

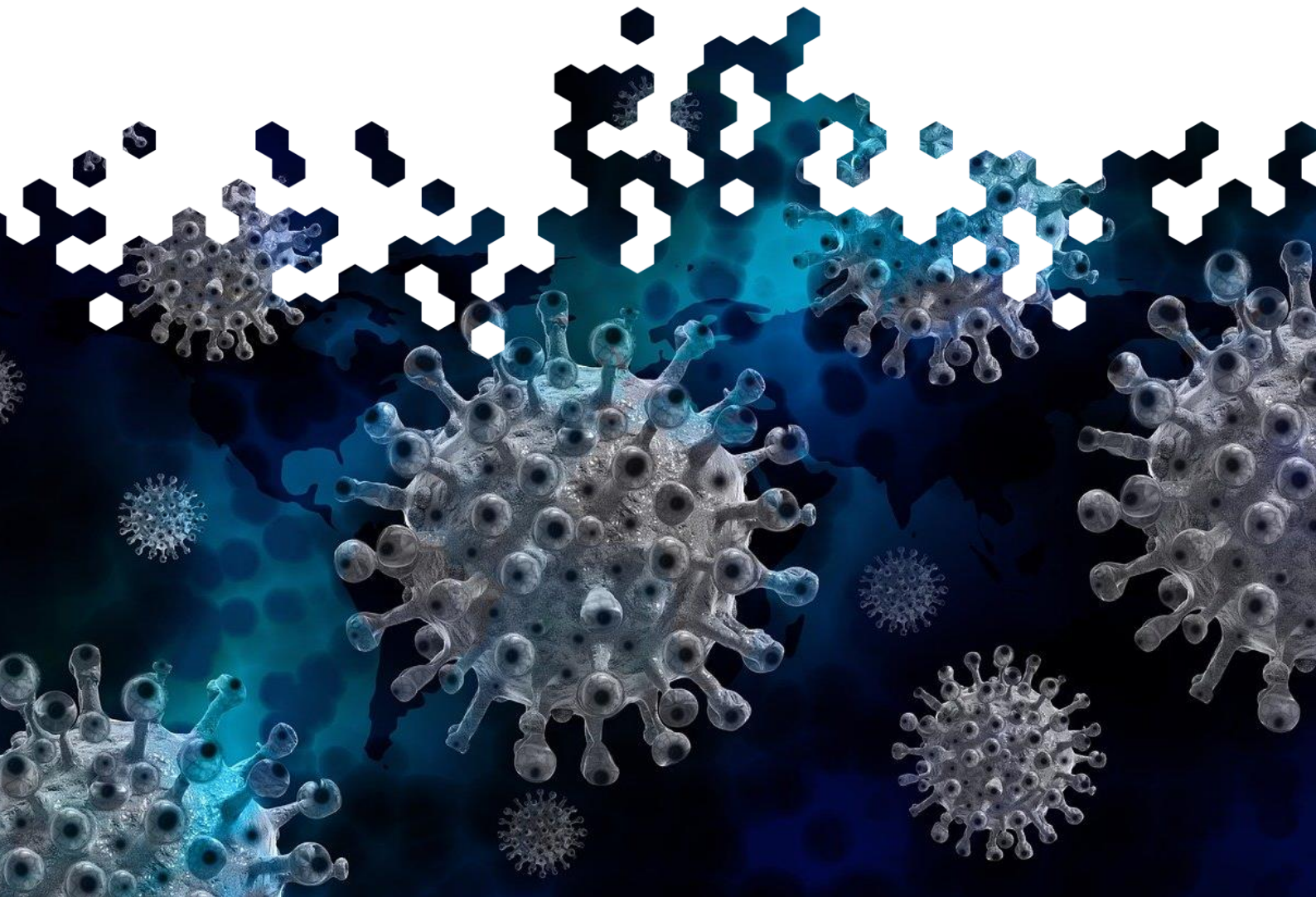


**STAR
IDAZ**

International
Research
Consortium on
Animal Health

Report of the STAR IDAZ workshops on coronavirus research roadmaps development

Online workshops
2, 8 and 10 October 2024



STAR IDAZ IRC is the 'Global Strategic Alliances for the Coordination of Research on the Major Infectious Diseases of Animals and Zoonoses - International Research Consortium'. It is a global consortium that brings together funders and programme owners for research on animal health to maximise funding for coordinated animal health research. To achieve its aim, STAR IDAZ facilitates networking among funders, researchers, industry experts, policymakers and other stakeholders to collaborate on research and innovation in the field of infectious animal diseases. This document was produced by SIRCAH, the Scientific Secretariat of the STAR IDAZ IRC.

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More information on STAR IDAZ IRC can be found at www.star-idaz.net

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Introduction

[STAR IDAZ International Research Consortium](#) (IRC) is a global initiative to address the coordination of research programmes at international level in the area of animal health and in particular infectious animal diseases including zoonoses (STAR IDAZ – Global Strategic Alliances for the Coordination of Research on the Major Infectious Diseases of Animals and Zoonoses).

Coronaviruses have been identified as a high priority research topic for the STAR IDAZ IRC, and through the identification of research gaps we aim to speed up the delivery of improved control methods for animal coronavirus outbreaks. The COVID-19 pandemic had a major impact at a global level, and a series of workshops were held in collaboration between STAR IDAZ IRC and the [UK International Coronavirus Network](#) (UK-ICN) in May 2023. During the Vaccine and Therapeutics workshop experts discussed post-COVID-19 experience, highlighting the vaccine knowledge derived from the pandemic that is applicable or not to animal coronavirus vaccinology. In a second workshop on Diagnostics and Surveillance experts agreed that coronavirus surveillance would benefit from improved cross-species knowledge and risk-based sampling; discussions focused on detection of recombinants. A third workshop on Epidemiology acknowledged that knowledge on epidemiology of coronaviruses is essential to predict, prevent and manage disease outbreaks. A report of these workshops can be found [here](#).

The results of the workshops held in May 2023, which was supported by a survey of 56 international participants, were used to inform the coronavirus research roadmap development workshops held online in October 2024 for the development of STAR IDAZ IRC coronavirus research roadmaps for disease control strategies, diagnostic tools and vaccine development. The research roadmaps will highlight the steps that need to be taken to focus research efforts where it is most needed, to improve efficiency in response to future animal coronavirus outbreaks.

2 October, 2024 - Workshop 1: Vaccines development

Facilitators: Dr Dalan Bailey / Dr Elma Tchilian

8 October 2024 - Workshop 2: Diagnostics

Facilitators: Prof. Linfa Wang / Dr Alessio Lorusso

10 October 2024 - Workshop 3: Control strategies

Facilitators: Prof. Wim van der Poel / Dr Karl Ståhl

Report of the workshops

More than 40 international experts participated in the 3 workshops on coronaviruses held online on 2, 8 and 10 October 2024 (agendas provided in Annex 1).

A set of generic STAR IDAZ research roadmaps were utilized to draft a coronavirus research roadmap for: 1) candidate vaccine development, 2) diagnostic test development, and 3) control strategies. The roadmaps, with the defined end-product/solution located on the right, provide a way of visualizing complex problems and breaking them down into manageable components by mapping the significant steps that have to be taken and problems that have to be solved in order to deliver the tools or strategies required.

Draft research roadmaps, based on the results of the previous gap analysis workshop, were circulated before the meetings and the experts were asked to review the draft highlighting the most important and urgent research needs.

The steps in the roadmaps, referred to as 'leads', were fulfilled with a body of scientific knowledge outlined by a research question ('What are we trying to achieve?', 'What is the problem we are trying to solve?') and broken down into more specific areas:

- Challenges ('What are the scientific and technological challenges/knowledge gaps needing to be addressed')
- Possible solution routes ('What approaches could/should be taken to address the Research Question?')
- Dependencies ('What else needs to be done before we solve this need')
- State of the art ('Existing knowledge including success and failures').

