BRIDGING THE GAP

Linking animal and human medicine through veterinary school research and One Health
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We have long understood the value of improving animal wellbeing as an end in itself, whether to companion animals or livestock. But increasingly we learn that our relationship with them is more complex than the moral obligation we feel today or the working relationship we have had for millennia. Their importance to humans extends to the fundamentals of our physical and even mental health – just as we, and our behaviour, are so important to them. At the centre of all this is veterinary research.

Coordinating with colleagues across many sectors, veterinary researchers work to bridge the gap between animal and human medicine. Veterinary schools are the natural place for their ground-breaking work. This publication showcases just a small example of veterinary school research and its impact on society, revealing the best examples of research submitted to the Research Excellence Framework in the UK, as well as work from colleagues in Ireland and the Netherlands.

The case studies cover a wide range of subject areas and their impact on the public is strongly apparent. By protecting livelihoods, creating millions of pounds of savings through disease prevention and control programmes, and generating private investment in innovative ways, it is absolutely clear that veterinary research is a great boost to the economy.

Beyond financial benefits, though, the case studies demonstrate the importance of veterinary research to society. Every example in this publication delivers benefits for the public that align to key Government objectives to protect public health and animal health and welfare.

Animals and humans have long been interdependent, but the nature of this dependence is always changing. Our health and animal health will likely face challenges of greater size and complexity. Therefore it is fundamental that world-class research, such as that undertaken in veterinary schools, is continued and vigorously supported.

Professor Nigel Gibbens CBE
Chief Veterinary Officer for the United Kingdom

“IT IS ABSOLUTELY CLEAR THAT VETERINARY RESEARCH IS A GREAT BOOST TO THE ECONOMY.”
The global population is expected to see an increase of 1 billion by 2030 and may increase a further billion by 2050. This rise in the population will result in greater pressures on resources and present major challenges to ensure food sustainability and security.

Disease in farmed animals can undermine food safety and animal welfare as well as weaken the sustainability of our food chain through substantial production losses and waste. This cost is felt not only in the loss of meat but also in the reduced yields of other crucial animal products such as milk and eggs. The impact of animal diseases can be catastrophic. The 2001 Foot and Mouth epidemic in the UK resulted in the slaughter of over four million livestock and was estimated to have cost the UK economy £8 billion. Therefore veterinary research is fundamental in ensuring the security of the food supply, as well as reducing the economic and safety risks connected to animal health.

The case studies that follow showcase research that veterinary schools have conducted to help improve the security of food animals against disease. The work ranges from creating genetic markers leading to improved selection methods to a range of health schemes that not only help minimise outbreaks but also reduce the conditions where diseases are likely to occur. The research has helped create savings through efficiency measures and reduced losses, benefitting producers, consumers and the overall economy. The veterinary schools’ research has also had valuable impact on government policy and best practice in the UK and globally.

Bovine mastitis, an inflammation of the mammary gland following bacterial invasion, is the foremost endemic infectious disease of dairy cattle worldwide. Mastitis is financially the most important disease of dairy cattle, causing animal production losses of more than £170m in the UK and $2bn in the USA. As well as the severe welfare implications, bovine mastitis has resulted in an increased environmental footprint. Furthermore, mastitis is one of the most common reasons for the use of antimicrobials in dairy cows. With current concerns regarding the emergence of antimicrobial resistance in agriculture, there is a widespread drive to reduce the use of antimicrobials in food-producing animals. In Great Britain, the incidence of mastitis in dairy cattle is between 45–65 cases per 100 cows per year.

Researchers at the University of Nottingham, funded by AHBD Dairy, have developed a nationwide control scheme to help combat the disease. The AHDB Dairy Mastitis Control Plan enables veterinarians and consultants to identify the best interventions for individual dairy farms and produce a farm specific preventive plan. The plan includes a novel piece of software to enable trained users to carry out the process. The control plan produces a hierarchical ranking of possible farm interventions, and places them in order of likely efficacy, dependant on the farm’s mastitis pattern. The AHDB Dairy Mastitis Control Plan encompasses the entire process: from farm diagnosis, to identification of the best control measure, to implementation of the measures on farms. Control measures could include making alterations to the cow’s environment, changing the milking procedure or changing nutrition for cows in their ‘dry’ period.

