Report of the workshops on Coronavirus gap analysis, 26 May Belfast
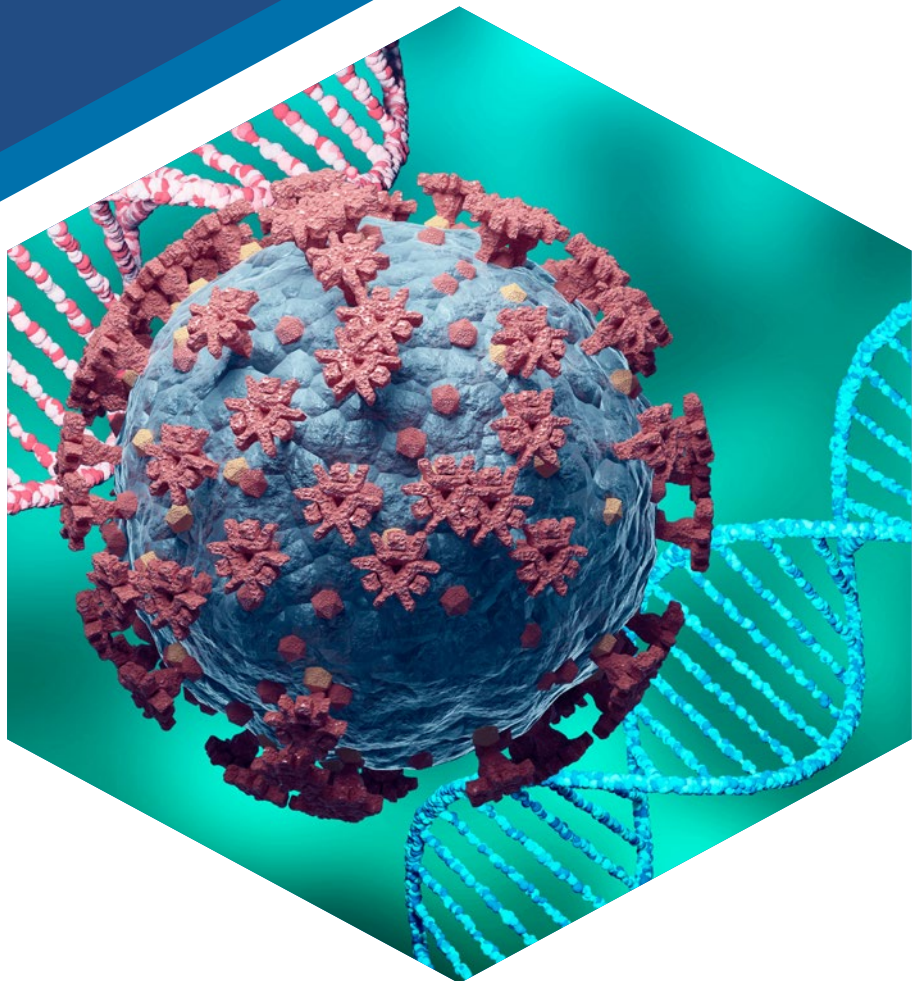
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More information on STAR-IDAZ IRC can be found at **www.star-idaz.net**

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Introduction

STAR-IDAZ International Research Consortium (IRC) and **UK International Coronavirus Network (UK-ICN)** co-organised a workshops aimed at identifying research gaps on coronaviruses. The workshop was held back-to-back to the **International Conference on Livestock, Companion Animals and Wildlife coronaviruses**, sponsored by the UK-ICN and **Ceva Animal Health**.

STAR-IDAZ (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). Research on coronaviruses is a high priority topic for STAR-IDAZ IRC, which aims to speed up the delivery of improved control methods for coronavirus outbreaks.

UK-ICN is a 4-year project (Oct 2021 – Oct 2025), funded by the Biotechnology and Biological Research Council (BBSRC) and the Department of Environment, Food and Rural Affairs (Defra) with the aim to provide a community gateway to facilitate and co-ordinate interactions between members, particularly at the animal-human-environment interface of coronaviruses.

