



THE IMPACT OF
VETERINARY RESEARCH

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Veterinary research is the study of animals, particularly their health, disease and behaviour, and informs and influences a far greater proportion of our lives than many people realise.

“**Veterinary research also contributes to the wider economy, since exotic and endemic diseases of animals cost the UK hundreds of millions of pounds...**”

Veterinary research contributes to quality and safety throughout the whole food chain. It plays a crucial role in human medicine through comparative studies, considers diseases that can cross from animals to humans, such as rabies and BSE, and is a key part of improving animal welfare and ensuring environmental sustainability.

Veterinary research also contributes to the wider economy, since exotic and endemic diseases of animals cost the UK hundreds of millions, even billions, of pounds each year in direct and indirect costs.

Veterinary research is carried out by individuals with a range of scientific backgrounds, including veterinarians. Research is undertaken at institutes and universities, by industry, including pharmaceutical companies, and in veterinary practices around the country. It is funded by government, charities such as the Wellcome Trust, and bodies such as the Horserace Betting Levy Board.

There are numerous examples of veterinary research leading the way in new developments in



Scientist preparing a sample in liquid nitrogen before examining it on a transmission electron microscope.

Photo: Wellcome Trust

biological sciences. For example, the first vaccine against a cancer-causing virus was against a chicken disease – Marek’s disease.

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Other examples of comparative studies, extrapolating work from animals to humans, include work on animal retroviruses such as feline immunodeficiency virus and jaagsiekte sheep retrovirus that have assisted in the search for a vaccine for human immunodeficiency virus (HIV). Investigations into *Salmonella enterica*, a bacterium capable of causing severe and potentially fatal food poisoning, have allowed us to understand how the bacteria spread from the initial site of infection to cause disease (page 4).

The challenges we face in our society today demand a major reliance on science and it is likely that this dependence will increase over the next several decades.

New challenges to veterinary research include the intensification of animal production, greater global movement of humans and animals, and the extreme weather events associated with climate change. All of these factors favour the emergence of new diseases, such as Bovine Spongiform Encephalopathy (BSE) in the UK or Nipah virus in Indonesia; or alter the geographical range of existing diseases, resulting in the monkeypox virus outbreak in mid-western US in 2003 or the blue-tongue outbreak in sheep in northern Europe in the summer of 2006 (page 6).

Veterinary research is a relatively small component of the research sector, but it plays a crucial role in the health of the UK human and animal population and has saved the economy millions of pounds. However, this network of researchers and institutes depends on secure and sufficient funding.



Veterinary research plays a critical role in ensuring the quality and safety of the food chain.

Photo: Moredun Institute

The Royal College of Veterinary Surgeons' vision for veterinary research in the UK is of a vibrant, sustainable, well-connected research platform where the veterinary research community competes internationally in attracting research income, produces high quality scientific outputs, ensures effective and efficient knowledge transfer and provides

excellent research training. The case studies on the pages to follow illustrate the diversity of veterinary research ongoing today, and its relevance to the health and welfare of all animals, including man.

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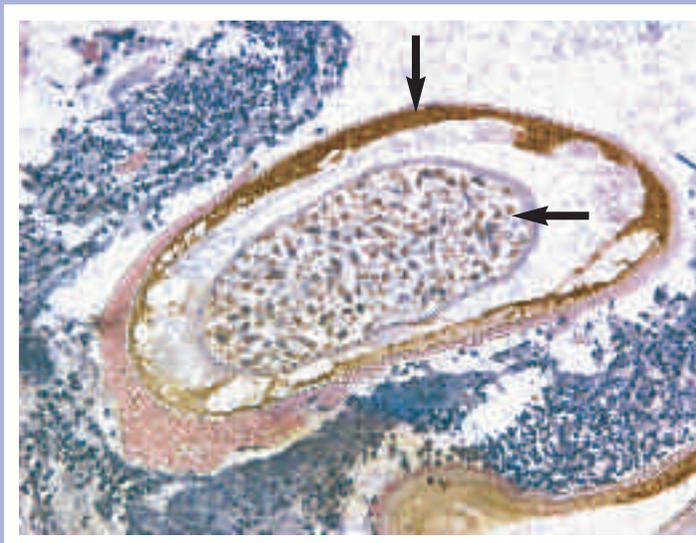
COWS ARE HELPING CURE RIVER BLINDNESS IN HUMANS