The AHDB Dairy Mastitis Control Plan has proved to be a huge success, with current analysis of farms in the scheme indicating a reduction in clinical disease of 10–20% per year. As a result, the programme has provided multimillion pound savings to the dairy industry estimated to be at £5–10m per annum. By reducing clinical and subclinical mastitis, the scheme has allowed dairy farmers to benefit financially, improve cow welfare, reduce their environmental footprint and improve the sustainability of milk production. The veterinary sector has also benefited from increased sustainability of the practice model, with a greater focus on disease prevention rather than treatment. The research and national control programme have also had an international impact by influencing other national disease policies and programmes, including in the Netherlands, Australia, Chile and the USA.
Infectious pancreatic necrosis is a viral disease that has been a major constraint on salmon aquaculture, spreading rapidly among salmon farms in Scotland and around the world. Typical mortality levels in an epidemic are approximately 25%, and severe outbreaks are known to kill as many as 80–90% of farmed fish.

Research at the University of Edinburgh demonstrated that host resistance is a heritable trait and that observed genetic differences are almost entirely due to variation in a single quantitative trait locus (a section of DNA that correlates with variation in a phenotype) of the salmon genome. Researchers found that the large effect of the quantitative trait locus on resistance was consistent in seawater cages and in controlled freshwater disease-challenge experiments. Fish which inherited two copies of the resistant variant of the quantitative trait locus from their parents had negligible mortality, whereas those that received the susceptible variant from both parents had mortality levels higher than 50% during epidemics.

Further study led to the investigation of the differences in gene sequence between salmon carrying resistant alleles and those carrying susceptible alleles by using sequencing technology. This has enabled the detection of more closely linked DNA sequence markers that show association with resistance to the infectious pancreatic necrosis virus at the population level. Incorporation of these improved markers into industry selective breeding programmes has further improved the accuracy and simplicity of genetic tests that enable the identification of resistant fish at an early stage.

As a result of the Edinburgh research, the salmon breeding company with which it was collaborating, Landcatch Natural Selection, implemented marker-assisted selection for infectious pancreatic necrosis resistance when selecting its elite and commercial populations. This was the first successful documented example of marker-assisted selection in any aquaculture species.

Analysis has shown that using marker-assisted selection to combat resistance reduces infectious pancreatic necrosis mortality by 25%. This has equated to an economic impact of £26.4 million. It has also led to the reduced ecological impact of salmon farming, as infectious pancreatic necrosis is an endemic infectious disease that affects both wild and farmed salmon. Landcatch Natural Selection has also developed DNA sequence chips that detect genes with a predisposition to disease. The chips will help improve the competitiveness and sustainability of the UK salmon industry. This new application of genomic technologies has been made possible by the success in finding genomic solutions to infectious pancreatic necrosis.
Combating neosporosis in cattle through herd health schemes

Researchers:
Trees, Williams and team

Neospora caninum is an important protozoan parasite infecting cattle and dogs with the disease neosporosis. It has its most serious effects in cattle, where it is considered responsible for 6,000 abortions per year in England and Wales alone. Worldwide farming losses in 2013 were estimated to be $1.3bn; two thirds of those losses occurred in dairy cattle and one third in beef. Global data indicates that 16% of dairy cattle are seropositive for neosporosis, which rises to over 40% in aborting cows. There are currently no effective drugs or vaccines to control neosporosis.

Research on neosporosis was initiated in 1996 after N. caninum was isolated for the first time in Europe by researchers at the University of Liverpool, and led to the development of a diagnostic enzyme-linked immunosorbent assay (ELISA). This serological test was aimed specifically at diagnosing Neospora-associated abortions, but was adapted and validated by the University of Liverpool for surveillance purposes. Subsequent epidemiological work stemmed from development and application of this test.

Between 1996 and 2010, researchers at Liverpool produced the first analysis of the relative importance of vertical transmission compared to post-natal infection of cattle. They showed that in normally calving N. caninum-infected cattle, transplacental transmission occurred in 95% of pregnancies and that an infected animal was seven times more likely to abort compared to uninfected cattle. The group’s research also showed that the parasite was more likely to cause abortion early in gestation. This was linked to foetal immuno-competence.

Research findings were used to create significant economic benefits for the UK’s cattle industry by collaborating directly with the Animal Health and Veterinary Laboratories Agency (AHVLA) and Myhealthyherd to design health herd schemes to reduce the economic impact of N. caninum. Between 2008 and 2009, two schemes were launched based on the advice from the group’s research: one a commercial scheme, Myhealthyherd; and the other, AHVLA’s Herdsure scheme. By obtaining herd health accreditation or joining Myhealthyherd, farmers could create their own herd health plans in conjunction with their vets, manage infectious disease, work out profit opportunities and obtain a health visa, to maximise the sale value of stock. To date, over 5,000 farms now use Myhealthyherd in England and Wales. The knowledge gained from the Liverpool research not only benefited UK dairy farmers but has also impacted the control of neosporosis worldwide.
Defining Government policy on Bovine tuberculosis

Researchers:
Kao, Mellor, Logue, Bessell, Orton and team

Bovine tuberculosis is caused by the pathogen *Mycobacterium bovis*, which infects livestock and wildlife. It has severe socio-economic consequences and an impact on animal health. In the absence of improved control, a recent official estimate of the projected economic burden to the UK over the next decade was predicted to be £1 billion.