During the workshops the moderators presented the roadmaps and additional inputs were provided by participants. At the end of each session a prioritization of the research needs was conducted utilizing a brainstorming interactive tool. After the workshop the roadmaps were left available for further refinements and to map details of current state of the art research projects.

Among the needs raised, that will be reported in the research roadmaps, were the need to improve affordability, and for research to develop delivery methods and long-term immunity of next generation vaccines (e.g. mRNA and viral vector vaccines), in particular the requirement for research on mucosal delivery systems. Research on antigen design and novel adjuvants for use across species were also highlighted, as was the need for research on multivalent vaccines.

The diagnostics workshop highlighted the need for development and validation of panCoV detection assays (virus and antibody-based) and standardization of protocols across laboratories. In recognition of the wide range of species that can act as reservoirs of coronaviruses, the need for species-independent serological test platforms was highlighted as was the need for a better understanding of host responses in the different species.

Participants of the control strategies workshop acknowledged the need for a better understanding of the socioeconomic drivers for disease emergence, and of the effect of climate change, landscape change and wild animal trade for disease emergence in wildlife and spillover to livestock/humans. A research priority highlighted in this workshop was to increase understanding of species susceptibility. In addition, future research should aim to determine effective and affordable vaccination strategies linked with surveillance and testing systems.

The complete list of research needs identified in the three workshops will be reported in the research roadmaps that, after validation by the STAR IDAZ Scientific Committee, will be published on the STAR IDAZ website.

Forward look

In alignment with the STAR IDAZ strategy, the main objective of the roadmaps is to support international research coordination and cooperation on coronaviruses. The STAR IDAZ IRC Partners, as research funders and programme owners, will endeavour to align their research programmes in order to address the research gaps identified in the roadmaps.

Acknowledgement

STAR IDAZ wish to thank each of the following coronavirus experts, who participated in the roadmap development workshops:

Last name	Name	Country
Alfonso	Pastor	CUBA
Alharbi	Naif	Saudi Arabia
Ali Ishag	Hassan	UAE
Bailey	Dalan	UK
Decaro	Nicola	Italy
Delahay	Dez	UK
Francis	Michael	UK
Haagmans	Bart	The Netherlands
Hashem	Anwar M	Saudi Arabia
Horton	Daniel	UK
Ishag	Hassan	?
Jaru-ampornpan	Peera	Thailand
Karlson	Erik	Camboge
Keller	Markus	Germany
Khalafalla	Abd Elmalik	UAE
Lacasta	Anna	Kenya
Lorusso	Alessio	Italy
Loy	John Dustin	USA
Markotter	Wanda	South Africa

Last name	Name	Country
McElhinney	Lorraine	UK
Penzes	Zoltan	Hungary
Pickering	Bradley	Canada
Quinteros	José A.	Australia/Chile
Rabbani	Masood	Pakistan
Roberts	Helen	UK
Saif	Linda	USA
Sol	Asaf	Israel
Stähl	Karl	Sweden
Tarlinton	Rachael	UK
Tchilian	Elma	UK
Thakur	Nazia	UK
Van der Poel	Wim	The Netherlands
Vervelde	Lonneke	The Netherlands
Wang	Linfa	Singapore
Wang	Qihong	USA
Whittaker	Gary	USA
Wood	James	UK
Yang	Shanshan	China

Annex 1: Agendas of the workshops

STAR-IDAZ workshop on coronavirus research roadmap – Vaccine

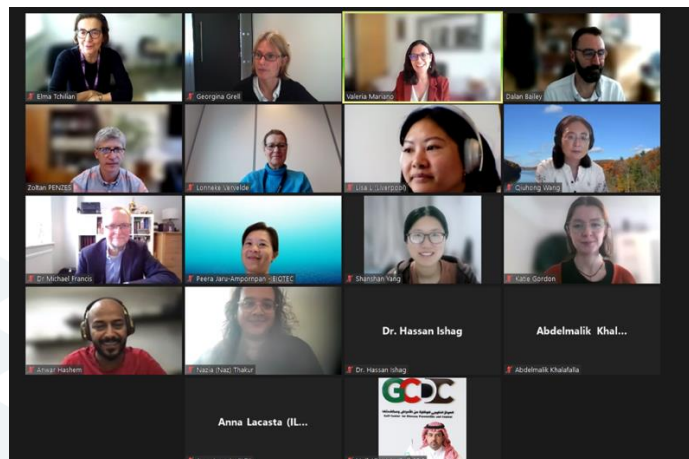
Wednesday 2 October 2024

13:00 – 15:00 CET – *Different Time Zone

13.00-13.20*	Welcome and Introduction on STAR-IDAZ IRC	Valeria Mariano, WOA, STAR IDAZ Secretariat
13.20-13.40	Focused discussion on research roadmap: part 1	Dalan Bailey, Pirbright
13.40-13.50	Priority research needs part 1: voting by online tools & short break	
13.50- 14.10	Focused discussion on research roadmap: part2	Elma Tchillian, Pirbright
14.10- 14.20	Priority research needs part 2: voting by online tools	
14.20-14.30	Break	
14.30-14.50	Focused discussion on research roadmap: part3	Elma Tchillian, Pirbright
14.50-15.00	Priority research needs part 3: voting by online tools	
15.00-15.20	Focused discussion on research roadmap: part 4	Dalan Bailey, Pirbright
15.20-15.30	Priority research needs part 4 by online tools: voting by online tools	
15.30-15.40	Wrap up and ongoing research projects	Dalan Bailey, Pirbright
15.40-16.00	Conclusion and next steps	Valeria Mariano, WOA, STAR IDAZ Secretariat

Objectives of the meeting:

To identify and prioritise research needs to develop vaccines for coronaviruses



STAR-IDAZ workshop on coronavirus research roadmap – Diagnostics

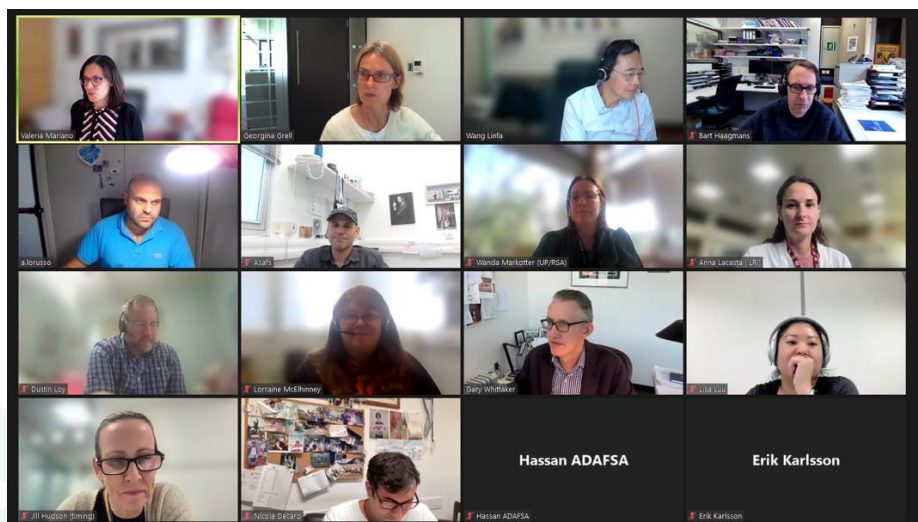
Tuesday 8 October 2024

13:00 – 15:00 CET – *Different Time Zone

13.00-13.20*	Welcome and Introduction on STAR-IDAZ IRC	Valeria Mariano, WOAAH, STAR IDAZ Secretariat
13.20-13.40	Focused discussion on research roadmap: part 1	Alessio Lorusso, IZSAM
13.40-13.50	Priority research needs part 1: voting by online tools & short break	
13.50- 14.10	Focused discussion on research roadmap: part 2	Linfa Wang, Duke Global Health Institute
14.10- 14.20	Priority research needs part 2: voting by online tools	
14.20-14.30	Break	
14.30-14.50	Focused discussion on research roadmap: part 3	Linfa Wang, Duke Global Health Institute
14.50-15.00	Priority research needs part 3: voting by online tools	
15.00-15.20	Focused discussion on research roadmap: part 4	Alessio Lorusso, IZSAM
15.20-15.30	Priority research needs part 4 by online tools: voting by online tools	
15.30-15.40	Wrap up and ongoing research projects	Linfa Wang, Duke Global Health Institute
15.40-16.00	Conclusion and next steps	Valeria Mariano, WOAAH, STAR IDAZ Secretariat