Before the workshops, a survey was circulated among the participants and the UK-ICN network, 56 respondents from 21 countries provided information on state-of-the-art research, challenges and possible solution routes. The findings of the survey fed the three gap analysis workshops focusing on:

Workshop 1: Vaccines and therapeutics

Facilitators: Prof. Louise Cosby / Dr Dalan Bailey / Dr Zoltan Penzes

Workshop 2: Diagnostics and surveillance

Facilitators: Dr Sharon Brookes / Prof. Margaret Hosie / Prof. Alan Radford

Workshop 3: Epidemiology

Facilitators: Prof. Richard Dez Delahay / Prof. Wim van der Poel / Dr Rachael Tarlinton

The results of the workshops will serve 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.

Report of the workshops

International coronavirus experts (n=67) of different disciplines from 11 countries participated in the research gap analysis workshops. Cyril Gay (USDA, STAR-IDAZ IRC Member) and Valeria Mariano (WOAH, STAR-IDAZ Secretariat) introduced the session presenting the STAR-IDAZ IRC and its roadmaps.

Participants, divided into three groups, started their discussion at results of the pre-workshop survey. Moderators facilitated discussions utilizing the World café method. At the end of each session a plenary discussion of main findings was held.

Workshop 1: Vaccines and therapeutics

Moderators: Louise Cosby, Dalan Bailey and Zoltan Penzes

Experts discussed post-COVID-19 experience highlighting what vaccine knowledge is applicable or not to animal coronavirus vaccinology. Spike vaccines had been successful against COVID-19 and their regulation and approval had been relatively quick during the emergency. This proved that the international research community (Academia & R&D pharmaceuticals companies) can team up quickly to respond. Despite the differences in animal vaccine pipelines, the same could potentially apply for any animal coronavirus vaccine, building on spike stabilisation strategies that might be universally applicable.

Consensus was expressed on the fact that a COVID-19 like sterilising immunity from vaccination might not be needed for animal vaccines to control disease. Unfortunately, as per COVID-19, the public's response to innovative vaccines, e.g. mRNA, appears unpredictable and there might be roadblocks to their use in animals destined for human consumption. There was a clear warning from COVID-19 that vaccine use will drive immune selection in the viral population and variant emergence as well as on the importance of breadth immunity generated by the vaccine. It was also clear that despite all efforts and knowledge, it may be difficult to prevent the global transmission of a highly transmissible animal coronavirus; highlighting the need for combined therapeutics.

Clearly one of the biggest differences between animal and human coronavirus vaccine strategies is the age of animals that are likely to be vaccinated and the vaccine administration; indeed, these factors may have a profound impact on efficacy, roll-out, affordability etc. More generally, the cost-effectiveness of vaccination versus control strategies such as slaughter, makes animal vaccination a more complicated solution, as does the threshold for intervention in any particular epidemic.

Concerns were raised about whether the same platform that has been so successful for human COVID-19 vaccination, e.g. mRNA, could be portable to other species, as extensive re-design might be needed at the molecular level for each host species. In addition, the mode of delivery will likely be different, the need for DIVA vaccines is more profound, and the safety thresholds for acceptance and rollout considerably different between humans and animals.

Knowledge gained from COVID-19 that will have an unclear bearing on future animal vaccines were also discussed, such as the importance of side-effects from vaccination and the role of related therapeutics e.g. monoclonals or antivirals. Therapeutics might seem unsuitable for livestock, for example, but would and are being used for companion animals and exotic zoo animals, where the threshold for intervention is much lower. There is also an unclear understanding of how the dependency on T-cell-derived versus humoral immunity in vaccination may differ between hosts, because for some species the basic immunology is not well characterised.

Thus, to support animal vaccine development, basic research is needed to better understand coronavirus immunity, especially longevity and memory cells. Advances are needed to identify correlates of protection (omics technologies may prove useful), associated cell markers and assays should be in place. Currently there is poor availability on those for many species if non-existent at all for others.

