VT0104

Bristol Veterinary Training and Research Initiative (VTRI) First Annual Appraisal Report 2005

1. The Defra/hefce/SHEFC Veterinary Training and Research Initiative (VTRI).

Origin

On the 23 July 2003 Defra announced its intention to develop a partnership aimed at underpinning research and development within veterinary sciences. Lord Whitty (the then Minister for Farming, Food and Sustainable Energy) was quoted “this initiative will allow us to build a structure that will foster the development of veterinary knowledge and skills needed to serve Britain’s future needs”.

To do this the Initiative’s central focus was to strengthen clinical research teaching and training, together with research capability in infectious diseases of animals in the UK.

By collaborating with the Higher Education Funding Council for England (hefce) and the Scottish Higher Education Funding Council (SHEFC), a total fund of £21.5M was secured for use over the next 5 years.

Primary Objectives

Two years ago Defra/hefce/SHEFC commissioned a competition for research/training programmes whose primary objectives were to;

1. Foster greater cooperation and collaboration between the vet schools, university departments, scientific research institutes and Government Agencies.

2. Develop a veterinary science skill base(s) which can address future animal health problems and offer a source of consultative expertise to the Government and industry.

3. Strengthen the research base in veterinary science required for a national capability to detect, track, analyse and control infectious disease.

4. Strengthen the veterinary research training infrastructure in order to support and sustain the national capability to prevent and control infectious diseases.

Applicants were asked to address research within one or more of the following categories:

- livestock and poultry endemic diseases;

- livestock and poultry exotic diseases;

- companion animal infectious diseases of public health importance.
In addition to the obvious topics proposals looked at emerging diseases, wildlife reservoirs, disease vectors and zoonotic pathogens that are asymptomatic in animals.

Emphasis was placed on proposals being designed to create an environment in which the national veterinary research capability would be enhanced and veterinarians and veterinary students were exposed to the excitement of high quality research, motivated towards research careers and may gain appropriate experience in scientific methodology to equip them for a future in research. A whole range of training opportunities were considered acceptable – such as: research leave for clinical teachers, short lecture courses to be given by non-teaching researchers (particularly in their own field of research), post doctoral support, PhD studentships, undergraduate dissertation topics during intercalated degrees, vacation scholarships for veterinary students, "seeing practice" opportunities for undergraduates at veterinary laboratories.

33 applications were submitted of which an independent scientific selection panel identified 5 proposals for funding.

The winning proposals were:

A £2M joint proposal from the Edinburgh (Prof Mark Woolhouse) and Glasgow (Prof Stuart Reid) schools with research focused on quantitative epidemiology.

A £4.5M proposal from the Liverpool School on the transmission, pathogen evolution and control of Food-borne zoonotic pathogens. (Prof Malcolm Bennett).

A £5.6M proposal from the Edinburgh School (Prof's Hugh Miller and Ivan Morrison) on functional genomics and immunology and their application to infectious diseases in ruminants.

A £3.6M proposal from Bristol (Prof Tom Humphrey and Dr Mick Bailey) on susceptibility to infection and diseases and the role of husbandry and welfare in driving microbial colonisation and immune development;

A £5M proposal from the Cambridge Vet School (Prof Ian McConnell) to determine disease dynamics/host pathogen relationships and establish a Cambridge Infectious Disease Consortium.
2. The VTRI Appraisal Meeting.

Peer review is used widely in Defra as a method of assessing the quality of research proposals, however there also needs to be an effective ‘real-time’ responsive monitoring facility to ensure quality science and training throughout the lifetime of the proposal. Defra’s experiences in funding large research programmes have benefited from an appraisal/review process and identified key criteria for its successful implementation.

1. First review to be at earliest opportunity (i.e. 1 year). This has the advantage of establishing the review process’s principles and expectations.

2. Ensure that the identification of research and training areas (in the case of this VTRI initiative), contractors and review mechanisms are a continuous and a connected process, with procedures made transparent to all parties at the earliest opportunity and preferably before the start of the process.

3. Promote interdisciplinary work groups within the research and training areas, where possible.

4. Be adaptable and flexible in response to the contractors’ abilities and interests during the course of the award.

5. Put an emphasis on the performance indicators: communication of findings through publications/presentations, establishment of domain experts through training and industrial (if appropriate) uptake of findings.

