Non-technical summary: Vaccines to protect against Nipah virus

Project duration
5 years 0 months

Project purpose
(b) Translational or applied research with one of the following aims: (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants

Key words
vaccine
pig
Nipah virus
Pseudorabies
Immunogenicity

Animal types	**Life stages**
Pigs	Juvenile

Retrospective assessment
The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits
Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.
What's the aim of this project?
To develop a safe and effective vaccine to prevent and aid control of Nipah virus outbreaks in pigs.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.
Why is it important to undertake this work?
The Nipah virus (NiV) poses a significant epidemic threat to South and Southeast Asia because of its broad host range and widespread distribution of fruit bats which act as a natural reservoir. Humans may become infected indirectly from bats or through exposure to infected pigs or other livestock species. Pig-to-human transmission was responsible for the first and still most severe NiV outbreak in Malaysia and Singapore in 1998-99. Despite the risk NiV poses, no vaccines are currently licensed for humans or pigs. NiV is listed as a priority pathogen by the World Health Organisation for research and development in the context of public health emergencies. NiV infection of pigs is also a “listed disease” notifiable to the World Organisation for Animal Health. The rare and sporadic nature of NiV outbreaks means that a vaccine for pigs has limited marketability. To overcome this challenge, we aim to develop a bivalent vaccine, which would induce immunity to both NiV and the

pseudorabies virus (PrV), which is widely vaccinated against in Asia. If successful, such a vaccine would reduce the risk of NiV outbreaks in pigs and the concomitant severe socioeconomic consequences and threat to public health.

What outputs do you think you will see at the end of this project?
Proof-of-concept that a PrV vector expressing NiV glycoproteins induces immune responses to both viruses, including responses that protect pigs against PrV.

Who or what will benefit from these outputs, and how?
The scientific community will benefit from the improved knowledge of the performance of a new vaccine approach. This could lead to the development of a safe and efficacious bivalent vaccine that results in prevention and control of NiV and PrV outbreaks, and consequently improved animal welfare, improved productivity in the pig industry, and reduced risk to public health. This would bring benefits to policy makers involved in livestock disease control, the pharmaceutical and veterinary sector, and the general public through improved food security and reduced incidence of zoonotic disease.

How will you look to maximise the outputs of this work?
All outputs from this project will be published in Open Access scientific journals; this will include unsuccessful vaccine approaches. Outputs of this work will also be disseminated to other stakeholders and the general public through press releases, presentations at meetings/congresses and social media channels.

Species and numbers of animals expected to be used
Pigs: 39

Predicted harms
Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.
Explain why you are using these types of animals and your choice of life stages.
Pigs are the only natural host for PrV and can act as an amplifying host for NiV. Since we aim to develop a bivalent vaccine to protect pigs against both viruses, they are the most suitable animal to evaluate vaccine immunogenicity and efficacy.

Typically, what will be done to an animal used in your project?
Typically, pigs used in this project will be immunised by injection of a live attenuated PrV vaccine candidate into the muscle. This will typically be conducted once or twice. Blood and nasal swab samples will be taken at intervals to characterise the immune response and to assess shedding of the vaccine. Vaccinated and unvaccinated animals may be challenged once by administration of virulent PrV into the nose. Blood samples and nasal swabs will again be taken at intervals to quantify levels of challenge virus and immune responses. This will typically be done twice weekly. Animals will then be culled humanely to assess tissue pathology and tissues will be collected to assess PrV loads and for further analysis of immune responses. The typical duration of an experiment is 42 days. Pigs will not be challenged with NiV within this project and instead blood samples will be collected from vaccinated pigs to determine levels of NiV-specific neutralising antibodies. The ability of vaccine candidates to protect pigs against NiV will be assessed by a European partner due

to the requirement for a Biosafety Level 4 Biocontainment facility suitable for housing pigs, which the UK does not possess.

What are the expected impacts and/or adverse effects for the animals during your project?
No clinical signs are expected in vaccinated pigs following vaccination or PrV challenge. Unvaccinated pigs are expected to develop clinical signs following PrV challenge. This is most likely presented as a rise in body temperature from 2 days post-infection. Pigs may stop eating and become reluctant to get up unless touched, or start to develop clinical signs of respiratory and neurological disease. All animals will be clinically monitored both post-vaccination and -challenge. Assessments and interventions as appropriate will be performed at predefined frequencies in the experimental protocol, including euthanasia to prevent further suffering if humane endpoints are met. The impact of blood sampling, swabbing and inoculation of vaccine or challenge virus will be both mild and transient.