Certainly, the production of new vaccines either live attenuated, subunit, mRNA or vector platform to allow rapid insertion of new sequences, should collaborate with diagnostic tools that allow us to distinguish infected from vaccinated animals (DIVA).

Regarding delivery systems, companion animals, wildlife and livestock have different requirements and no universal delivery system could be recognized. If it was considered that the best way for vaccination should be the one mimicking the natural way of infection, such as through intra-nasal (IN) and intra-pulmonary (IP) routes, this cannot be always practicable.

For companion animals the delivery system can take several forms, as animals might be easily handled and owners are inclined to accept higher price technologies for the health of their pets. Unfortunately, the same cannot apply to wildlife and livestock.

Livestock and wildlife delivery systems should take into consideration the possibility for mass vaccination in a cost-effective way. For livestock, mass administration through feed, water and aerosol were discussed. However, additional studies should be carried out to overcome the challenges to produce aformulation that is stable in different environmental conditions (temperature, humidity, pH of water…), effective dosage and cost-effectiveness. Moreover, interaction with other vaccination strategies for booster activity and safety for the animal, operators, environment and future animal products should be further investigated.

Additional difficulties apply for wildlife delivery systems, as vaccines should be administrable without approaching the animal. Considering the main affected wildlife species as bats, deer, birds, mustelids and felids, different administration routes could be contemplated depending on the species. Controls between inter-vaccine interference and safety of vaccination (no toxic effect) for animal, operator, environment and animal products are of paramount importance for the veterinary sector. Last but not least, frequent vaccine updates due to arising mutations/recombination will be essential for effectiveness and are not possible without continuous surveillance of new strains. This requires government co-operation and support for a 'One Health' approach for research and surveillance funding, fostering collaboration among public and private, and animal and human vaccine companies. Social scientists will be of foremost importance to help, not only with vaccine hesitancy, but also on engaging government and public opinion for a One Health approach, increasing acceptance that some diseases have no boarders among countries nor species and finding ways for collaboration.

Workshop 2: Diagnostics and surveillance

Moderators: Margaret Hosie, Sharon Brookes and Alan Radford

Experts agreed that coronavirus surveillance would benefit from an improved cross-species knowledge and risk-based sampling. Currently surveillance is usually conducted by governmental bodies targeting livestock, but it would be beneficial to extend the surveillance targets including companion animals and wildlife. It would be sought to identify animals with unusual patterns of disease (syndromic surveillance) that could be selected for more in-depth analyses. Moreover, an understanding of which species are susceptible to which coronaviruses, and where these species occupy similar habitats, needs further research.

Detection of recombinants is of utmost importance for surveillance of coronaviruses and discussions were held on the best ways to detect them. Recognising that sequencing everything is not feasible, targeted sequencing should be the solution. To be achievable, an increased understanding of virology is essential. In particular, viruses at greatest risk of recombination should be identified, with investigation of the hotspot regions of recombination that could be targeted for PCR amplification and sequencing, or experimental (cell culture) studies. Moreover, studies should be carried out of the species at greatest risk of hosting recombination and by what mechanism.

With respect to diagnostic tests for surveillance, serology for prior exposure to coronavirus antigens could represent a testing approach, effective also for surveillance in multiple species. However, these tests need to be antigen specific, kept up to date for relevant coronaviruses, with high specificity and sensitivity.

Diagnostic tests should be available for use in variable locations, and, pen-side testing, e.g. lateral flow test (LFD), could be developed for a panCoV approach and then followed up for lineage specific, either as advanced pen-side test or later in the laboratory. Other options could be represented by: (i) Find the Agent (FTA) card to transport genome without cold chain, for coronaviruses this needs validation/accreditation; (ii) lab-in-a suitcase PCR/nanopore sequencing, for which further development is still required.