Thirty years ago, the new electron microscope allowed minute structures inside cells to be visualised for the first time. Researchers examining a particular group of worms – the filarial nematodes – described how the cells of the worms were heavily populated by bacteria that seemed to be ‘normal’ inhabitants. Their function wasn’t clear, but it was noted that, should they be essential to the worm, they might be a target for drug treatment. This was potentially important because there was no safe and effective drug to eliminate the filarial nematodes that cause severe diseases like river blindness (onchocerciasis), elephantiasis in humans and heartworm infection in dogs.

Yet, inexplicably, this discovery was forgotten until the 1990s. At that time, veterinary researchers at the University of Liverpool, working with colleagues in Germany and Cameroon and funded by the World Health Organisation, were testing different potential drugs for the control of river blindness. They were evaluating drugs in African cattle that were naturally infected with a closely related parasite.

Although the worm in cattle is very similar to the parasite that causes river blindness in people, cattle don’t go blind – indeed they are clinically unaffected – but they provide a means of assessing the effect of drugs on worms.

By chance, one cow was given an antibiotic to treat a bacterial skin infection, and the researchers observed that it cured the cow’s onchocerciasis. Concurrently, scientists elsewhere reported bacterial proteins and DNA in homogenates of filarial worm tissues. Suddenly the findings of the 1970s were ‘re-discovered’ and several teams began systematic, controlled trials investigating the activity of antibiotics against filarial worms.



Cross-section of an onchocerciasis-causing worm. In the centre is the uterus full of larvae. The brown colour in the tissues around the margins of the worm (↓) and within the larvae of the uterus (←) is specifically staining millions of bacteria.

Image: University of Liverpool

The Liverpool / German / Cameroon team were the first to describe in a controlled experiment that antibiotic treatment could kill a filarial nematode, the implication being that the bacteria are essential for worm survival. Further work has shown that the suppression of the bacteria over many weeks is necessary to achieve worm death.

Meanwhile, medical researchers have been carrying out trials in Africa on humans affected by either onchocerciasis or lymphatic filariasis and the promising results provide the greatest advance in the treatment and control of these infections for many years. Moreover, the Liverpool team has gone on to use the same cattle model to demonstrate for the first time that it is possible to vaccinate against onchocerciasis.

Whilst the vaccine is not practical for large-scale human use, the results are crucial proof of principle that immunisation is possible against this infection and provide a valuable impetus in the development of a human vaccine for onchocerciasis.

Taken together, the drug and vaccine research in cows shows what a key contribution veterinary research can make in the fight against human disease.

Langworthy and others (2000) Proceedings of the Royal Society, 267, 1063-1069

Gilbert and others (2005) Journal of Infectious Diseases, 192, 1483-1493

Tchakouté and others (2006) Proceedings of the National Academy of Sciences, 103, 5971-5976

AVOIDANCE TACTICS OF *SALMONELLA ENTERICA*

The Bacterial Infection Group (BIG) at the University of Cambridge's Department of Veterinary Medicine studies several bacterial pathogens involved in human and animal disease. One such pathogen is *Salmonella enterica*, a bacterium that can infect humans and domestic animals causing severe, potentially lethal, infections such as typhoid fever and acute gastro-enteritis (food poisoning).

Tackling these diseases is becoming increasingly difficult because the bacteria are developing resistance to antibiotics and the vaccines currently available are not always effective. The BIG's current research investigates several aspects of the interaction of these bacteria with the immune system to gain a clearer understanding of how the bacteria infect the host and how the immune system fights them.