6. Expect contractors to promote the visibility of Defra/funding bodies and their support.

The Appraisal Panel

In selection of the panel emphasis has been put on appraisers being well qualified in the areas that they are to reviewing, have current or recent active research experience and be familiar with training/teaching amongst veterinary or similar scientific professions. The remainder of the Panel will be comprised of Funders representatives and the VTRI Secretariat.

The Appraisal process

The lead proposer of each of the VTRI grants must ensure that evidence of progress is reported and made available to the VTRI Secretariat at least a month before each respective visit. This evidence should include the following:

- Annual reports (SID4 forms as published on the Defra web site)
- or a summary of progress,
- minutes of VTRI Programme Management meetings,
- GANTT Charts/ project management tools,
- details and explanation/reasons of changes to original programme proposal.
- Details of recruitment/appointment to research/training programmes (including qualifications and background information).
• Information on any other relevant grant awards that could benefit the VTRI research/training programmes (i.e. evidence of sustainability).

This information will be forwarded to the Appraisal Panel to act as a ‘template’ of progress with which to carry out an assessment during each Appraisal visit. After each visit a report is prepared detailing the Appraisal Panel’s conclusions.
3. Bristol Veterinary Training Research Initiative Proposal: VT014

Project description:

Concerns about antibiotic and growth promoter usage in agriculture have stimulated interest in sustainable alternatives for controlling infectious diseases, particularly where replacement systems could improve animal welfare. To optimise these systems, it is important to examine the whole, multi-factorial, infection process. Veterinary undergraduates and graduates are uniquely placed to acquire this broad view of infectious disease.

Susceptibility to infection depends on many factors involving pathogen, host, environment and husbandry. These factors are particularly important in the case of intensively farmed pigs and chickens. Husbandry systems will affect the dose of pathogen delivered, while strain of pathogen and individual susceptibility will determine the outcome of exposure to any particular dose. Intensive production systems facilitate the spread of pathogens by aerosols or by the faecal-oral route. However, individual susceptibility is also influenced by factors controlled by the husbandry system. Thus, chickens and pigs exposed to salmonella in aerosols are highly susceptible to infection at very low doses, compared to the very high ones necessary when bacteria are administered orally. The newborn animal has an undeveloped immune system, particularly at mucosal surfaces, and requires colonisation by commensal micro-organisms to expand immunological compartments and repertoire. Increasing resistance to infection with age may be attributable either to microbial competition or to expanded immunological capacity. These, in turn, are affected by factors such as diet, social mixing, pain and temperature. This project brings together expertise in microbiology, immunology, behaviour and welfare to address the key question of the extent to which husbandry influences susceptibility to infectious disease.

The project is divided into three programmes. The hypothesis to be explored is that manipulation of animal environments in husbandry systems affects microbial load, immunological competence and social and physiological ‘stress’ and that these factors contribute to disease susceptibility. An integrated series of work programmes will be undertaken, which will use controlled experimental approaches to address:

- The role of early-life colonisation with commensal flora in determining host susceptibility to disease using germ-free pigs and chickens given a defined flora
- The relative importance of host genetics and environment in determining susceptibility to disease using in-bred chicken lines as models
- The effect on disease susceptibility of environmental manipulation, focusing on social disruption of the kind experienced by pigs at mixing after weaning, or chickens when moved from rearing to laying
- The effect of source of pathogen challenge from the environment on disease susceptibility, using aerosol and oral exposure to *Salmonella* in chickens

Date of Appraisal Visit: 19\textsuperscript{th} July 2005

VTRI Appraisal Panel Review of Progress

Are the proposal's objectives adequately addressed and described? (If not are the reasons why clearly stated?)

The objectives of the proposal are well laid out with the research side being particularly clearly detailed. There is also a good mix of objectives for the training programme though the success of this aspect will be more difficult to judge. The teams from the three institutions (Bristol, Institute of Animal Health, Institute of Food Research) clearly work well together and there is considerable scientific added value from these alliances.

Are there any flaws in the approaches being tested?

With Programme 2, the VTRI Appraisal Panel was uncertain of how useful the results of the social intervention experiments would be, however the methodology allowed researchers to ask several questions, and it appears that they were aware of the limitations of their data.

