol*. 2023. 23, 189–199.

Mambelli F, de Araujo A, Farias JP, de Andrade KQ, Ferreira LCS, et al. An Update on Anti-COVID-19 Vaccines and the Challenges to Protect Against New SARS-CoV-2 Variants. *Pathogens*. 2025. 14.

Barouch DH. Covid-19 Vaccines - Immunity, Variants, Boosters. *N Engl J Med*. 2022. 387, 1011–1020.

Holmes EC and Harvey E. Diversity and evolution of the animal virome. *Nature Rev Micro*. 2022. 6:321-334.

Grange ZL, Goldstein T, Johnson CK, et al. Ranking the risk of animal-to-human spillover for newly discovered viruses. *PNAS*. 2021. 118 (15) e2002324118.

Hulswit RJG, de Haan CAM, Bosch, BJ. Coronavirus spike protein and tropism changes. *Advs in Virus Research*. 2016. 96 (29-57).

V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nature Rev Micro*. 2021. 19 (155-170).

Ruiz-Aravena M, McKee C, Gamble A, Lunn T, Morris A, et al. Ecology, evolution and spillover of coronaviruses from bats. *Nature Rev Micro*. 2021. 20 (299-314).

Kane Y, et al. Animal models, zoonotic reservoirs, and cross-species transmission of emerging human-infecting coronaviruses. 2023. *Annual Rev of Animal Biosci*. 11 (1-31).

Lamers MM and Haagmans BL. SARS-CoV-2 pathogenesis. 2022. *Nature Rev Micro*. 20 (270-284).

Hidalgo P, Valdes M, Gonzalez RA. Molecular biology of coronaviruses: an overview of virus-host interactions and pathogenesis. 2021. *Boletin Med Hos Infant Mex*. 78 1:41-58.

Escudero-Perez B, Lalande A, et al. Host-pathogen interactions influencing zoonotic spillover potential and transmission in humans. 2023. *Viruses*. 15 (3), 599.

Brackman M, Zysset D, et al. The WHO BioHub system: experiences from pilot phase. 2023. *BMJ Global Health*. 8.

A framework for tomorrow's pathogen research. *Bulletin of the atomic scientists*. 2024.

Laboratory biosafety manual. 4th Edition. Geneva: *World Health Organization*. 2020. License: CC BY-NC-SA 3.0 IGO.

World Health Organization

World Health Organization
Avenue Appia 20
1211 Geneva
Switzerland

www.**who**.int

R&DBlueprint
Powering research
to prevent epidemics

PREPARE