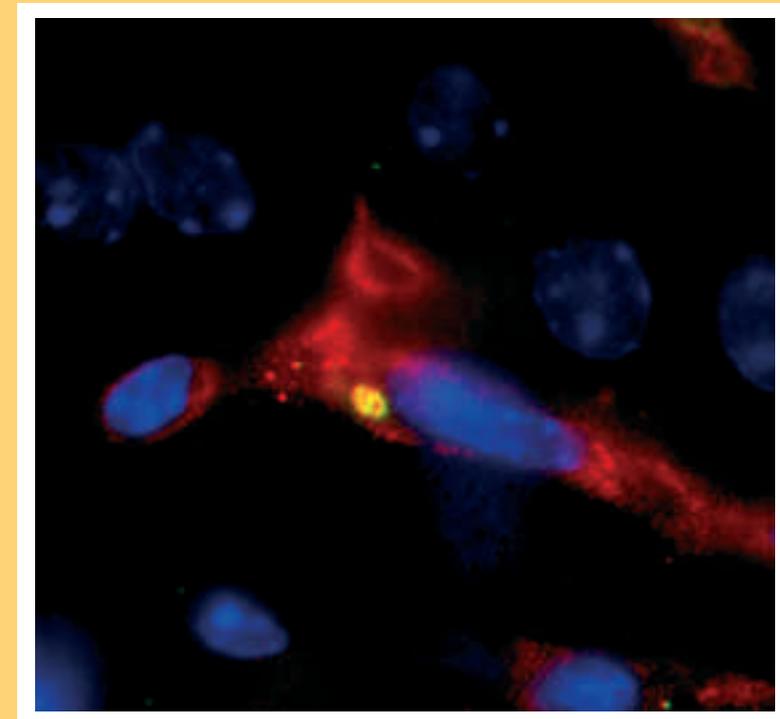
Using advanced microscopy techniques to see bacteria present within individual host cells, researchers in the BIG have found that, during its growth in the tissues, *S. enterica* rapidly kills host cells at the site of infection and spreads to previously uninfected ones. This suggests that the bacteria are continuously escaping from established areas of infection to keep one step ahead of the escalating immune response.

“Tackling these diseases is becoming increasingly difficult because the bacteria are developing resistance to antibiotics and the vaccines currently available are not always effective.”

The BIG is currently using mathematical models to improve vaccine design so that it stops this spread of the infection more effectively. Complementary work is studying the key mechanisms used by cells of the immune system to restrain the growth of bacteria within host cells. This has led to identification of the toxic substances produced by immune cells that enable them to achieve this.

However, the picture is complex. Several strategies cunningly devised by bacteria to prevent them being killed by these substances have also been identified. To counteract this, B cells and T cells (both subsets of immune cells called lymphocytes) continuously need to exchange signals for the activation of protective immunity and the BIG is currently identifying the precise nature of these activating signals.

Brown SP and others (2006) PLoS Biol. 4, 2091-2098
Ugrinovic S and others (2003) Infect. Immun, 71, 6808-6819
Menager N and others (2007) Immunology 120, 424-432



*A multi-fluorescence microscopy image of Salmonella enterica (green-yellow) within a CD18+ liver phagocyte (red). The cell nuclei are stained blue. Most phagocytes contain only one or few bacteria because *S. enterica* continuously escape from infected to non-infected phagocytes during their growth in tissues. This is likely to be a mechanism that allows the bacteria to remain one step ahead of the immune response.*

Image: University of Cambridge

CLUES FOR INJURY-FREE EXERCISE FROM HORSE FRACTURES

Success as an athlete depends upon training all the systems of the body so that they contribute to performance but avoid injury. Each system requires a different training input to achieve this balance. In the flat racing industry, lameness remains the most important cause of days lost from training. The most important injuries causing lameness are fractures. These do not always involve complete breaks in the bone but include 'stress fractures'. These are painful cracks in the bone that, if loading continues, may progress to a complete break but do not initially do so. Such fractures are not only common in horses but also in military recruits, track and field athletes, ballet dancers, figure skaters and gymnasts.

