World Organisation for Animal Health

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# WOAH Collaborative Centre Reports Activities 2024

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## CENTRE INFORMATION

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|---|---|
| ***Title of WOAH Collaborating Centre** | Viral Genomics and Bioinformatics |
| ***Address of WOAH Collaborating Centre** | Medical Research Council |
| ***Tel:** | +441413302541 |
| ***E-mail address:** | massimo.palmarini@glasgow.ac.uk |
| **Website:** | www.cvr.ac.uk |
| ***Name Director of Institute (Responsible Official):** | Emma Thomson |
| ***Name (including Title and Position) of Head of the Collaborating Centre (WOAH Contact Point):** | Massimo Palmarini |
| ***Name of the writer:** | David L Robertson |

## TOR 1 AND 2: SERVICES PROVIDED

1. Activities as a centre of research, expertise, standardisation and dissemination of techniques within the remit of the mandate given by WOAH

| Category | Title of activity | Scope |
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| | | The CVR has received a funding award from UK Research and |

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| Disease control (true) | UKRI Funding to Tackle Viral Threats and Enhance Epidemic Preparedness | Innovation (UKRI) as part of its work to tackle infections. The funding will enable the establishment of the "One Health Computational Network" (OHCN), an interdisciplinary project focused on predicting, detecting, and preventing viral diseases that threaten humans, animals, and plants. The OHCN will integrate genomic, population, and ecological data to provide new insights and tools for epidemic preparedness, building on the latest advances in computational methods, including artificial intelligence (AI). The research aims to build an innovative interdisciplinary research network that will link datasets across sectors and develop new computational tools to predict the risk and spread of emerging and reemerging viruses across susceptible populations, assess the early detection of emerging viruses at the human-animal interface using enhanced surveillance methods, and predict evolutionary changes in viruses that could affect their phenotype and virulence. By capitalising on the rapid developments in AI and computational biology, the OHCN will help to advance the understanding of viral disease emergence and develop new methods for preventing future outbreaks. The project will include virtual workshops and an in-person symposium to foster interdisciplinary collaboration and identify innovative approaches for epidemic preparedness. |
| Training, capacity building (true) | Viral Bioinformatics and Genomics Training Course | Viral genomics and bioinformatics deliver bespoke training to a range of CVR trainees, including postdoctoral researchers and PhD students, as well as external training to international partners with the aim of stimulating collaborations, supporting capacity building and increasing the CVR's response capacity. The 2024 external Virus Genomics and Bioinformatics course ran in Glasgow in August. The focus is on Linux/Unix command line analysis and using software for analysing NGS sequencing data. Topics include data formats, read cleaning, de novo sequence assembly and reference alignment, consensus and variant calling, multiple alignment and phylogenetics, relevant statistics, metagenomics and virus discovery, and transcriptomics. Attendees were from 5 different countries, including from the US and Israel. 10 out of the 17 attendees were from an organisation affiliated to the WOAH. The team also play a major role in designing and delivering external Viral bioinformatics and genomics courses in collaboration with Wellcome Connecting Science. Since 2022, see https://coursesandconferences.wellcomeconnectingscience.org/our-events/global-training/ |
| Zoonoses (true) | Studies on H5N1 in Cattle | A collaboration between the CVR, the Roslin Institute, the Pirbright Institute and the UK Animal & Plant Health Agency, confirmed that pasteurised cows' milk (the form typically sold for human consumption) should have effectively eliminated any influenza virus in it. The study was in response to an outbreak of H5N1 influenza in American dairy cattle. This ongoing outbreak – the first time a virus of this sort has spread in cattle – led to high levels of potentially dangerous virus being shed into milk in some parts of the USA. This |