Objectives of the meeting:

To identify and prioritise research needs to develop diagnostic tests for coronaviruses



STAR-IDAZ workshop on coronavirus research roadmap – Control Strategies

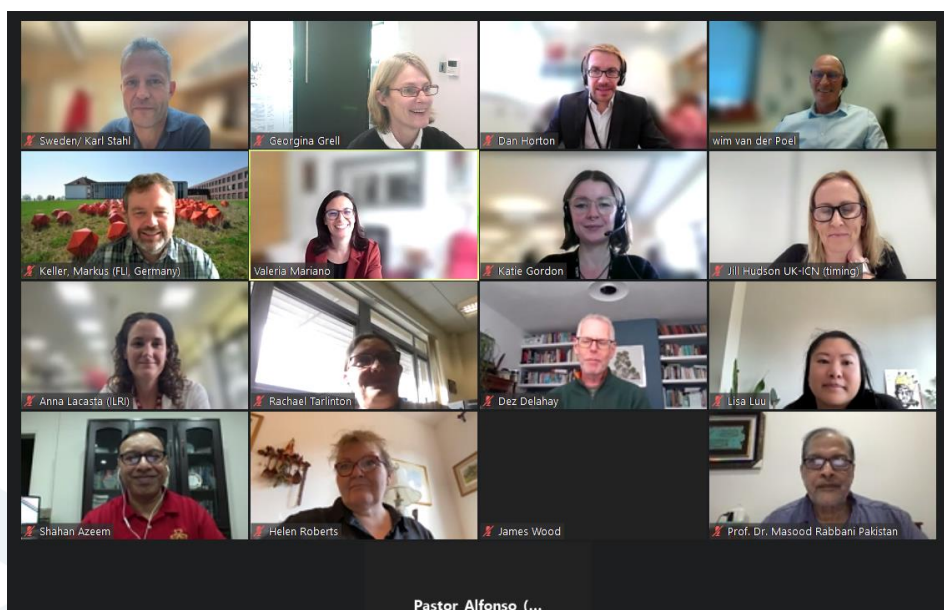
Thursday 10 October 2024

13:00 – 15:00 CET – *Different Time Zone [here](#)

13.00-13.20*	Welcome and Introduction on STAR-IDAZ IRC	Valeria Mariano, WOAH, STAR IDAZ Secretariat
13.20-13.40	Focused discussion on research roadmap: part 1	Karl Ståhl
13.40-13.50	Priority research needs part 1: voting by online tools	
13.50- 14.10	Focused discussion on research roadmap: part 2	Wim Van der Poel
14.10- 14.20	Priority research needs part 2: voting by online tools	
14.20-14.30	Break	
14.30-14.50	Focused discussion on research roadmap: part 3	Karl Ståhl
14.50-15.00	Priority research needs part 3: voting by online tools	
15.00-15.20	Focused discussion on research roadmap: part 4	Wim Van der Poel
15.20-15.30	Priority research needs part 4: voting by online tools	
15.30-15.40	Wrap up and ongoing research projects	Wim Van der Poel
15.40-16.00	Conclusion and next steps	Valeria Mariano, WOAH, STAR IDAZ Secretariat

Objectives of the meeting:

To identify and prioritise research needs for coronavirus control strategies



Annex 2

Synopsis of Discussion 1: Vaccine Types and Vectors for Animal Coronavirus Vaccines

The discussion focused on the various types of vaccines and vectors currently in use or under development for animal coronaviruses. Participants highlighted the successes, challenges, and potential future directions for vaccine platforms, particularly in livestock, pets, and poultry.

Types of vaccines in use

The group noted the wide range of commercial vaccines for animal coronaviruses, including both inactivated and live attenuated vaccines. These vaccines have been successfully deployed in animals like cattle, dogs, cats, poultry, and pigs. However, the majority target the spike (S) protein of coronaviruses, inducing strong antibody responses. While these vaccines reduce disease severity, their ability to prevent infection entirely remains limited, particularly in the face of emerging viral variants.

Live attenuated vaccines are favoured for their ability to stimulate both B- and T-cell responses, along with mucosal immunity, which is critical for respiratory pathogens. However, concerns about the safety of live attenuated vaccines were raised, particularly regarding their potential for reversion to virulence or recombination with wild-type viruses, which could lead to the emergence of new, virulent strains. Inactivated vaccines, while safer, often require adjuvants to boost immune responses and typically induce weaker cellular immunity.

Advances in vaccine platforms

Emerging vaccine technologies were discussed, including viral vector vaccines and RNA-based vaccines (such as mRNA). While RNA vaccines have garnered attention due to their rapid development and efficacy in human COVID-19 vaccines, concerns were raised about their cost, affordability, and application in large-scale animal vaccination programmes. The group also acknowledged that while RNA vaccines hold promise for inducing broader immunity, particularly against variants, their role in animal coronaviruses remains in early stages.

Viral vector vaccines, which have been used effectively in poultry, were highlighted as another promising platform. These vaccines can elicit robust immune responses and could be tailored to include multiple strains of a virus. The discussion suggested that vector vaccines may provide a middle ground between traditional live attenuated vaccines and newer technologies like mRNA.

Mucosal immunity and delivery methods

Mucosal immunity was identified as an important factor in controlling coronaviruses, particularly for respiratory diseases. Vaccines delivered via mucosal routes (e.g., intranasal or oral vaccines) are more effective at providing localized immunity at the site of infection. Traditional intramuscular vaccines, while effective in generating systemic immunity, may not provide sufficient mucosal protection, which is key to preventing viral transmission.

The discussion also touched on the ease of administration for different vaccines. In some cases, traditional vaccines, such as spray vaccines for poultry, remain highly practical due to their cost-effectiveness and ease of deployment. In contrast, newer technologies like mRNA vaccines would require more complex delivery systems, such as injections, making them less practical for large-scale use in livestock.

Challenges and knowledge gaps

Participants identified several key challenges in the development of new vaccine platforms:

- **Strain variation:** the need for vaccines that provide cross-protection against multiple viral strains was emphasized. The current reliance on strain-specific vaccines leaves gaps in protection when new variants emerge.
- **Safety concerns:** the risk of reversion or recombination in live attenuated vaccines is a persistent issue. Rational design of vaccines through reverse genetics, which can decrease mutation rates and limit recombination, was proposed as a potential solution.
- **Regulatory and public acceptance:** the group also discussed challenges related to regulatory approval and public perception, particularly concerning genetically modified organisms (GMOs). While new technologies may offer improved safety and efficacy, they often face stricter regulatory hurdles and potential resistance from consumers, particularly in the animal agriculture sector.

Future directions

The consensus was that while traditional vaccines (inactivated and live attenuated) will remain central to controlling animal coronaviruses, there is significant interest in exploring next-generation vaccines such as mRNA and viral vector vaccines. Further research is needed to improve affordability, delivery methods, and long-term immunity (both mucosal and systemic).