Expected severity categories and the proportion of animals in each category, per species.
What are the expected severities and the proportion of animals in each category (per animal type)?
The expected severity for pigs that are vaccinated and pigs that are vaccinated and challenged is mild. The expected severity for control pigs that are unvaccinated and challenged is moderate.

It is estimated that 85% of pigs will be in the mild severity category and 15% of pigs in the moderate severity category.

What will happen to animals used in this project?
Killed

Replacement
State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.
Why do you need to use animals to achieve the aim of your project?
Due to the complex nature of the immune system, it is not currently possible to study immune responses to vaccination and to determine whether vaccines are protective without the use of animals.

Which non-animal alternatives did you consider for use in this project?
Cell culture-based systems will be used to generate and characterise vaccine candidates, cultivate vaccine and challenge virus strains and to evaluate virus-neutralising antibody characteristics. NiV glycoprotein expression by recombinant PrV vectors will be confirmed in cell culture prior to their evaluation in animals.

Why were they not suitable?
No replacement options are available to replace the whole animal at this time as an entire organism, including the immune system, need to be present.

Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

How have you estimated the numbers of animals you will use?

Animal numbers to be used have been estimated using data previously collected from similar studies or from relevant published literature in consultation with a statistician.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

Statistical analysis of data collected from previous related studies. Samples will be stored in a biobank, and we will maximise collection of samples post-mortem to facilitate further investigations without the requirement for additional animal experiments.

What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?

Use of in vitro models to characterise novel PrV vaccine constructs. Basing study design on recently conducted relevant studies.

Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

Pigs are the natural hosts for PrV and are the target species for a bivalent PrV-NiV vaccine. Whilst PrV has a broad host range, PrV strains that are attenuated in pigs may still cause a fatal infection in other species e.g., mice. The pig is therefore the most suitable animal to study the effectiveness of live attenuated PrV-based vaccine candidates.

A well characterised live attenuated PrV strain will be selected to be engineered to express membrane anchored NiV glycoproteins. We have previously evaluated live attenuated PrV strain expressing soluble forms of NiV glycoproteins - this vaccine candidate was safe, induced PrV-specific immune responses comparable to the parental PrV vaccine, but the immune responses to the NiV glycoproteins could be improved.

Vaccinated and unvaccinated control pigs will be challenged with a well characterised virulent PrV strain. This enables us to assess protection against clinical disease as well as by reduction in virus loads.

Animals will be inoculated with vaccine or challenge virus in the smallest volume commensurate with the aims of the procedure.

Why can’t you use animals that are less sentient?

Pigs are the natural hosts for PrV and are the target species for a bivalent PrV-NiV vaccine. Whilst PrV has a broad host range, PrV strains that are attenuated in pigs may still cause a fatal infection in other species e.g., mice. The vaccine approach has already been evaluated in pigs and was shown to be immunogenic so there is no value in using other less sentient animal models.

How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?
Animals will be housed together with bedding and other items of enrichment. Highly trained animal technicians will monitor these animals throughout the day, ensuring they are comfortable and to maximise their welfare status. We have 24/7 CCTV surveillance which can be used to monitor the animals' behaviour over time.

Pre-study meetings involving the Named Veterinary Surgeon (NVS), Named Animal Care and Welfare Officer (NACWO), and animal services staff will be held to discuss any advances in animal care. Meticulous records will be kept of behavioural, physiological, immunological, and virological measures in order to identify predictive markers and refine humane endpoints. All experiments will be followed by a wash-up meeting to discuss all aspects of the study.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?
Adherence to the ARRIVE guidelines for reporting these studies, as well as reference to the Federation of European Laboratory Animal Science Associations' (FELASA) guidelines for pig health monitoring to help ensure the most robust health assurance for animals used in this study. FELASA guidelines for administration of substances has been used to limit the maximum volumes for each of the routes.

How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?
Through continued continued professional development (CPD) and frequent review of the Center for Alternatives to Animal Testing (CAAT) and the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) websites, I will keep informed about advances in the 3Rs. Included in CPD will be annual attendance at relevant science conferences.