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| | | raised concerns about human infections from contaminated milk, including the risk that this could allow the virus to adapt to humans and cause a new pandemic. The study confirmed that without pasteurisation, milk can be a source of infectious influenza viruses, including H5N1 influenza virus. While H5N1 infections of humans are rare, when human infections do occur they have the potential to be extremely serious. |
| Zoonoses (true) | Studies on Blue Tongue Virus | Our BTV online resource includes: a database of BTV sequences linked to isolates, with curated metadata and pre-built multiple sequence alignments for all 10 segments, which may be downloaded in user-defined section, and an analysis tool providing genotyping, and visualisation of submitted segment 2 sequences. (http://btv-glue.cvr.gla.ac.uk/#/home). We are currently advising Marc Guimera and Caroline Wright from the Pirbright Institute on experimental design and associated bioinformatic analyses of superinfections and reassortment in BTV. The CVR team used a naturally occurring vector-borne viral disease of ruminants, bluetongue, as an experimental system to uncover the fundamental mechanisms of virus-host interactions resulting in distinct clinical outcomes. As with most viral diseases, clinical symptoms in bluetongue can vary dramatically. We reproduced experimentally distinct clinical forms of bluetongue infection in sheep using three bluetongue virus (BTV) strains. Infected animals displayed clinical signs varying from clinically unapparent, to mild and severe disease. We collected and integrated clinical, haematological, virological, and histopathological data from each infected and uninfected control animal. We subsequently used machine learning to select the key viral and host processes associated with disease pathogenesis. We identified and experimentally validated five different fundamental processes affecting the severity of bluetongue: (i) virus load and replication in target organs, (ii) modulation of the host type-I IFN response, (iii) pro-inflammatory responses, (iv) vascular damage, and (v) immunosuppression. Overall, we showed that an agnostic machine learning approach can be used to prioritise the different pathogenetic mechanisms affecting the disease outcome of an arbovirus infection (doi: 10.1371/journal.ppat.1012466). |
| | | CVR researchers are part of a consortium taking a multipronged approach to risk assess in depth the current clade 2.3.4.4b H5N1 avian influenza viruses for human spillover infection and pandemic potential. The contemporary viruses will be compared with those of the early 2000s, and with other influenza viruses that did cause human pandemics in 1968 and 2009. State of the art approaches will be used to study virus/host molecular interactions and define how these vary with different isolates of the clade 2.3.4.4b virus and between different host species. The interactions the virus makes with the human airway from children and adults will be considered, to understand who is most likely to be infected by and transmit the virus and who is most at risk of disease. Modelling approaches will be |

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| Zoonoses (true) | Studies on Avian Influenza | incorporated to inform surveillance, asking where and how the virus is most likely to infect mammals that could serve as intermediate hosts. Systems by which mitigations such as antiviral drugs or vaccines could be assessed will be developed, if the virus were indeed to jump species. CVR researchers have also proposed a novel method, using likelihood-free rejection sampling, to evaluate the properties of an outbreak of swine-origin influenza A(H1N2)v in the United Kingdom, detected in November 2023. They have generated historical estimates of the probability that the outbreak had died out in the days following the detection of the first case, with the method suggesting that the outbreak could have been said to be over with 95% certainty between 19 and 29 days after the first case was detected, depending upon the probability of a case being detected. The method requires minimal data to be effective, and while calculations were performed after the event, the real-time application of the method has potential value for public health responses to cases of emerging viral infection (doi: 10.1098/rsif.2024.0168). |
| Zoonoses (true) | Studies on Mpox | Increased human-to-human transmission of monkeypox virus (MPXV) is cause for concern, and antibodies directed against vaccinia virus (VACV) are known to confer cross-protection against Mpox. We used 430 serum samples derived from the Scottish patient population to investigate antibody-mediated cross-neutralization against MPXV. By combining electrochemiluminescence immunoassays with live-virus neutralization assays, we showed that people born when smallpox vaccination was routinely offered in the United Kingdom have increased levels of antibodies that cross-neutralize MPXV. Our results suggest that age is a risk factor of Mpox infection, and people born after 1971 are at higher risk of infection upon exposure. |
| Disease Control (true) | Exploring the Potential of Transmissible Vaccines to Safeguard Ecosystems | Large-scale vaccination of most wild animals will require the development of new technologies that are compatible with the ethical and safety considerations of a variety of stakeholders. Self-disseminating or 'transmissible' vaccines are a potentially viable, but controversial option for to immunize wildlife at unprecedented scales. An inter-sectorial group of researchers, including from the CVR have proposed a series of commitments to advance a common goal of developing transmissible vaccines in a safe, equitable, and transparent manner (doi: 10.1126/science.adn3231). |
| Zoonoses (true) | Virus naming standardisation | Participation in the International Committee on Taxonomy of Viruses (ICTV). David Robertson is a member of the ICTV Executive Committee, since 2020. Richard Orton is a member of the ICTV Herpesvirales study group and Joseph Hughes is a member of the ICTV Parvoviridae study group. |
| | | RABV is a neglected zoonotic disease that causes tens of thousands of human deaths each year, with a near 100% mortality rate after the onset of symptoms. The virus is a member of the Lyssavirus genus, within the Rhabdoviridae family, which is characterised by a single stranded, negative-sense RNA genome. Vampire bat transmitted |