The participants concluded that collaborative, multi-disciplinary efforts between academia, industry, and regulatory bodies are crucial to accelerating the development and deployment of these vaccines. Ensuring that vaccine platforms are adaptable to emerging variants, safe for large-scale use, and acceptable to both regulators and the public will be key to success.

Synopsis of Discussion 2: Attenuated Organisms, Adjuvants, Expression Systems, and Protective Antigens

This discussion covered several key aspects of vaccine development for animal coronaviruses, including the role of genetically attenuated organisms, the use of adjuvants, the importance of expression systems for antigen production, and the identification of protective antigens beyond the widely studied spike protein.

Attenuated organisms and genetic resistance

Participants began by discussing the potential for creating genetically modified animals that are resistant to coronavirus infections through strategies like receptor knockouts or selective breeding. While this approach is technologically feasible, concerns were raised about the unintended consequences of making animals refractory to one virus while potentially increasing their susceptibility to other pathogens like bacteria or parasites. A more holistic approach was suggested, focusing on enhancing overall resilience rather than making animals resistant to a single virus.

There was also discussion about the economic and commercial implications, especially in the poultry industry, where genetic modifications could impact productivity. For example, genetically modified birds might experience changes in growth rates or yield, which could negatively affect the highly performance-driven industry. In contrast, natural resilience through selective breeding could provide a more balanced approach without altering the animals' broader health profile.

Adjuvants

Adjuvants were highlighted as critical for boosting immune responses, particularly in vaccines that rely on inactivated viruses or subunit vaccines. Concerns about proprietary adjuvants were raised, especially in cases where their use might lock manufacturers into long-term commercial agreements that increase costs or limit flexibility in vaccine development. Participants stressed the need for more research into novel adjuvants that can be used across different species and vaccine platforms, emphasizing the importance of generating both humoral and cell-mediated immune responses.

It was also noted that different adjuvants may be more appropriate depending on the species, with companion animals often requiring different formulations than livestock due to market preferences and performance demands.

Expression systems

The production of viral antigens using various expression systems was another key focus. Participants discussed the use of bacterial, yeast, mammalian, and plant-based expression systems for producing antigens at scale. While mammalian systems offer the highest fidelity in terms of producing correctly folded proteins, they are more expensive and complex to manage at scale. In contrast, bacterial and yeast systems offer cost-effective and scalable solutions but may struggle with producing more complex proteins like the coronavirus spike in its full form.

For livestock vaccines, scalability and cost were noted as key concerns, with participants suggesting that industrially established systems are more likely to be used for large-scale vaccine production due to their lower costs and easier scalability. This is particularly important for mass vaccination campaigns in economically sensitive sectors like poultry and cattle.

Protective antigens

While the spike (S) protein remains the most commonly targeted antigen for coronavirus vaccines, the discussion acknowledged the potential benefits of including other structural proteins, such as the nucleocapsid (N), membrane (M), and envelope (E) proteins, to broaden immune responses. The spike protein alone may not offer sufficient protection across all coronavirus variants, and adding other proteins could lead to stronger cell-mediated immune responses and improve cross-strain protection.

Participants emphasized the need for more research to determine the protective efficacy of non-spike antigens, particularly in achieving broader immunity against different strains and variants. For example, while spike-targeted vaccines can be effective against the homologous virus, adding antigens from the N or M proteins might help stimulate T-cell responses that recognize conserved regions across multiple strains, offering broader protection.

However, the challenge of combining multiple antigens into a single vaccine was also discussed, particularly from a manufacturing and regulatory perspective. Creating multivalent vaccines that target different proteins or strains can complicate the production process and lengthen development timelines.

Challenges and future directions

- **Economic considerations:** in the context of animal production systems, the commercial viability of vaccines is crucial. Participants stressed the importance of developing vaccines that are not only effective but also cost-efficient for industries like poultry and livestock, where margins are tight.
- **Antigen stability:** ensuring that antigens are stable across different conditions, including during storage and administration, is a key challenge. Unstable antigens can lead to reduced vaccine efficacy, particularly in challenging field conditions where cold chain logistics may not be guaranteed.
- **Broadening immunity:** there was a clear consensus that future vaccines need to focus on broadening immune responses, both by targeting additional antigens and by stimulating stronger T-cell-mediated immunity.

Overall, the discussion highlighted the complexity of balancing scientific innovation with commercial viability in developing vaccines for animal coronaviruses. Collaboration between academia, industry, and regulatory bodies will be essential in advancing these technologies and addressing the practical challenges associated with mass vaccination in animal populations.

Synopsis of Discussion 3: Virulence Factors, Immunomodulators, Host Responses, and Mechanisms of Protection

The discussion revolved around several critical aspects of coronavirus pathogenesis and immune responses in animal hosts, focusing on the identification of virulence factors, immunomodulators, the host immune response to natural infection, and mechanisms of both antibody and cell-mediated immunity.

Virulence factors

Participants highlighted the importance of understanding viral virulence factors that contribute to disease severity and transmission. Many virulence factors in coronaviruses are encoded in the 3' end of the genome, which exhibits significant variability across species. The group emphasized the need for systematic approaches, such as using *in vitro* cultures, organoids, and proteomics, to identify and characterize virulence factors in various animal species. Detailed studies have already been conducted on porcine coronaviruses, but many knowledge gaps remain for other species.

The role of non-structural proteins (NSPs) and accessory proteins in modulating host immune responses was also explored. These proteins may vary across different coronaviruses, influencing viral replication, immune evasion, and the severity of infection. Understanding how these proteins interact with host pathways is crucial for identifying potential therapeutic targets and designing more effective vaccines.

Immunomodulators

Coronaviruses employ a range of immunomodulatory strategies to evade host immune responses, such as altering interferon responses or modulating cytokine production. The discussion highlighted the potential of targeting these immunomodulatory mechanisms to enhance vaccine efficacy. The variability of these factors across different coronavirus species complicates the development of broad-spectrum vaccines, necessitating more detailed research to identify universally targeted pathways.

The group also discussed the challenges of using live attenuated vaccines that aim to remove viral immunomodulators. While these vaccines could theoretically provide better protection by allowing for stronger immune responses, there is a risk that excessively attenuated viruses might not replicate enough to stimulate sufficient immunity. Balancing virus attenuation with immunogenicity remains a major challenge in live vaccine development.

Host immune responses

A key point of the discussion was the host immune response to both natural coronavirus infections and vaccines. The importance of generating both antibody-mediated and T-cell-mediated responses was emphasized. Participants noted that most research on coronavirus vaccines has focused on antibody responses, often neglecting the crucial

role of T-cell immunity. In many cases, animals demonstrate protection against disease even in the absence of measurable antibody titres, suggesting a critical role for T-cell responses.

However, the measurement of T-cell responses remains technically challenging, particularly in species other than humans and mice. There was a call for the development of better immunological tools to measure T-cell responses and correlate these responses with protection. The use of interferon assays, cytokine profiling, and single-cell RNA sequencing was suggested as ways to better understand host immune responses in various animal species.

The role of mucosal immunity was also discussed, with several participants advocating for the development of vaccines that target mucosal sites, such as the respiratory and gastrointestinal tracts. Mucosal vaccines have the potential to provide a first line of defense against coronaviruses by preventing viral entry, but more research is needed to optimize their design and delivery.

Mechanisms of protection

Understanding the mechanisms of protection against coronaviruses remains a key research priority. Participants emphasized that future vaccine development should focus on inducing broadly protective immunity that includes both humoral and cellular responses. There was also discussion about the role of non-neutralizing antibodies in protection, particularly through mechanisms like antibody-dependent cellular cytotoxicity (ADCC), which could contribute to viral clearance even when neutralizing antibodies are not present.