The participants discussed in more depth the usefulness of a panCoV test for high throughput screening, which should be highly sensitive and capable of detecting all samples requiring further testing with more specific tools. A priority is the development of tests that can be used in all host species, rather than detecting all coronaviruses. However, a better understanding of the pathogenesis of infection, to determine the optimal samples for testing, is required. Serological methods most useful for panCoV screening were again recognized as these are cost-effective, sensitive, high throughput, can detect antibodies in all species and can be used in the field.

Genomics (sequencing) and metagenomic analyses cannot be utilised yet as a front-line screen as they are time consuming and expensive. Nevertheless, standardised next generation sequencing (NGS) and bioinformatic methods for more routine recombination detection are needed, particularly those based on long-reads. In addition, more consistent sharing of sequence data and associated metadata, including the possibility of biobanking important samples with their sequence, would facilitate a One Health surveillance. Accessibility to biobanks and open-data sharing should also be improved, as researchers should have access to both positive and negative results for population analyses.

Metagenomic approach to virome/pathobiome could be utilised to characterise pathogens when the traditional diagnosis has not been reached. Training and skills exchange programmes would be beneficial to speed up knowledge sharing and effective surveillance.

The importance of standardisation between labs was highlighted, with particular needs for determining cut-off values and protocols for sampling.

Additional discussed related topics were: (i) the potential use of drone technology to speed up delivery and collection from the field to hubs for processing of samples; (ii) improvement of population/environmental sampling (previous experiences for SARS-CoV-2 could be adapted for other CoVs); and (iii) better use of environmental metadata to enrich predictive models including artificial intelligence/machine learning.

Experts recalled the importance of fostering biosecurity and biosafety in counteracting new variants, changed pathogenicity and susceptibility and to support disease control measures. Finally, in order to improve current disease responsiveness, policies that allow faster approval of new technologies and more flexible regulations/standards based on updated scientific evidence would be of the utmost importance.

Workshop 3: Epidemiology

Moderators: Rachael Tarlinton, Dez Delahay and Wim van der Poel

Knowledge on epidemiology of coronaviruses is essential to predict, prevent and manage disease outbreaks. Emerging infectious disease transmission models are key to identifying new emerging pathways and preparing for the unknown. Nevertheless there are gaps in the models for veterinary coronaviruses and on methods for assessing risks of disease emergence related to land use change.

Sustainable data collection underpins knowledge on disease epidemiology and should take into consideration the involvement of different stakeholders (veterinarians, farmers, citizens, medical practitioners, hospitals, researchers…). Social scientist and incentives should be considered to increase acceptability of data sharing, as well as privacy policy for safe, anonymous collection of data. Appropriate ad hoc communication campaigns should be envisaged.

In the veterinary sector, adapting existing disease surveillance systems in livestock, wildlife and companion animals for coronavirus surveillance could be a way of proceeding. Moreover, surveillance for coronaviruses in under-represented species with significant human contact (e.g. horses) and protocols for syndromic surveillance should be developed. A syndrome definition is essential for horizon scanning alert systems.

For active and passive surveillance, sampling techniques, safe handling and transport should be standardized through the use of guidelines and protocols that should be carefully disseminated by ad-hoc training for staff. This will allow a more coordinated surveillance in different sectors and regions. Definition of target species will be essential as well as communication of test results from different testing setting. QR codes could be utilised to obtain results from the lab and be associated with official reporting of metadata.

Gaps on data integration, analysis and big data analysis and management should be addressed, developing means of collating and integrating disparate coronavirus surveillance data (from wildlife, companion animals and livestock). More can be done on data integration for a One Health approach. Collaboration with the human sector can help in increasing awareness on transmission pathways (human-animal-human), susceptible species, potential reservoirs, carriers, and subsequent control measures that could be undertaken.

Data analysis capacity could be improved using machine learning approaches to recognize significant patterns in coronavirus surveillance data, including sequence data (e.g. warranting further investigation and/or consistent with an emerging issue).

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John Hardham

Katrina Campbell

Ken Lemon

Kyle Perrins

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STAR-IDAZ
International Research
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