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| Zoonoses (true) | Rabies virus (RABV) genome data resource | rabies virus is an agriculturally important and pervasive zoonotic threat in much of North, Central and South America. Studies have included longitudinal monitoring of and/or field experiments in wild bats and livestock in Peru (since 2007), Belize (since 2014) and Costa Rica (since 2022), viral genomics and phylogenetics, and spatiotemporal modelling of emergence risk. In collaboration with Kirstyn Brunker we maintain an online resource (RABV-GLUE - http://rabv-glue.cvr.gla.ac.uk/#/home) which provides an analysis tool providing genotyping, analysis and visualisation of submitted FASTA sequences. The data is organised in a database of RABV sequences and metadata from NCBI, updated daily and arranged into major and minor clades. Pre-built multiple-sequence alignments of NCBI sequences, can be downloaded in user-defined sections. Notable recent publications from our work on rabies include: doi: 10.1098/rspb.2023.1739; doi: 10.1073/pnas.2216667120; doi: 10.1126/sciadv.add7437; doi: 10.1098/rspb.2022.0860. |

# TOR 3: HARMONISATION OF STANDARDS

2. Proposal or development of any procedure that will facilitate harmonisation of international regulations applicable to the main fucus area for which you were designated

| Proposal title | Scope/Content | Applicable Area |
|---|---|---|
| Standards for high throughput sequencing, bioinformatics and computational genomics | Massimo Palmarini, Ana Da Silva Filipe and Joseph Hughes have updated the "Standards for high throughput sequencing, bioinformatics and computational genomics" chapter for the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. The chapter was sent for the first round of review comments in October. | Laboratory Expertise<br>Training and Education |

3. In exercising your activities, have you identified any regulatory research needs* relevant for WOAH?

Yes

## Research need 1

**Please type the Research need:** Regulatory research is needed on the standardisation and harmonisation of whole viral genomes sequencing and associated standardisation of bioinformatic analyses. Guidelines on the sharing of raw data and transparency of the tools used for consensus sequence generation are needed.

**Relevance for WOAH** Standard Setting,

**Relevance for the Code or Manual** Manual,

**Field** Diagnostics, Vaccines,

**Animal Category**

**Disease:**

**Kind of disease (Zoonosis, Transboundary diseases)** Zoonosis,

**If any, please specify relevance for Codes or Manual, chapter and title**

(e.g. Terrestrial Manual Chapter 2.3.5 - Minimum requirements for aseptic production in vaccine manufacture)

*Answer:*

**Notes:**

*Answer:*

4. Did your Collaborating Centre maintain a network with other WOAH Collaborating Centres (CC), Reference Laboratories (RL), or organisations designated for the same specialty, to coordinate scientific and technical studies?

Yes

| Name of WOAH CC/RL/other organisation(s) | Location | Region of networking Centre | Purpose |
|---|---|---|---|
| Padova WOAH Centre, Italy and Pirbright Institute, UK | Italy and UK | Europa | Research led by scientists at the CVR, and linked to the Padova WOAH Centre, identified the human gene BTN3A3, which is commonly expressed in our airways, as a key human defence against avian flu. Through a series of extensive tests, we were able to show that the BTN3A3 gene is vital to protecting humans against avian flu, as most strains of the virus cannot get past its defences. We were able to show that avian flu viruses like H7N9 (which has infected more than 1,500 individuals with 40% case fatality rate) have a genetic mutation that allows them to 'escape' the blocking effects of the BTN3A3 gene. Tracking the history of influenza pandemics in humans, we were also able to link BTN3A3 resistance with key influenza virus types. All the human influenza pandemics, including the devastating 1918- |

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| | | | 19 global flu pandemic and the swine flu pandemic in 2009 were caused by influenza viruses that were resistant to BTN3A3. As result, this study suggests that having resistance to this gene may be a key factor in whether any flu strain has human pandemic potential. Pinto, R.M., Bakshi, S., Lytras, S. et al. BTN3A3 evasion promotes the zoonotic potential of influenza A viruses. Nature 619, 338–347 (2023). https://doi.org/10.1038/s41586-023-06261-8 With researchers at the UK Pirbright Institute we are members of the UK G2P2 (SARS-CoV-2 focussed) andTrailMap-OneHealth (influenza focussed) consortia. |

# TOR 4 AND 5: NETWORKING AND COLLABORATION

5. Did your Collaborating Centre maintain a network with other WOAH Collaborating Centres, Reference laboratories, or organisations in other disciplines, to coordinate scientific and technical studies?