Several knowledge gaps were identified, particularly in relation to how protection is conferred in the absence of strong antibody responses. The role of protective T-cell epitopes was highlighted, with calls for more research into identifying and incorporating these epitopes into vaccine design. Additionally, the group acknowledged that while T-cell responses are crucial, excessive T-cell activation could exacerbate disease, as seen in certain coronaviruses like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Striking the right balance between immune activation and control is essential.

Challenges and future directions

- Reagent development: a major challenge discussed was the lack of species-specific immunological reagents, particularly for livestock and wildlife species. The development of high-quality, validated antibodies and cytokine reagents was identified as a priority for improving research and vaccine development.
- Collaboration with industry: there was also discussion about the need for collaboration between academia and industry to develop reagents and immunological tools that are relevant for veterinary applications. The commercial viability of these reagents remains a concern, as companies may not invest in tools with limited profit potential.

The discussion concluded with an emphasis on the need for multi-disciplinary approaches to tackle these challenges, combining insights from virology, immunology, genomics, and vaccine development.

Synopsis of Discussion 4: Virus-Host Interactions, Animal Challenge Models, and Pathogen Genome

The final discussion covered three key topics essential to understanding and controlling animal coronaviruses: virus-host interactions during the viral life cycle, animal challenge models for testing vaccines, and the significance of the pathogen genome in shaping vaccine strategies.

Virus-host interactions

The group emphasized the importance of understanding how coronaviruses enter host cells, replicate, and persist within various animal species. Several aspects of virus-host interactions were discussed, including the virus's ability to switch hosts and tissue tropism (the ability of a virus to infect different tissues or organs). A key challenge highlighted was identifying how coronaviruses evolve to infect new species, particularly in livestock and companion animals, and why certain strains cause severe disease while others do not.

Entry pathways were discussed in detail, with recognition that while some coronaviruses, such as human SARS-CoV-2, have well-defined receptors like ACE2, others in animals, such as infectious bronchitis virus (IBV) in poultry, still lack clearly identified receptors. This presents a challenge in understanding viral pathogenesis and developing targeted vaccines. Additionally, there was discussion on how non-structural and accessory proteins contribute to virus-host interactions, influencing viral replication, immune evasion, and disease severity.

The lack of tools to study early immune responses in livestock species was acknowledged as a significant knowledge gap. Understanding the initial immune reactions during infection, especially in production animals, could help in the design of more effective vaccines that prevent viral persistence and transmission.

Animal challenge models

The discussion also addressed the development and standardization of animal challenge models for testing vaccine efficacy. While there are established models for some animal species, such as poultry, the group acknowledged challenges in accurately representing the natural course of infection in other species, particularly where recombinant viruses may emerge. Standardized challenge models were recognized as critical for ensuring that vaccines can be effectively evaluated across different species and that findings are comparable across laboratories.

Several participants highlighted the difficulty of reproducing the natural transmission cycle of viruses in laboratory settings, particularly for wildlife or reservoir species such as bats, which are thought to harbour many animal coronaviruses. The need for better correlates of protection in animal models was emphasized. For example, in cattle, maternal antibody levels can predict the protection conferred to calves, which could potentially reduce the need for constant challenge experiments in vaccine development.

However, limitations still exist in many species, particularly in measuring the full range of immune responses (including T-cell responses), which are necessary for robust vaccine efficacy assessment. This leads to reliance on antibody titres, which may not provide the full picture of vaccine-induced protection.

Pathogen genome

The discussion concluded with a focus on the importance of genomic sequencing for understanding coronavirus evolution and virulence. There was widespread recognition that while large-scale genomic efforts have been conducted for human SARS-CoV-2, similar initiatives for animal coronaviruses lag behind. The importance of next-generation sequencing (NGS) was highlighted for monitoring the emergence of new variants and understanding genetic mutations that could influence virus transmission and vaccine escape.

One significant topic was the evolutionary pressure exerted by vaccines, leading to potential immune escape variants. In this regard, the ability to track viral mutations in real-time, as done with human COVID-19, was seen as a key tool for future animal vaccine strategies. However, challenges remain in ensuring that genomic data from animal populations is collected and analyzed effectively. Participants suggested that a centralized repository of animal coronavirus sequences could help identify significant genetic changes and guide vaccine updates.

Finally, the use of platform-based vaccines, which can be easily updated with new antigens as the virus evolves, was discussed. This approach could be more cost-effective and practical in addressing the continual evolution of coronaviruses in animal populations.

Conclusion

In summary, the discussion highlighted the critical role of understanding virus-host interactions, improving challenge models, and leveraging genomic sequencing to inform vaccine development for animal coronaviruses. Collaboration between research institutions, industry, and regulatory bodies will be key to addressing these challenges and ensuring that future vaccines are safe, effective, and adaptable to new viral threats.

Annex 3

Synopsis of Discussion 1: Diagnostics, Validation and Technology Optimisation

The discussion revolved around the challenges and goals in developing rapid and reliable diagnostic tests for coronaviruses, particularly focusing on strains with zoonotic and pandemic potential. Participants emphasized the need for a clear understanding of the problem they aim to solve, which is identifying relevant coronaviruses and their strains. They acknowledged the vast diversity of coronaviruses, which complicates diagnostics.

Diagnostics

Key challenges include determining which coronavirus species/strains to prioritize for detection, ensuring accessible and cost-effective testing solutions, and addressing the immune response across different host species. The group also considered the necessity for diagnostics that can cater to both agricultural and companion animals, acknowledging the close human-animal interactions that could pose risks.

The conversation suggested focusing on multi-species diagnostics and exploring pan-coronavirus tests (it can be pan-family, pan-genus, pan-subgenus or pan-clade). Several innovative approaches were proposed, including point-of-care tests, portable laboratory solutions, and improved metagenomic methods for pathogen characterization. The discussion also focused on diagnostic testing of clinical cases and to a lesser extent on virus discovery. In most countries, sample collection in healthy animals/populations could only be achieved under regulated research licences. Ultimately, the team aims to streamline their objectives, clarify the distinctions between diagnostics and discovery, and prioritize efforts based on the potential pandemic risks associated with specific coronaviruses.

Validation

The discussion focused on the validation of coronavirus diagnostics, emphasising the need for effective tools to detect known and unknown coronaviruses, particularly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Participants acknowledged that while coronaviruses are not entirely unknown, new variants or novel viral species pose challenges with respect to test specificity and the choice of matrices.

Key points included the lack of harmonized validation protocols and the necessity for standardized internal controls, particularly for portable polymerase chain reaction (PCR) tools. Issues such as sample integrity and reference materials were highlighted, along with the importance of organizational coordination and public-private partnerships for improving diagnostic accuracy. Overall, the discussion aimed to identify solutions to enhance testing reliability and standardization across laboratories.

Technology optimisation

Key challenges identified included reducing time and costs, understanding cross-reactivity among coronaviruses, and enhancing next-generation sequencing (NGS) technologies for field use. Solutions proposed involved the development of RNA analytical assays, fostering public-private partnerships, and ensuring easier bioinformatics data sharing. Emphasis was placed on harmonizing protocols for sample collection and transportation while minimizing cold chain dependencies. Participants also highlighted the importance of agile transfer processes for clinical materials and building local laboratory capacity to enhance diagnostic capabilities and reduce logistical barriers.

Synopsis of Discussion 2: Disease-Stage Specific and Host Responses

The discussion revolved around the intricacies of host responses to coronavirus infections, specifically focusing on the disease-stage-specific responses and the biomarkers associated with them. Participants emphasised the need for clear definitions and understanding of the terms used in the context of host-pathogen interactions, diagnostics, and the development of effective vaccines and treatments. The challenges of diagnosing asymptomatic infections capable of virus transmission were highlighted, and the conversation underscored the necessity for species-specific research and collaborative efforts.