Response from the Bristol Consortium:
The social intervention studies are at the crux of this particular programme. The whole point is to examine whether and how environmental stressors likely to be encountered by pigs or chickens during husbandry procedures impact on their behaviour, stress physiology, immunology and microbiology. The results should inform us of whether such procedures have a significant effect on any of these measures and of how the different measures inter-relate. We will also gain information on whether different individuals show different profiles of response and whether this can be predicted by measures of their early behavioural characteristics, as suggested by current ideas concerning the existence of different strategies for coping with environmental challenge.

For the challenge studies in Programme 3, could the proposer’s comment on the influences of different \textit{Salmonella} Typhimurium and \textit{Salmonella} Enteritidis phage types and how infected bird responses might vary with phage type?

Response from the Bristol Consortium:
We recognise that the phage types (PTs) of the \textit{Salmonella} species used are likely to have an impact on host-pathogen interactions. Change in PT is often the result of alterations in the fine structure of bacterial lipopolysaccharide (LPS). LPS is a major effector and stimulator of the immune response elicited by salmonella, although many other antigens can be involved. The impact of this has been studied, although not to a great extent in chickens, because of concerns about the protective nature of salmonella vaccines when animals are challenged with different strains. Changes in LPS could reduce the efficacy of vaccination by allowing salmonella to partially evade the immune response. The immunoglobulin (Ig) IgY targets LPS and small changes in LPS structure can reduce antibody binding, presumably through changes in affinity.
These changes can also give the bacterium resistance to two mechanisms of immune response; the alternative complement pathway stimulated by bacterial LPS...
and the classical complement pathway initiated by IgM or IgY, as alteration of LPS prevents binding of the membrane attack complex, which lyses bacterial cells. The IgA response, which agglutinates bacterial cells, may also be affected by changes in LPS. In the US it has proved necessary to use a combined PT4 and PT8 vaccine to allow improved protection of chickens. This area requires investigation as the importance of antibody responses may be governed by salmonella serovar concerned and the infection site. Thus IAH have recently demonstrated that although enteric salmonella induce strong antibody responses these may not be required for clearance from the intestine. Indeed, B cell-deficient bursectomised chickens clear infection as fast as intact ones at both primary infection and during re-challenge infection (Beal et al., in press Infection and Immunity). In addition to potential effects on host immune responses, work in consortium laboratories, and at collaborating centres in the US, has shown that LPS structure will influence the degree of persistence in chicken reproductive tissues and S. Enteritidis (SE) PTs differ in this respect. LPS expression also appears to be important in colonisation of the intestinal tract. There is a need to examine the impact of SE PT on host-pathogen interactions, particularly in chickens. This is outside the scope of this study, although an application has been made to DEFRA to examine this. The decision to use the PTs of SE and S. Typhimurium (STM) chosen was taken because they are known to be able to infect chickens and whole genome sequence data are available. We also believe that there will be fundamental conserved aspects of pathogen behaviour common to all PTs of SE and STM.

Are there weaknesses in experimental design? (If yes please suggest recommendations to rectify the weaknesses).

The projects are at different stages of maturation. The programme of research involving stress in weaning pigs is the least mature and the animal model (inbred or mixed) needs resolving in order to ensure progression to the microbiological and immunological endpoints. It is possible that this model may not prove to be suitable even when the two different pig strains are mixed together. It is important to characterise the model to be used as quickly as possible.

Response from the Bristol Consortium:

We will be characterising the model in experiments starting in January 2006, which should be completed later in the year. We think it highly likely that the model will work when the two strains are mixed together since it is well known that outbred strains can detect, and are aggressive to, unfamiliar animals. What our initial study will show is whether inbred pigs can do the same when mixed with other inbred individuals. If so, the inbred Babraham line will be especially suitable for this work from an immunological point of view, since genetically coded immune characteristics should be the same across all individuals and hence any change in immune function should be attributable to environmental effects (e.g. on gene expression). The milestone relating to this is not due till October 2007. The first pig experiments are planned for March 2006.

Is the training offered as part of the proposal sound? (Could you also please comment on the quality of training and realisation as part of the proposal)?

This proposal has a very strong training element and it is clear that the entire School is committed to encouraging veterinary research.

The changes in the admissions policy and the assigning of appropriate personal tutors to mentor students will be very valuable in cultivating research interests amongst students.
The training opportunities at both PhD and postdoctoral level are very good. At all three institutions registration for higher degree appraisal, mentoring and critical mass are very well organised. Scientific supervision of graduate students appears excellent.

The vacation scholarships for the both sixth form students and intercalating students are exciting opportunities. They are highly competitive and involve stimulating theory and practical work that will stimulate academic interest amongst students and also provide a good opportunity for personal development for the brightest students.

For the intercalating students the agreement sought from the RCVS that practice counts towards 6 weeks of their compulsory EMS endorses the scholarship, and anticipates that it makes it more attractive to students to participate.

The thinking behind the importance of research leadership training and viewing PhD students as early career researchers is the right one and we hope that this is continued throughout their study and that those students are encouraged to publish and develop their own research careers.

The training offered is wide ranging and covers all aspects from student selection through the undergraduate course to PhD and Post Doctorate opportunities. The attempt to select students who have a career in research in mind from the start of their undergraduate course is particularly innovative. A danger must be that expectations are raised which cannot be realised in the long term due to the lack of opportunities post PhD, etc. It is therefore important that when these students progress through the system the posts are available to allow career development. Otherwise the initiative will be lost.

**Response from the Bristol Consortium:**
We are grateful for the endorsement of the different training initiatives in the project. The importance of continuing to timely career paths is recognised and will be addressed.

**Recommendation 1:**
*The Initiative's long-term future and/or eventual successor should be carefully considered particularly in respect to post-PhD opportunities in professional research.*

A lot of emphasis is placed on intercalated degrees and the idea of having a reasonably large cohort progressing together is sensible. This gets round the problem of losing contact with their peers when taking time out to do an intercalated degree and should help to develop a culture that this is a worthwhile experience from a career point of view.

**Recommendation 2:**
*Secondments and short-term attachments opportunities for trainees to gain experience in “state of the art” laboratories could be considered.*

**Can you please comment on the success of recruitment of applicants within this programme?**

There is a good uptake of veterinary undergraduates interested in research vacation scholarships and a steady flow of veterinary undergraduates intercalating. The inclusion of research in the undergraduate veterinary course as an examined section is an excellent way forward as is selection of students with a research focus.
Recruitment of PhD students from a veterinary degree is a problem, though not unexpected two of the five posts are filled by overseas students. One post of the remaining three is almost certain to be filled by a vet shortly. The two remaining posts ideally should go to vet students or vet graduates but basic science graduates could be appointed as an alternative. It is crucial to appoint students of high quality and not to rush to appointment. Recruitment of post docs to date is good.

Response from the Bristol Consortium:
We are pleased to see that the review panel has suggested that we take time to find good candidates for the PhD places and we will take this suggestion on board. The three outstanding places have been advertised with a closing date of December 2 2005. One Bristol veterinary undergraduate, who intercalated in the last academic year, and one other local student, will apply for the studentships. With this in mind, it may be necessary for us to delay the start of one or two of the studentships until October 2006.

What progress has been made on establishing collaborations and associated activities?
There is evidence of good active collaboration between Bristol University, the Institute of Animal Health and the Institute for Food Research. All of the collaborators actively participated in the presentations and the close contact between all three should have a beneficial effect on the programme and allow wider experience of research by veterinary undergraduate and graduate students at Bristol. Further to this there is limited collaboration with Liverpool University (supervision of a PhD student by Prof Humphrey). The VTRI participants might benefit from a greater level of communication, and perhaps the suggestions of a proposed web-portal and participants attending each other’s 2-year review might be a good way to achieve this.

Collaboration exists at formal and informal levels. Formal meetings are held every 2-4 months of the Steering Committee. Video linkage was discussed as a way to enhance ease of communication and collaboration.

Response from the Bristol Consortium: The level and frequency of contact between members of the Bristol-led consortium is good and recently IFR has established a web site for data generated by the consortium, in addition to the more general site at Bristol. We would welcome greater contact with other VTRI projects.

Recommendation 3:
To contribute to a combined VTRI session at the next AVTRW conference to promote the programme and showcase developments.

Recommendation 4:
Website development to interlink all VTRI sites.

Do you consider the progress made in the first year to be sufficient?
Excellent progress has been made with regard to developing training elements and stimulating demand for research amongst future Veterinarians.

The research programmes promise much but the first year has been spent mainly on planning and learning techniques with few results to report. Considerable work has been undertaken to refine the methodologies of the different programmes including
testing methodologies, and identifying areas of uncertainty where results may not be conclusive in proving one theory or another.

There is an apparent underspend of the funds allocated in the first year and this needs further investigation.

Response from the Bristol Consortium: We welcome the positive comments about the research programme. We are now reaching a stage when method refinements are being completed. It is planned that the gnotobiotic detailed analysis of germ-free animals are planned to begin in early 2006.

Recommendation 5:
A report on actual spend should be provided to the funders in order to explain the underspend reported in the first year.

The Appraisal Panel felt that it was prudent to bring up the issue of sustainability. From the presentations given it was clear that the Germ-Free Poultry facility was a significant part of the Bristol VTRI infrastructure and as such should be considered as a potential income generating opportunity. To this end the Panel suggest that some time be devoted to determining how best to market such a facility.

Is any relevant subject matter or evidence not addressed or under-represented? (Include evidence from within or outside the proposal – please give details)
The Veterinary School should approach the central University administration to see if it is possible to recruit PhD students from the intercalated BSc students before their clinical training. This may offer a small stream of students per year.

Recommendation 6:
To approach the University administration to see if the PhD offered through the Bristol VTRI can be incorporated into the intercalated BSc course.

Please give an overall evaluation for this programme particularly with respect to the VTRI’s objectives of strengthening veterinary clinical research, teaching and training.

The programme has had a good start. There is a real commitment to enhance the standing and importance of research in the veterinary degree at the University of Bristol and this will yield good results for the veterinary profession in the future. The science is excellent and should proceed well. Recruitment of PhD students is the problem (this was anticipated) and steps are being taken to address this.

An excellent attempt has been made to meet the first year’s objectives of this VTRI programme of research and training development. The team running this initiative is up and running and the members are working well together. There is a good spirit and enthusiasm in the group which augers well for the future. The training programme is innovative and should deliver.

The Appraisal Panel are concerned about the lack of veterinary applicants for both the PhD posts and the Postdoctoral positions. The demand being created for research careers at student selection and undergraduate levels will take time to filter through the system and will not help in the life time of the current programme. It was re-iterated again from the original funding meetings that there should be more candidate sharing and general cooperation between each of the vet schools to make best use of ‘research inspired’ recruits.
The research programme is planned in great detail but understandably it is too early for much in the way of results yet. Nevertheless even in the absence of positive results it will have an important role to play in introducing veterinary graduates to research processes.

Recommendation 1:
The Initiative’s long-term future and/or eventual successor should be carefully considered particularly in respect to post-PhD opportunities in professional research.
Response from the Bristol Consortium: We recognise the importance of sustaining this training initiative and are committed to apply for funds from as many sources as appropriate to ensure continued training of veterinarians.

Recommendation 2:
Secondments and short-term attachments opportunities for trainees to gain experience in “state of the art” laboratories could be considered.
Response from the Bristol Consortium: Several exchange visits within the consortium are planned and possibilities for short term training placements at other relevant institutions are being considered.

Recommendation 3:
To contribute to a combined VTRI session at the next AVTRW conference to promote the programme and showcase developments.
Response from the Bristol Consortium: This is being actively explored and Dr Bailey is taking this forward for VT104. One suggestion was to encourage each VTRI consortium to submit abstracts especially from PhD students and post-docs to AVTRW aiming to constitute a full session at the conference. We would welcome any DEFRA support for such an initiative.

Recommendation 4:
Website development to interlink all VTRI sites.
Response from the Bristol Consortium: We agree that the various VTRI websites should be interlinked and would welcome initiatives by DEFRA to support the development of interlinking all VTRI websites.

Recommendation 5:
A report on actual spend should be provided to the funders in order to explain the under spend reported in the first year.
Response from the Bristol Consortium: We have now up-dated the spending figure to the actual spend. The remaining discrepancy between projected and actual spend mainly reflects the 4 month extension of most milestones dates agreed with DEFRA in 2005 and delays in recruitment for some posts.

Recommendation 6:
To approach the University administration to see if the PhD offered through the Bristol VTRI can be incorporated into the intercalated BSc course.
Response from the Bristol Consortium: Discussions with the University administration are on-going.