Yes

| Name of WOAH CC/RL/other organisation(s) | Location | Region of networking Centre | Purpose |
|---|---|---|---|
| WOAH Expert Group for SARS-CoV-2 | Global | Europe | Richard Orton is a member of this group. |
| WOAH Emerging Diseases Group | Global | Europe | Richard Orton is a member of this group. |

# TOR 6: EXPERT CONSULTANTS

6. Did your Collaborating Centre place expert consultants at the disposal of WOAH?

Yes

| Name of expert | Kind of consultancy | Subject |
|---|---|---|
| David Robertson | Expert | Computational and evolutionary analysis of viruses |
| Massimo Palmarini | Expert | Avian influenza viruses - Virus and host genetics determinants of cross-species transmission |
| Pablo Murcia | Expert | Molecular virology of influenza viruses |
| Richard Orton | Expert | Computational analysis of virus genome sequence data |
| Joseph Hughes | Expert | Virus evolution and bioinformatic training |
| Ana da Silva Filipe | Expert | Sequencing strategies for animal and human viruses |

# TOR 7: SCIENTIFIC AND TECHNICAL TRAINING

7. Did your Collaborating Centre provide advice/services to requests from Members in your main focus area?

Yes

*Joseph Hughes provided advice on a bioinformatics tool for mutation surveillance in highly pathogenic H5N1 genomes to the WOAH Reference Laboratory for Avian Influenza and Newcastle Disease (Isabella Monne and Alice Fusaro). The manuscript currently under review.*

8. Did your Collaborating Centre provide scientific and technical training, within the remit of the mandate given by WOAH, to personnel from WOAH Members?

Yes

a) Technical visit : 0

b) Seminars : 0

c) Hands-on training courses: 57

d) Internships (>1 month) : 0

| Type of technical training provided (a, b, c or d) | Content | Country of origin of the expert(s) provided with training | No. participants from the corresponding country |
|---|---|---|---|
| C | 2024 Viral Bioinformatics and Genomic Training Course | UK, Italy, US, Israel, Belgium | 17 |
| C | Viral Genomics and Bioinformatics – Asia course | Held at OUCRU, Ho Chi Minh City, Vietnam with researchers from across Asia attending. | 24 |
| C | Genomics and Clinical Virology course | Wellcome Genome Campus, Cambridge. Clinical researchers from across the globe attended. | 16 |

# TOR 8: SCIENTIFIC MEETINGS

9. Did your Collaborating Centre organise or participate in the organisation of scientific meetings related to your main focus area on behalf of WOAH?

Yes

| National/International | Title of event | Co-organiser | Date | Location | No. Participants |
|---|---|---|---|---|---|
| Internationally | Advances in Strategies for the control of rabies transmitted by vampire bats | Rita Ribeiro (CVR), Elsa Cardenas Canales, Maria Magdalena Ramirez Martinez. | 2024-10-30 | Autlán de Navarro, Mexico (& broadcast on Facebook) | 100 |
| Internationally | International Conference for World Rabies Day | Rita Ribeiro (CVR), Jesus Rodriguez Chavez | 2024-09-27 | Cajamarca, Peru (& zoom) | 75 |

# TOR 9: DATA AND INFORMATION DISSEMINATION

10. Publication and dissemination of any information within the remit of the mandate given by WOAH that may be useful to Members of WOAH

a) Articles published in peer-reviewed journals:

14

*Hinsch, M., Robertson, D. L. and Silverman, E. (2024) Evolutionary rescue effect can disappear under non-neutral mutations - a reply to Zhang et al. (2022). Nature Communications, 15(1), 10676. (doi: 10.1038/s41467-024-54828-4)*

*Murcia, P. R. , Chambers, T. M., Daly, J. M., Pusterla, N., Damdinjav, B., Ulaankhuu, A. and Mojsiejczuk, L. (2024) Should the equine*

*community be concerned about the emergence of the H5N1 subtype of highly pathogenic avian influenza in US cattle? Equine Veterinary Journal, (https://doi.org/10.1111/evj.14439)*

*Li, Y.-T., Ko, H.-Y., Hughes, J. , Liu, M.-T., Lin, Y.-L., Hampson, K. and Brunker, K. (2024) From emergence to endemicity: highly pathogenic H5 avian influenza viruses in Taiwan. Nature Communications, 15(1), 9348. (doi: 10.1038/s41467-024-53816-y)*

*Kuhn, J. et al. (2024) Investigations on the potential role of free-ranging wildlife as a reservoir of SARS-CoV-2 in Switzerland. Viruses, 16(9), 1407. (doi: 10.3390/v16091407)*