“ In the flat racing industry, lameness remains the most important cause of days lost from training. ”

Revealing the processes by which bones use the loads applied to them as stimuli to become strong enough to resist fracture has been a long-term pre-occupation at the Royal Veterinary College (RVC), however, experiments can only reveal so much. The acid test is to see which training regimens are the most successful in preventing fracture in the field. To do this, the workers at the RVC accessed the daily training details and veterinary records of 1,178 horses over two seasons. These data confirmed a relationship between the incidence of fracture and the exercise

distances trained at canter (<14m/s) and high speed (\geq 14m/s). This relationship suggests that the balance between the bones' loading at high and low speed may be more important to their predisposition to injury than the absolute number of loading cycles.

“ In young horses at the start of training, the cumulative amount of exercise at high speed is associated with reduced risk of fracture. ”

In addition, in young horses at the start of training, the cumulative amount of exercise at high speed is associated with reduced risk of fracture, whereas that at a canter is associated with an increase. These findings are consistent with the results from experiments in the laboratory which show that bones' adaptive responses to loading are related to high strains, which would be caused by high loads, and high strain rates, which would be associated with fast work.

This study is only the first of many needed to establish the training programme that is optimum to produce strong bones resistant to fracture. Once ascertained it must be combined with the



Horses racing to the finish at Windsor. Studies have revealed that high impact exercise produces a beneficial response from bone cells.

Photo: RCVS

optimum regimen for speed and endurance. These data should make racing safer for the horses and reduce wastage due to injury. They are unlikely to make it any easier to choose winners!

Verheyen KLP and others (2006) Bone, 39(6), 1322-30.

BLUETONGUE SPREADS CLOSER TO UK SHEEP POPULATION

Bluetongue is a serious disease of ruminants, particularly sheep, and is caused by a bluetongue virus (BTV). Infected sheep may lose condition, have muscle degeneration, develop respiratory distress and can die. Bluetongue was once a disease only found in Africa and Asia and parts of the Americas but in the last ten years has been encroaching northwards through southern and eastern Europe, coincident with increasing temperatures in Europe.

The first outbreaks in northern Europe originated directly from a source outside Europe and were reported in the summer of 2006 in the Netherlands, Germany, France, Luxembourg and Belgium.

New genetic techniques developed at the Institute for Animal Health (IAH) to improve identification of the virus types in Europe have made it possible to identify from which regions of Africa and the Middle East these viruses have come.

We also know that *Culicoides imicola*, an Afro-Asian species of midge that is a major vector of BTV, has spread widely throughout southern Europe in recent times. It has brought with it five different types of BTV, originating from different parts of Africa, the Middle East and Asia (see right). For example, type 1 virus, similar to viruses present in India, entered Europe via Anatolian Turkey. Type 2 virus entered Europe from the south, possibly from sub-Saharan Africa, where it is endemic, or by moving across North Africa via animal trade routes.

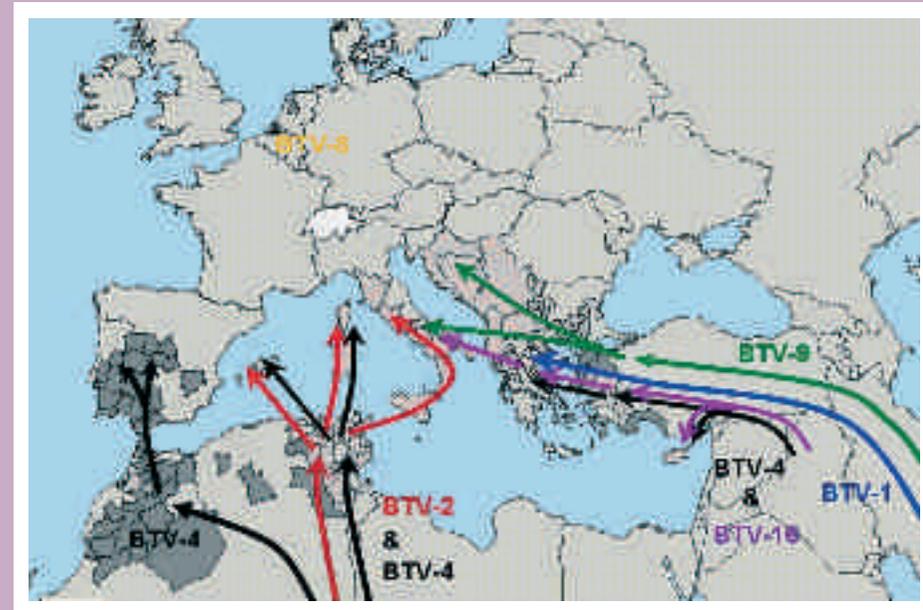
Genetic analysis also revealed that the type 16 BTV in Europe had probably originated from a vaccine strain of virus, that is the vaccine had mutated back to a disease-causing form. Novel vaccines are being developed to avoid this reversion. Recent research at the IAH has revealed that the strain of BTV that caused northern Europe's first ever outbreaks in 2006 was not closely related to those present in southern Europe, but was serotype 8, which is found in sub-Saharan Africa. Details of its route to northern Europe remain a mystery.

IAH research has also shown that the midge *Culicoides imicola* is not the only species of midge capable of transmitting BTV. Rather, two other species complexes that are already widely established, especially in northern Europe (including the UK), are also capable of spreading the virus, highlighting the potential for its further spread.

Climate change is likely to exacerbate the levels of risk. Current research at IAH is concentrating on developing new generations of safer vaccine, and assessing the threats posed to UK livestock by these viruses under existing and future climate scenarios.

This work was supported by the Biotechnology and Biological Sciences Research Council, the Department for Environment, Food and Rural Affairs, the European Commission and the Wellcome Trust.

Mertens PP and others (2007) Journal of General Virology, in press
Purse BV and others (2005) Nature Reviews, Microbiology, 3, 171-181



Genetic analysis of bluetongue viruses isolated in Europe has revealed not only that five types of the virus (1, 2, 4, 9 and 16) have entered the region since 1998, but also the routes by which they came. Serotype 8 has been isolated from the 2006 outbreak in northern Europe; its provenance is currently unclear.

Image: Institute for Animal Health

DID YOU KNOW THAT IN...

1880

Griffith Evans, who studied at the Royal Veterinary College (RVC), discovered the first disease-causing trypanosome (*Trypanosoma evansi*) in horses in India.

1892

John McFadyean developed the first laboratory in Britain devoted exclusively to veterinary diagnosis and research, and in 1900 he proved that African horse sickness, a serious and fatal disease of horses, mules and donkeys, was caused by a virus.

1897

Bernhard Bang, a Danish veterinarian, was the first scientist to use tuberculin on cattle, and realised its importance in identifying infected animals. He went on to develop control measures for bovine tuberculosis that led to a dramatic decrease in the incidence of the disease. In 1897, Bang also discovered the bacterium *Brucella abortus* to be the cause of “undulant fever” in cattle. This organism can infect and cause chronic disease in humans.

1923

Gaston Ramon, a French veterinarian working at the Pasteur Institute, manipulated the deadly diphtheria and tetanus toxins into effective vaccines.

1945

Robert (“Robin”) Coombs, graduate of the Edinburgh Veterinary School, published a method to detect the agglutination of red blood cells in the presence of antibodies. This became known as the Coombs Test and is used for cross-matching blood types prior to transfusions and the diagnosis of a number of autoimmune diseases. For example, it is used in diagnosing haemolytic disease of the newborn associated with a rhesus negative mother.

1950s

Walter Plowright, Fellow of the Royal College of Veterinary Surgeons, developed a vaccine against the cattle plague rinderpest. Due to the success of the vaccine, rinderpest is predicted to be the first animal disease to be eliminated worldwide by 2010.

1970

Vaccination against Marek’s disease was introduced using a vaccine developed by **Peter Biggs**, a Fellow of the Royal College of Veterinary Surgeons and a graduate of the RVC. This was the first example of an effective vaccine against a naturally occurring cancer in any species.

1996

Peter Doherty, an Honorary Fellow of the Royal College of Veterinary Surgeons, was awarded the Nobel Prize for Physiology or Medicine for his work on immune recognition.

Produced on behalf of the RCVS Research Subcommittee

Cover photo: Moredun Institute