Disease-Stage Specific Response

The segment on disease-stage-specific responses highlighted the complexity and vagueness in categorizing how different stages of disease manifest in various hosts. Participants argued that this complexity necessitates defining critical questions for research. They express concerns regarding asymptomatic infections that can still lead to virus transmission and subsequent symptomatic infections in other host species, stressing the importance of differentiating between symptomatic and asymptomatic cases. Samples from asymptomatic but infectious hosts may not be collected in the absence of licensed research/surveillance. The discussion touched upon the need for diagnostic development that accurately reflects the various disease stages and suggested focusing efforts on specific coronaviruses rather than broadly categorizing them, as this can help streamline research and diagnostics. A more general diagnostic development pipeline could then be generated from the focused studies.

Host antibody response

The host antibody response section discussed the necessity of developing robust animal models to study coronavirus infections. It pointed out that understanding the immune response in various species is crucial because of the wide variety of animal hosts. Participants emphasised the importance of developing detection platforms and reagents that can assess acute and convalescent phases of infection. They also highlighted the challenges associated with cross-reactivity among different coronavirus species in antibody detection and the need for rapid, easy antibody detection methods. Furthermore, the conversation indicated that while molecular detection methods may be species-independent, T-cell responses present significant challenges, advocating for focused research in this area. On the other hand, a species-independent platform for antibody detection is feasible and it has already been used during the COVID-19 pandemic, but needs more development for use in different animal species.

Host cell-mediated response

Cell-mediated immune responses, particularly involving T cells, play a crucial role in detecting past coronavirus infections. Recent research indicates that T cells can be utilised as powerful diagnostic tools for identifying previous exposures to SARS-CoV-2, even in populations globally, such as in Africa, Asia, and South America. This response is notable because many individuals have shown specific T cell reactivity against coronaviruses that predate SARS-CoV-2, indicating potential cross-reactivity and long-lasting immunity. While these findings are promising, further research is needed to develop practical diagnostic applications, especially concerning T cell biomarkers in both humans and animals.

Synopsis of Discussion 3: Host-Pathogen Interactions and Sample Types

Host-pathogen interactions (including identification of "susceptible", "exposed", "infectious" or "recovered" status)

The discussion revolved around the complexities of diagnosing coronavirus infections and understanding host-pathogen interactions. The speakers outlined four distinct categories related to the host's status: susceptible, exposed, infectious, and immune. Most susceptible hosts may not be identified until they exhibit disease signs following exposure (natural or experimental). A prediction of susceptibility may be possible by detecting host cell receptors where those are known for specific viruses. Exposed hosts can be identified through antibody tests. Infectious hosts can be identified when they actively shed the virus, posing a risk of transmission to other animals. The challenge lies in differentiating between these categories, especially in identifying those who are susceptible or exposed.

The conversation emphasised the need for realistic diagnostic tools for each category, mentioning that serological tests can indicate past exposure, but cross-reactivity between different coronaviruses complicates interpretations. For infectious hosts, traditional PCR methods may not suffice; virus isolation is necessary to confirm active shedding of the virus.

The participants also discussed the potential for using subgenomic RNA detection as a standardized diagnostic method to distinguish between infectious and non-replicating virus states. They noted the importance of this differentiation for better understanding viral transmission and infection dynamics. Overall, the conversation highlighted the challenges in developing effective diagnostics while acknowledging that some methods remain more suited for research than clinical diagnostics.

Sample types

Various sample types are utilized for diagnosing coronavirus infections, with an emphasis on standardized, safe sampling methods and effective transportation protocols. Diagnostic sampling must adhere to regulatory guidelines, which can be challenging due to local policy implications. There are significant distinctions between diagnostic sampling and general surveillance, as the former is focused on symptomatic cases, whereas the latter often involves restrictions, especially in sampling subclinical animals.

An understanding of the pathogenesis in different hosts is pivotal as coronavirus infections may be gastrointestinal for which shedding may be detected in faecal swabs/samples or respiratory for which oropharyngeal swabs/samples may be of greater diagnostic value. Understanding the likely duration of shedding post infection and even post clinical signs would also be useful.

The conversation highlighted the importance of virtual biobanking, where secure data-sharing platforms facilitate collaboration among research entities to track available samples and their associated data. This ensures transparency and aids in developing diagnostic tests, including PCR and antibody assays, by leveraging a network of collected clinical samples to assist in test validation. Ultimately, effective policies and guidelines are essential for enhancing diagnostic sampling practices and fostering collaborative efforts in coronavirus research and surveillance.

Synopsis of Discussion 4: Characterization, Organism Detection and Genetics

The discussion on characterization focused on understanding the genetic, biological, and antigenic properties of major coronaviruses affecting animal and public health.

Characterization

Key research questions include identifying the determinants of virulence and characterizing tissue tropism. The group emphasized the need for standardized tools for biological characterization and the implementation of genomic sequencing strategies to analyze genetic similarities among coronavirus lineages.

To address these challenges, they proposed broad sharing of innovative genetic strategies and the establishment of models to predict viral behaviour based on sequence evolution. Enhancing in vitro and organoid characterization of novel isolates and developing standardized animal models were also highlighted as essential steps.

Organism detection

In the realm of organism detection, the focus was on effective methods to identify coronaviruses across different species. Challenges identified included the cost-effectiveness of sample collection and the sensitivity of detection methods. The group discussed the necessity of field tests and rapid reporting systems to facilitate effective monitoring.

Solutions proposed included low-resource sampling methods, next-generation sequencing (NGS) for field applications, and the development of rapid, sensitive detection techniques. They emphasized the importance of understanding regional ecological specifics to tailor surveillance strategies effectively, as different coronaviruses exhibit varying epidemiological patterns, necessitating targeted approaches to detection and monitoring.

Direct detection

The direct detection section focused on the rapid identification of coronaviruses across various species. Significant challenges in this area include the cultural isolation of diverse coronaviruses, often complicated by low viral loads in field samples and high genome heterogeneity. To enhance detection, there is a need for improved virus isolation systems, broad-range culture collections, and organoids. Modifying existing cell lines to increase sensitivity towards different coronaviruses is also crucial. Understanding the specific cell entry receptors for each coronavirus is essential for advancing detection methods. Addressing these gaps requires sharing resources, training in genetic manipulation techniques, and developing a comprehensive understanding of viral dependencies.

Genetics

The genetics discussion emphasised developing affordable field tests for genetic detection and characterization of coronaviruses. Challenges include genetic similarities among coronavirus lineages, field adaptations, and the need for bioinformatics support for interpreting virulence factors. Proposed solutions involve establishing standardized protocols, developing multiplex PCR methods, and improving purification techniques for sequencing. Effective training in bioinformatics is critical, alongside implementing regulatory measures for data reporting. A systematic approach to linking genetic characterization with risk assessment is necessary for enhancing diagnostics and understanding viral behaviour, ensuring that comprehensive systems for virus characterization are accessible and usable in various global settings.

Final Workshop Summary and Prioritisation

The final session focused on prioritizing research with the most significant impact on coronavirus studies. Participants voted on various research topics, using a thumbs-up system to indicate their preferences. Key findings from the voting revealed a consensus on several critical areas, including the validation and harmonization of pan-coronavirus detection assays and the development of species-independent serological test platforms. Enhanced sequencing technologies for low-quality samples and the standardization of detection protocols were also highlighted as vital.

In addressing urgent research needs, participants identified improvements in pan-coronavirus tests and standardized typing methods as top priorities. Additional urgent areas included the establishment of standardized reagents and proficiency panels, cross-species testing development, and enhanced sequencing and bioinformatics pipelines. The need for broad surveillance tests across different species and sharing negative data were also emphasized, alongside the importance of tech transfer and training among labs. The discussions underscored a commitment to collaborative efforts in virus isolation, characterization, and the establishment of shared guidelines for research, ultimately aiming to improve responses to viral threats. The outcomes will inform an executive summary of research gaps and priorities, guiding future research directions in the field.

Annex 4

Synopsis of Discussion 1: Control Strategies, Socioeconomics, Cost-Benefits, and available tools

The discussion in this section focused on developing control strategies for emerging coronaviruses with zoonotic and pandemic potential. The group emphasized the importance of effective and affordable disease control measures to sustainably prevent spillover from wildlife to domestic animals and to humans.

Control

Participants highlighted the need for early detection, efficient control during outbreaks, and the importance of addressing possible negative consequences of, and affected stakeholders' potential resistance to, traditional control methods such as culling and movement restrictions. Additionally, spillback from livestock to wildlife is a critical challenge, with potential risks for wildlife health, and thus possible negative effects on biodiversity, due to replicated and excreted viruses. The group underscored the importance of examining transmission interfaces to better understand disease dynamics and risks.

The establishment of early warning systems, improving surveillance to understand the occurrence and dynamics of coronaviruses in various regions, and risk mapping to identify crucial interfaces between humans, domestic animals, and wildlife was proposed to catch emerging diseases early. The session concluded with a call for clear communication to policymakers to support the implementation of effective but proportionate strategies.

Socio-economic factors

The discussion focused on the socio-economic drivers influencing disease emergence, particularly at the wildlife-livestock interface. Participants emphasized the importance of understanding these drivers, which include the roles of wildlife, livestock, and pets (including legal or illegal trade of all these categories) in relation to disease dynamics. There was notable concern about the socio-economic implications of livestock and pet management, highlighting the different motivations behind pet ownership and livestock farming.

Stakeholders

Challenges in disease control include social acceptance of control strategies. Participants suggested solutions like social feasibility and acceptability studies. The conversation also addressed the impact of misinformation on public perception, particularly regarding diseases that may not pose significant human health risks. Participants advocated for further research into decision-making processes among policymakers, emphasizing the need to consider risk aversion and funding priorities.

Cost-benefit

The discussion addressed the importance of cost-benefit analysis in implementing control measures for wildlife diseases. Emphasizing the need to demonstrate benefits, participants highlighted the economic impacts on farmers and wildlife managers, who often bear the costs of disease management. Additionally, the ecological damage caused by disease spillback was noted, stressing the need to consider environmental impacts alongside economic factors. Stakeholder acceptance was acknowledged as a crucial element, with a suggestion to integrate relevant points from earlier discussions to enhance the analysis.

Control tools

In this discussion on control tools, participants emphasized the importance of effective communication with stakeholders regarding the benefits of preventive measures, despite challenges in demonstrating immediate cost savings. They noted the significance of surveillance strategies and the need for robust data-driven modelling for animal disease control. Additionally, there was consensus on the necessity of biosecurity measures across livestock, wildlife, and human interactions, alongside addressing environmental impacts, in a 'One Health' framework. The conversation highlighted the integration of technology, such as early detection systems, to improve control measures. Participants also recognized the role of tailored communication strategies to enhance cooperation from pet and livestock owners.

Synopsis of Discussion 2: Genetic Selection, Pathogen Inactivation, Modelling Interventions, Contact and Transmission Networks, Prevalence and Warning Signals

Genetic selection

The discussion revolved around the genetic selection of livestock to enhance resistance to infections and diseases. Participants emphasized the need for improved access to genetic resources, such as high-quality genome sequences and affordable testing for various species, including wildlife and pets. The conversation touched on the importance of understanding both host and pathogen genetics, as well as on the potential for CRISPR technology to create disease-resistant animals. Additionally, there was a proposal to explore natural breeds for their inherent resistance traits and the development of affordable testing tools for assessing genetic qualities in livestock. The need for solutions to address challenges in genetic selection is a key focus.

Pathogen inactivation

The discussion focused on developing effective methods to inactivate viruses in farming settings, including considerations for pets and wildlife. Participants highlighted challenges with regulatory compliance, especially regarding the use of disinfectants and testing protocols. They noted that existing methods work theoretically but face practical difficulties in field situations. A major concern was the reliance on PCR or other molecular tests, which can yield false positives even after disinfection, complicating the declaration of farms as pathogen-free.

Solutions such as optimizing testing facilities and promoting composting as a natural inactivation method in resource-limited countries were suggested as potential approaches to enhance virus control. It was highlighted that pathogen inactivation in laboratory settings requires facilities and expertise for BSL3/CL3 working. Diversity across individual laboratory policies may hinder the standardization practiced for determining pathogen inactivation.

Modelling interventions

Participants emphasized the difficulty of gathering data from wildlife populations to parameterize models effectively. They pointed out the challenges in utilizing fragmented molecular epidemiology data and the necessity for both disease dynamics and risk modelling to understand disease progression and test interventions. Concerns were raised about the unrealistic expectation of predicting which pathogens will emerge and where, with suggestions to focus on modelling resilience and population susceptibility instead. The session concluded with acknowledgment of the complexities involved and the need for better resources and training in this area.

Contact networks and transmission pathways

The discussion focused on understanding and quantifying contact networks and transmission pathways of coronaviruses, particularly in wildlife and their role in spreading the virus within populations. Challenges include insufficient knowledge of wildlife disease occurrences, making it difficult to identify unusual outbreaks, as well as asymptomatic and pre-symptomatic transmission.

Solutions discussed involve improving models of transmission and enhancing data collection on genetic characterisation of wildlife coronaviruses to trace the emergence of new variants. The importance of understanding interactions between wildlife and domestic animals was highlighted to prevent potential outbreaks and ensure effective control strategies.

Prevalence and cost of disease

Key challenges include the high costs of extensive surveillance and difficulty in justifying interventions due to the lack of tangible economic value assigned to wildlife. Participants emphasized the importance of risk analysis for surveillance, standardizing wildlife monitoring, and understanding both short- and long-term disease burdens. Additional points highlight the challenges in measuring disease costs and the pathogen's survival in the environment, which contributes to transmission risks. Overall, effective surveillance and funding remain crucial for managing wildlife diseases and preventing outbreaks.

Warning signals and monitoring

The conversation shifted to the development of effective early warning systems for coronaviruses, emphasizing challenges such as poor surveillance and limited resources. Participants stressed the need to prioritize monitoring interfaces that are likely sources of disease transmission between wildlife, domestic animals, and humans. The value of citizen science in wildlife surveillance was noted as an important contribution. Other discussions highlighted the need for cost-effective, continuous surveillance systems and improved diagnostic tools for wildlife diseases. Additionally, a seasonal pattern of virus outbreaks, raises awareness of environmental influences on disease dynamics.

Synopsis of Discussion 3: Host Range, Vectors, and the Role of the Environment

Host range

The discussion focused on understanding the host range of coronaviruses, aiming to identify factors enabling these viruses to infect various species, including humans. Key challenges highlighted include a lack of cell culture systems and laboratory tools for many host species, hampering research on receptor studies and transmission dynamics. Ethical and financial constraints complicate experimental infections, necessitating alternative methods like cell-culture, in-vitro and ex-vivo models. The need for well-funded studies to differentiate between transient and sustained infections in wildlife populations was emphasised as essential for understanding spillover events and developing effective vaccines.

Wildlife

The discussion focused on strategies to prevent disease spillover (and spillback) between wildlife and humans. Key challenges identified include surveillance limitations and insufficient data. Participants emphasized the need to understand vectors involved in virus transmission and the impact of land use changes on spillover events. They discussed the role of extractive industries, climate change, and biodiversity loss in influencing wildlife behaviour and disease spread. Suggested solutions included raising awareness about the connection between biodiversity loss and disease emergence among the public and stakeholders.

Livestock

Participants highlighted issues like the lack of vaccination in backyard poultry compared to commercial farms, which can contribute to virus shedding. They discussed the challenges livestock face during winter when indoor space is limited, increasing exposure between animals and caretakers. The need for enhanced surveillance and understanding of these dynamics was emphasized to mitigate risks.

Humans

Participants highlighted various challenges, including land use, socio-economic factors, and environmental degradation that increase zoonotic transmission chances. Emphasis was placed on cross-sector collaboration between human and veterinary health. The conversation also stressed the importance of addressing live animal trade as a key factor in pandemic prevention and maintaining high laboratory biosecurity standards. Identifying virus adaptations to humans was considered vital for effective prediction and response to future outbreaks.

Vectors

The conversation focused on the topic of disease vectors in relation to coronavirus transmission. While mechanical vectors were discussed, it was acknowledged that they play a minimal role in coronavirus transmission.

Environment

The discussion shifted to the role of environmental factors, particularly within some farming systems, in the transmission patterns of viruses. Participants highlighted that coronaviruses have the capacity to mutate in various situations. One suggested solution to mitigate risk involves stopping the farming of hyper-susceptible species, such as mink and raccoon dogs, although this approach was not universally accepted. There was consensus that human activities significantly drive the emergence of viruses, including the choice of pet species and the associated legal frameworks. Challenges related to the proximity of farms and the lack of regulations were noted, emphasizing the need for legal frameworks to ensure animal health. The most urgent research area identified was understanding the drivers of the emergence of pathogenic viral strains, particularly those that pose a significant threat to mammals and humans. This focus is essential for anticipating and mitigating future pandemics.

Synopsis of Discussion 4: Host-Pathogen-Environment, Co-Infection, Host Genetics and Pathogen Genome

Host-pathogen-environment interaction

The discussion revolved around various challenges and considerations in understanding host-pathogen-environment interactions, particularly in relation to wildlife and disease management. Participants highlighted the importance of improving the understanding of these interactions to implement effective control methods for disease. A key challenge is identifying the transmission pathways and impacts of environmental factors.

Participants re-iterated the knowledge gaps within the role of wildlife for disease transmission, and that an absence of these data restricts the use of epidemiological modelling. The conversation highlighted the significance of studying wildlife in this context, noting that variations in host responses across species complicate understanding of disease

dynamics. Longitudinal studies in wildlife were particularly emphasized, pointing out the complexities of multi-host interactions in wildlife populations.

Potential solution routes included the development of appropriate *in vitro* models and ex-vivo models for wildlife animals (e.g. organoids or other cell culture systems) for basic study of infectivity in a range of host cells. It is important to note that laboratory adaptations to viral strains can occur, which can be a limiting factor for cell culture models.

The discussion reflected a collaborative effort to tackle the complexities of host-pathogen interactions, emphasizing the need for more robust data collection methods, innovative research approaches, and a focus on wildlife in disease management strategies. The participants recognized the intricate challenges in distinguishing between various disease states and the necessity for long-term studies to inform effective control measures.

Co-infections

The discussion focused on the implications of co-infection in disease transmission and diagnosis, highlighting its impact on recombination and disease expression. Co-infection, whether with viruses or other pathogens, complicates diagnostics, particularly in wildlife, where the pathogen community is often unknown. The conversation emphasized the challenges posed by multiple pathogens in treatment and recovery, especially when antibiotics are used, leading to stress and antibiotic resistance (AMR) issues. The need for whole-genome sequencing for accurate detection was noted, along with the potential of alternatives to antibiotics, such as immunopotentiating agents and probiotics, to manage infections. The importance of understanding the normal host virome and microbiome was stressed for effective diagnosis and treatment strategies.

Host genetics

The discussion centred on how host genetics influence susceptibility to viruses and other variants. It highlighted the role of gene editing and bioinformatics in understanding these genetic factors. Challenges in livestock genetics projects were mentioned, particularly regarding data management and the difficulty farms face in recording and correlating phenotypes with genotypes. The absence of a standardized reporting system for SNP chip data and a public repository for genetic data complicates progress in this area, leading to issues with data accessibility and labelling.

Pathogen genome

The conversation shifted to the pathogen genome, emphasizing the importance of understanding genetic factors that contribute to increased pathogenicity. However, identifying specific genomic components linked to transmission in wildlife animals remains tricky, because of the challenges with a lack of appropriate cell models which restricts our ability to isolate live viruses. The discussion also highlighted the need for BSL3 facilities and expertise to conduct this type of research. Overall, the dialogue underscored the need for effective monitoring and genomic analysis to enhance disease management and better understand viral dynamics.

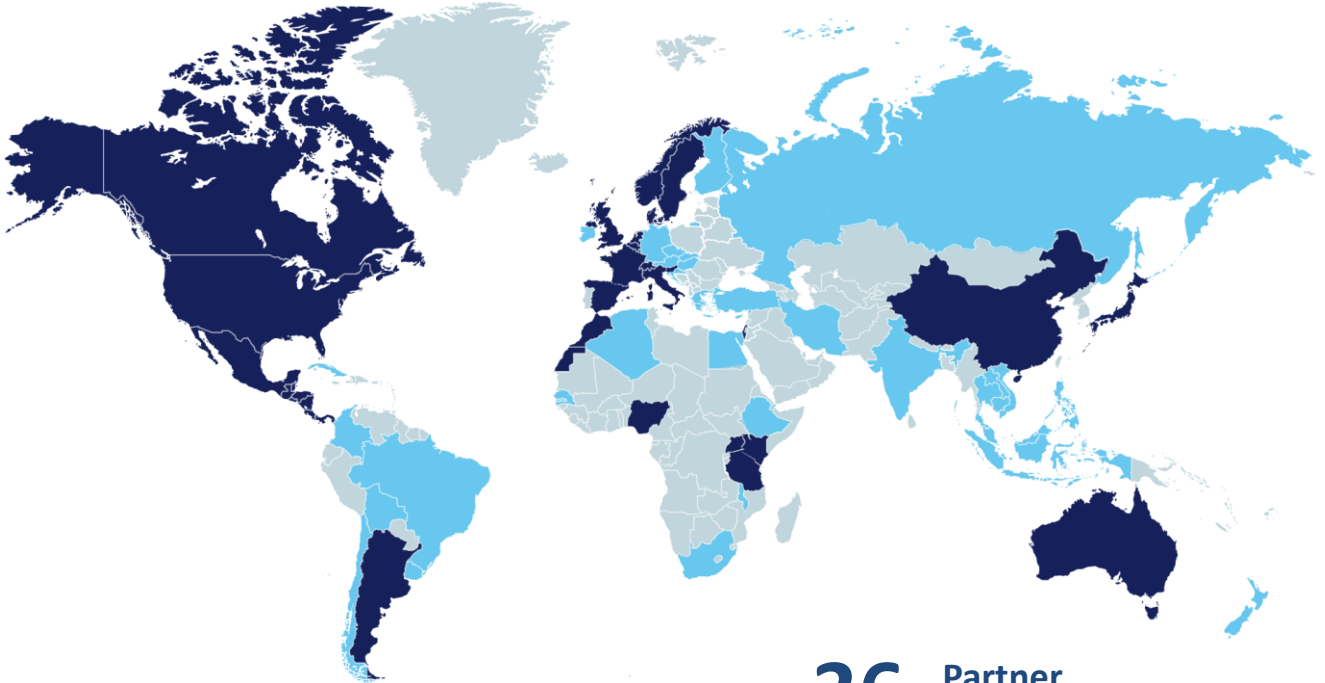


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