*Fozard, J. A., Thomson, E. C. and Illingworth, C. J.R. (2024) Epidemiological inference at the threshold of data availability: an influenza A(H1N2)v spillover event in the United Kingdom. Journal of The Royal Society Interface, 21(217), 20240168. (doi: 10.1098/rsif.2024.0168)*

*Herder, V. et al. (2024) Correlates of disease severity in bluetongue as a model of acute arbovirus infection. PLoS Pathogens, 20(8), e1012466. (doi: 10.1371/journal.ppat.1012466)*

*Farrell, M. J. , Le Guillarme, N., Brierley, L. , Hunter, B., Scheepers, D., Willoughby, A., Yates, A. and Mideo, N. (2024) The changing landscape of text mining: a review of approaches for ecology and evolution. Proceedings of the Royal Society B: Biological Sciences, 291(2027), 20240423. (doi: 10.1098/rspb.2024.0423)*

*Hinsch, M., Silverman, E. and Robertson, D. L. (2024) Whole-System Pandemic Modelling Including Pathogen Evolution. In: 18th Social Simulation Conference (SSC23), Glasgow, UK, 04-08 Sep 2023, pp. 63-71. (doi: 10.1007/978-3-031-57785-7_6)*

*Streicker, D. et al. (2024) Developing transmissible vaccines for animal infectious diseases. Science, 384(6693), pp. 275-277. (doi: 10.1126/science.adn3231)*

*Gonzalo Nadal, V. et al. (2024) Suspected tick-borne flavivirus meningoencephalomyelitis in dogs from the UK: six cases (2021). Journal of Small Animal Practice, 65(2), pp. 132-143. (doi: 10.1111/jsap.13682)*

*Dunbar, D., Babayan, S. A. , Krumrie, S. , Haining, H., Hosie, M. J. and Weir, W. (2024) Assessing the feasibility of applying machine learning to diagnosing non-effusive feline infectious peritonitis. Scientific Reports, 14, 2517. (doi: 10.1038/s41598-024-52577-4)*

*Hüttl, J. et al. (2024) Serological and molecular investigation of SARS-CoV-2 in horses and cattle in Switzerland from 2020 to 2022. Viruses, 16(2), 224. (doi: 10.3390/v16020224)*

*Dee, K., Manali, M., Bissett, L. , Bone, J., Magill, C., Davis, C. , Willett, B. J. and Murcia, P. R. (2024) Smallpox vaccination campaigns resulted in age-associated population cross-immunity against monkeypox virus. Journal of General Virology, 105(6), 001999. (doi: 10.1099/jgv.0.001999)*

*Furnon, W. , Cowton, V., De Lorenzo, G. , Patel, A. and Palmarini, M. (2024) Evolution of enhanced innate immune suppression by SARS-CoV-2 Omicron subvariants. Nature Microbiology, 9, pp. 451-463. (doi: 10.1038/s41564-023-01588-4)*

b) International conferences:

3

*Laura Mojsiejczuk presented work entitled "Combining genomic and epidemiological data to track the spread of equine influenza" at the International Equine Infectious Diseases Conference in Deauville, France*
*(30th September – 4th October 2024).*

*Nardus Mollentze and Rita Ribeiro presented at the Rabies in the Americas Conference in Buenos Aires Argentina (https://www.ritaconference.org/rita-home-2024/). This conference is attended by a mix of academics, managers and international*

*health organizations.*

*David L Robertson presented research on applying machine learning/AI models to virus genome sequence variation data at the Preparing for the Next Pandemic: Evolution, Pathogenesis and Virology of Coronaviruses, a Cold Spring Harbour Asia meeting, Awaji, Japan.*

c) National conferences:
1
*David L Robertson presented research on applying machine learning/AI models to virus genome sequence variation data at the Virus Genomics, Evolution and Bioinformatics at Wellcome Connecting Science meeting, Wellcome Genome Campus, UK.*

d) Other (Provide website address or link to appropriate information):

11. What have you done in the past year to advance your area of focus, e.g. updated technology?
*We have increased our IT hardware as follows:*

*RAM increase 4x (from 1TB to 4TB).*
*Based on additional thread counts, RAM and newer CPU architecture:*

- *If the workload is highly parallelized on zeta this is about 6× – 8× faster than rho.*
- *If your workload is single-threaded, zeta is still ~1.5× – 2× faster per thread.*

*zeta-gpu is a new addition in 2024; 96 threads, 4x Nvidia A30 GPUs, 1TB RAM*

*For sequencing:*
*NextSeq2000 from Illumina, for higher throughput and cheaper sequencing, and the P2 Solo from ONT to support projects requiring longer reads at higher depths.*

12. Additional comments regarding your report: