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SID 5 Research Project Final Report

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Project identification

1. Defra Project code: CSA 6689/VT0105
2. Project title: The Cambridge Infectious Diseases Consortium
3. Contractor organisation(s): Department of Veterinary Medicine
   University of Cambridge
   Madingley Road
   Cambridge
   CB3 0ES
4. Total Defra project costs (agreed fixed price): £ 1,159,300
5. Project: start date ..... 01 January 2005
   end date ..... 31 December 2009

6. It is Defra's intention to publish this form.
Please confirm your agreement to do so.....**YES** ☒ **NO** ☐

(a) When preparing SID 5s contractors should bear in mind that Defra intends that they be made public. They should be written in a clear and concise manner and represent a full account of the research project which someone not closely associated with the project can follow.

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In all cases, reasons for withholding information must be fully in line with exemptions under the Environmental Information Regulations or the Freedom of Information Act 2000.

(b) If you have answered NO, please explain why the Final report should not be released into public domain

Executive Summary

7. The executive summary must not exceed 2 sides in total of A4 and should be understandable to the intelligent non-scientist. It should cover the main objectives, methods and findings of the research, together with any other significant events and options for new work.

Overall

The Cambridge Infectious Diseases Consortium (CIDC) was established to provide a multi-institutional, world class quality environment for infectious disease research addressing important questions and for the recruitment and training of high quality veterinarians into careers in infectious disease research. The programme has been a demonstrable success in achieving these overall aims.

The institutions that have played a key role in the consortium include the Department of Veterinary Medicine, the Department of Zoology and The Department of Pathology in the University of Cambridge, The Wellcome Trust Sanger Institute (WTSI), The Animal Health Trust, The Veterinary Laboratories Agency (VLA), The Institute of Animal Health (IAH), The Institute of Zoology (London: IOZ) and the University of Pretoria.

In terms of research infrastructure, the programme has successfully consolidated or established research and education collaborations with all of the participating institutions, including VLA, IAH, IOZ, WTSI and AHT. Since the inception of CIDC, additional collaborative research funds have supported collaborative projects in infectious disease dynamics with all of these institutions. Subject areas have included bovine Tuberculosis, Bluetongue serotype-8 vaccination, bat rabies and other viral infections and swine and equine influenza.

On the education and training front, the programme has successfully:

a) introduced 23 veterinarians into research programmes (far more than the 14 initially planned for at the application stage); a further 2 veterinarians have been funded on other, external funds and 3 of the current fellowship have gained their own personal Fellowship funding from the Wellcome Trust and are now completing their PhDs within CIDC. Of the 22, 11 have successfully completed PhD or other programmes. These fellows have been placed in research programmes in 4 University of Cambridge departments, VLA, IAH, AHT, IOZ and Sanger (WTSI). Diseases studied have included Foot and Mouth Disease, avian influenza, swine and equine influenza, henipaviruses and rabies like viruses in bats, bovine Tuberculosis (problem herds) and Tuberculosis in wild living mammals (meerkats).

Without specific additional funding, this programme will be difficult to sustain, although some aspects of it have been taken up by the Wellcome Trust. However, importantly, the programme has demonstrated very clearly that we can provide veterinarians with no prior research experience with an excellent training environment which can prepare them to be independent, internationally competitive research scientists.

The success of the programme is demonstrated clearly by the positions that these graduate students have gone on to; 10 of these 11 are in fully funded postdoctoral positions, including within Defra funded programmes in VLA and IAH and on a number of Wellcome Trust programmes. A further 11 are still on time to complete.

b) established a training programme for practicing veterinarians in clinical research methods and

trained a large number (67) through this course. This is a far greater number than initially envisaged. The course is now a registered with the RCVS and a financial structure for its sustainability has been identified.
c) established an infectious disease dynamics (DDU) / epidemiology unit in Cambridge University with links into several other departments which is now undertaking high quality infectious disease research in animals. The interactions of DDU members across the consortium has resulted in a substantial change in the nature of the science that others have been undertaking. Individuals in DDU have gained their own personal funds. A key infectious disease modelling course developed during the 5 years of the CIDC funding has now been taken up and run as a highly successful Wellcome Trust Advanced Course. The outputs from scientist have been published in highest ranking journals, including in the last 2 years in Science, PLoS Biology and Journal of the Royal Society Interface, as well as in many leading discipline specific journals such as Journal of Virology, Proceedings of Royal Society (B), Equine veterinary Journal, International Journal of Biostatistics and Vaccine.
d) provided an excellent environment for post-doctoral training in infectious disease dynamics, with 2 of the post-docs working in CIDC programmes having gained their own Fellowship funding as a result (with further scientists being attracted in from the outside). Within the environment in Cambridge, this personal funding provides a key mechanism for sustaining the programme.
e) established a new 3rd year undergraduate honours course, the Dynamics of Infectious Diseases (DID) course, focused on the dynamics of animal and zoonotic infections. Significant proportions (>25%) of all Cambridge veterinary students have been selecting this voluntary course, as well as a proportion of natural scientists and medical students. The course is now being sustained with support from the University. We have also provided high quality training in transboundary disease control, particularly for clinical veterinary students in their 5th year.

Research
The directly funded research programme in Mammalian Influenza A dynamics was the subject of a sub-contract with The Animal Health Trust in Newmarket. The programme has met all milestones and achieved all objectives in the funded programme of research in the quantitative dynamics of mammalian (swine and equine) influenza. In particular, we have:
- successfully undertaken long chain influenza transmission studies in both pigs and horses with viruses adapted for transmission in the two respective species. Studies in both species were undertaken in both immunologically naïve animals, as well as in animals that had partial immunity derived from traditional vaccination approaches. These studies were designed to test the hypothesis that rates of within and between host adaptation, or mutation rates of the adapted viruses are higher in animals which have prior immunity which therefore drives selection, particularly at transmission.
- with additional funding from the Wellcome Trust, including individual fellowships, successfully developed a sequencing pipeline at WTSI for deep sequencing analysis of the viral genetic diversity found within individual hosts. We have studied samples from pigs and horses infected in experiments by the natural respiratory contact transmission route and have also started to use the approach to study naturally occurring epidemics in both vaccinated (Newmarket) and naïve (Australian) hosts. The results have demonstrated that a) there is considerable diversity of viruses within natural hosts b) a considerable proportion of this diversity transmits, at least between immunologically naïve hosts and c) transmission chains longer than those practically achievable experimentally in large animals are often needed for changes at the consensus level to occur. This work has formed the basis for important aspects of the Combating Swine Influenza (COSI) awards. We have also studied adaptation of an avian virus in swine tissues including natural, air interface, pig tracheal explants.
- demonstrated, using cutting edge antigenic cartographic methods, the key antigenic determinants in equine H3N8 influenza and how this virus has evolved over 40 years. It has also quantified issues of original antigenic sin following equine influenza vaccination which have broad applicability to the study of repeated dosing with multivalent vaccinal products.

The programme has exceeded all commitments made through high quality delivery and generation of additional funding based on the core support from Defra and Hefce. It has has met all milestones agreed at the outset. Importantly, the highly successful fellowship programme has addressed the key objective of the Veterinary Training and Research Initiative (VTRI) in successfully demonstrating the potential for introducing large numbers of veterinarians into high quality research careers.

8. As a guide this report should be no longer than 20 sides of A4. This report is to provide Defra with details of the outputs of the research project for internal purposes; to meet the terms of the contract; and to allow Defra to publish details of the outputs to meet Environmental Information Regulation or Freedom of Information obligations. This short report to Defra does not preclude contractors from also seeking to publish a full, formal scientific report/paper in an appropriate scientific or other journal/publication. Indeed, Defra actively encourages such publications as part of the contract terms. The report to Defra should include:
   - the scientific objectives as set out in the contract;
   - the extent to which the objectives set out in the contract have been met;
   - details of methods used and the results obtained, including statistical analysis (if appropriate);
   - a discussion of the results and their reliability;
   - the main implications of the findings;
   - possible future work; and
   - any action resulting from the research (e.g. IP, Knowledge Transfer).

SEE ATTACHED FILE

References to published material

9. This section should be used to record links (hypertext links where possible) or references to other published material generated by, or relating to this project.

A selection of the >100 refereed publications output from the project are here. A further 90 are in an Annex in the main report. Conference proceedings can be found against individual fellows in the main report.
- Restif, O., Grenfell, B.T. (2005). Integrating life history and cross-immunity into the evolutionary dynamics of pathogens. Proceedings of the Royal Society series B. (published online doi:10.1098/rspb.2005.3335)
- Wood, J.L.N., Kelly, L., Cardwell, J. & Park, A.W. (2005) Results of a quantitative risk assessment of the risks of reducing swabbing requirements for the detection of Taylorella equigenitalis. Vet Rec 157, 41-6
- Wood, J.L.N., Newton, J.R., Chanter, N. & Mumford, J.A. (2005) The association between respiratory disease and bacterial and viral infections in British racehorses. Journal of Clinical Microbiology 43, 120-6
- Deardon, Gilmour, Butler, Phelps & Kennedy (2006) Designing field experiments which are subject to representation bias. Journal of Applied Statistics, 33, 7, 665-680.
- Restif, O. and B. T. Grenfell. (2006) Integrating life history and cross-immunity into the evolutionary dynamics of pathogens. Proceedings: Biological Sciences 273, 409-416.
- Tildesley, Savill, Shaw, Deardon, Brooks, Woolhouse, Grenfell & Keeling (2006) Optimal reactive vaccination strategies for an outbreak of foot-and-mouth disease in Great Britain. Nature, 440, 1080, 83-6
- Balkissoon, D. Staines, K., McCauley, J., Wood, J.L.N., Young, J., Kaufman, J. & Butter, C. (2007) Low frequency of the Mx allele for viral resistance predates recent intensive selection in domestic chickens. Immunogenetics 59, 687-691
- Restif O. and B. T. Grenfell. 2007. Vaccination and the dynamics of immune evasion. Journal of the Royal Society Interface 4, 143-153
- Benfield, C. T. O, Lyall, J. W., Kochs, G. & Tiley, L. S. (2008). Asparagine 631 variants of the chicken Mx protein do not inhibit influenza replication in primary chicken embryo fibroblasts or in vitro surrogate assays. Journal of Virology, 82, 7533-7539
- Grant AJ, Restif O, McKinley TJ, Sheppard M, Maskell DJ, and Mastroeni P. (2008) Modelling within-host spatiotemporal dynamics of invasive bacterial disease. PLoS Biology 6, e74 doi:10.1371/journal.pbio.0060074.
- Hayman, D.T.S., Fooks, A.R., Horton, D., Suu-Ire, R., Breed, A.C., Cunningham, A.A. & Wood, J.L.N. (2008) Antibodies against Lagos Bat Virus in Megachiroptera from West Africa. Emerging Infectious Diseases 14, 926-8
- Bryant, N.A., Rash, A.S., Russell, C.A., Ross, J., Cooke, A., Bowman, S., MacRae, S., Lewis, N.S., Paillot, R., Zanoni, R., Meier, H., Griffiths, L.A., Daly, J.M., Tiwari, A., Chambers, T.M., Newton, J.R., and Elton, D.M. (2009) Antigenic and genetic variations in European and North American equine influenza virus strains (H3N8) isolated from 2006 to 2007. Vet Microbiology 138, 41-52.
- Drewe, J.A., Madden, J.R. & Pearce, G.P. (2009) The social network structure of a wild meerkat population: 1. Inter-group interactions. Behavioral Ecology and Sociobiology 63, 1295-1306.
- Feldman K.S., Foord A., Heine H.G., Smith I.L., Boyd V., Marsh G.A., Wood J.L., Cunningham A.A., Wang L.F. (2009) Design and evaluation of consensus PCR assays for henipaviruses. Journal of Virological Methods 161, 1, 52-57
- Horton, D. L. Voller K., Haxton, B., Johnson, N., Leech, S.,Goddard, T.,Wilson, C., McElhinney, L.M and Fooks, T. European bat lyssavirus type 2 in a Daubenton's bat in Scotland.(2009). Veterinary Record 165, 383-4.
- Mastroeni P., A. Grant, O. Restif and D.J. Maskell (2009) A dynamic view of the spread and intracellular distribution of Salmonella enterica. Nature Reviews Microbiology 7, 73-80
- McKinley, Trevelyan J., Cook, Alex R. and Deardon,Rob (2009) Inference for epidemic models without likelihoods. The International Journal of Biostatistics 5, 1, article 24 doi: 10.2202/15574679.1171.
- Nunes, S.F., Murcia, P.R., Tiley, L.S., Brown, I.H., Tucker, A.W., Maskell, D.J. and Wood, J.L. (2009) An ex vivo swine tracheal organ culture for the study of influenza infection. Influenza Other Respiratory Viruses 4, 7-15.
- Park, A.W., Daly, J.M., Lewis, N.S., Smith D.J., Wood, J.L.N., Grenfell, B.T. (2009) Quantifying the Impact of Immune Escape on Transmission Dynamics of Influenza. Science 326, 726–728.
- Restif, O. (2009) Evolutionary epidemiology 20 years on: Challenges and prospects. Infection, Genetics and Evolution 9, 1, 108-123 doi:10.1016/j.meegid.2008.09.007
- Murcia*, P.R., Baillie*, G.J., Daly, J., Elton, D., Jervis, C., Mumford, J.A., Newton, J.R., Parrish, C.R., Hoelzer, K., Dougan, G., Parkhill, J., Lennard, N., Ormond, D., Moule, S., Whitwham, A., McCauley, J.W., McKinley, T.J., Holmes, E.C., Grenfell, B.T.& Wood, J.L.N. (2010) The intra- and inter-host evolutionary dynamics of equine influenza virus. Journal of Virology in press