Bovine tuberculosis is one of many infections in animals that are subject to veterinary surveillance. This involves screening, collecting samples and analysis with the aim of rapidly identifying and controlling threats to animal and human health. Surveillance of bovine tuberculosis involves government-sponsored testing of all herds at regular intervals with additional testing in slaughterhouses.

In 2009, Scotland was granted regional OTF status (Officially Tuberculosis Free), at which point the majority of cattle herds in Scotland were tested on a standard four-year cycle. Following this, researchers at the University of Glasgow were appointed by the Scottish Government to develop a risk-based bovine tuberculosis surveillance model specifically designed for Scotland. Based on the risk factors identified for Scotland, the resultant predictive statistical model used detailed information on the past patterns of herd outbreaks to calculate the probability that any given herd would be free from infection with *Mycobacterium bovis*. Analysis revealed that by giving consideration to these risk factors, only 65% of Scottish herds would require regular (four-year interval) testing to replicate the detection rates achieved under the conventional system.

Subsequently, the team worked with members of the Animal Health and Welfare Veterinary Laboratory Agency (AHVLA), which is responsible for implementation of bovine tuberculosis testing, as well as the Chief Veterinary Officer for Scotland, to identify the most appropriate surveillance model to implement through existing AHVLA channels in Scotland. Previously, the four-year testing cycle and annual costs for bovine tuberculosis control in Scotland averaged £2 million a year. The revised cycle, while maintaining Scotland’s OTF status, translated into the exemption of more than 30% of Scottish herds from routine testing, with an associated government saving of £150,000. The revised policy also provided savings to the Scottish farming industry in the region of £100,000 and limited the risks of bovine tuberculosis testing to farmers, veterinarians and cattle. The success of the ground-breaking research has been highlighted by the civil service as best practice policy-making and provided the opportunity to transform industry practices and livestock surveillance policy across the UK and beyond.
Developing control strategies against an infectious cattle disease

Researchers:
Gormley and team

Since the early 1990s, a comprehensive bovine tuberculosis (BTB) testing and control programme for cattle has been implemented in Ireland, with current annual costs of approximately €60m. However, the badger population acts as a reservoir for *Mycobacterium bovis* infection and contributes to the persistence of tuberculosis infection in associated cattle populations. The choices for dealing with tuberculosis in the badger reservoir host are often limited by conservation and social concerns, though targeted vaccination against tuberculosis is an option that could directly facilitate the advancement of BTB eradication in affected areas by reducing the burden of infection in badgers.

Investigators at University College Dublin are engaged in a programme of research with the objective of improving diagnostics of bovine tuberculosis and to develop a vaccine to control the disease in badgers. The BCG vaccine has been chosen for use based on its availability, low production cost and widespread experience of its application in domestic and wild animals, and humans. Studies with captive badgers have established that vaccination of badgers with BCG, when delivered by a variety of routes, can protect badgers against tuberculosis.

The University College Dublin team has also carried IFN-gamma testing on the national cattle herd to assist in the eradication of bovine tuberculosis. In the period 2014-2015, approximately 52,000 blood samples were submitted to the University College Dublin laboratory, which continues to conduct research to help improve testing performance. The laboratory is also conducting studies to investigate the underlying causes of false positive results in the skin test. These false positives may constrain against eradication of the disease in cattle, and the objective of this research is to overcome this impediment.

The ongoing costs of BTB disease control programme in Ireland remain a significant burden on the national Exchequer and the farming sector. Arising from the research carried out at University College Dublin, Ireland is now implementing a comprehensive interim strategy to minimise transmission from badgers while maintaining and enhancing the existing measures to control cattle-to-cattle transmission. The incorporation of BCG vaccination of badgers into the national bovine tuberculosis eradication programme has the potential to reduce the time frame for eradication. For the first time in the history of the programme, this time frame has become short- to mid-term, possibly as short as 15 years after a vaccine roll-out.
Animals, like humans, can experience pain and suffering as well as comfort and contentment. With millions of food and companion animals in the UK, animal welfare is a major public concern. This relates not just to animal health but to our own: recent studies show the positive impacts companion animals have on the health of their owners.\(^3\)

The UK companion animal market, as well as the equine industry, is steadily growing, with both currently worth billions to the economy. Not only is this beneficial to UK GDP but it reiterates the growing demand to maintain the health of these markets. Continued research undertaken at the veterinary schools has helped improve equine and companion animal welfare, particularly against genetic and chronic diseases.

In farm animals, good welfare practice not only endorses ethical treatment of animals but also reduces the risk of disease. Environments which do not fulfil basic needs can cause adverse effects on an animal's health by increasing its susceptibility to pathogens.\(^4\) This negatively affects industries that rely on farmed animals and their products. It reduces sustainability, food safety and quality, and increases carbon footprints. The biggest concerns relating to welfare are of course ethical. Farmed animals should experience a good standard of living in conditions that encourage health and wellbeing. Veterinary research has worked to improve the conditions of farm animals in both the UK and Europe. The impact on policy has been vast, with many European directives being heavily influenced by the veterinary schools’ work.

The case studies that follow highlight the importance of veterinary research on animal welfare. As well as improving breeding programmes and treatment for chronic conditions, veterinary research has played a significant role on welfare policy. From improving housing conditions to changing transportation methods of animals, the work has helped set a standard for animal welfare. Along with influencing policy-makers in the UK and Europe, many of the veterinary schools’ studies have been cited as evidence for changes in welfare policy across the globe.

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Bettering care for feline chronic kidney disease

Researchers:
Elliott and team

Chronic kidney disease (CKD) is a common ailment with cats in the UK. Recent studies report that approximately 3.6% of cats may suffer from CKD and that renal disorders were the most common cause of mortality in cats over five years old.

Researchers at the Royal Veterinary College aimed to understand the epidemiology of feline CKD and aid identification of the burden of disease within the UK cat population. Working in partnership with the animal charity PDSA, which runs primary care practices nationally, the team recruited cats with CKD for a longitudinal study. This long-term strategy has yielded landmark publications in areas of hyperphosphataemia, hypertension and proteinuria. All of these are proven to be important factors in management of CKD. The group demonstrated that hyperphosphataemia and hyperparathyroidism could be treated by use of clinical renal diets therefore effective treatment was associated with improved survival. This work informed international recommendations for target levels in managing hyperphosphataemia with diet and feed additives. Furthermore, the recognition that the clinical outcome of a CKD patient was associated with the severity of proteinuria at diagnosis was considered a seminal observation that has changed thinking about feline CKD. This discovery has led to the publication of international guidelines that monitoring proteinuria is an essential component of the management of the feline CKD patient.

Subsequently, the research has attracted repeated investment from pet food manufacturers to work with the group to improve diets for cats with CKD, as well as being used by veterinary pharmaceutical and diagnostic companies to inform product development. In addition, companies have provided in-kind contributions of clinical renal diets used within the charity clinic of the PDSA and the Beaumont Sainsbury Animal Hospital, to provide high-quality treatment for owners who otherwise could not afford to treat their cats. More than 1,000 cats and their owners have benefited from this provision of free treatment and have taken part in ongoing research.

The research has also helped inform the development and improvement of dietary therapy for cats with CKD. The group’s work has stimulated the launch of two feed additives for the restriction of phosphate in the feline diets, two drug products for the management of proteinuria associated with CKD and has also underpinned the development of new diagnostic products. Furthermore, the International Renal Interest Society, which works to educate practitioners worldwide, has used the team’s research to inform its diagnostic algorithms and treatment recommendations.
Developing a carrier test for a fatal equine genetic disease

Researchers:
Carter and team

Foal immunodeficiency syndrome (FIS) is an inherited equine disease which has caused much concern in the equine industry. First reported in fell ponies in 1997, FIS is a 100% fatal disease that affects foals of 4–12 weeks.

Research conducted at the University of Liverpool identified the key biological defects in affected foals: profound anaemia and loss of B lymphocytes leading to reduced immunoglobulin production. This would cause foals to succumb to opportunistic infections. In addition to its significance for equine welfare, the data showed that FIS is a novel immunodeficiency, providing insight into mammalian immune system function.

Further study showed that FIS had an autosomal recessive genetic basis. This explained why affected foals were being produced after matings of clinically normal mares and stallions which were FIS carriers. Consequently, the mutated gene was spreading undetected in the equine population, increasing the likelihood of the disease being passed to other breeds by crossbreeding. The team utilised the equine genome and identified microsatellite markers that clearly dictated strong FIS linkage to chromosome 26. The location of the aberrant genetic mutation was confirmed and refined with a whole genome single nucleotide polymorphism array identifying 54,600 equine single nucleotide polymorphisms, and enabling a genome-wide association study. Following this, further sequencing identified the single nucleotide polymorphism completely associated with FIS. A test was developed to identify this in samples and was made available to owners to enable identification of FIS carriers prior to breeding.

The principal impact of the group’s research is the provision and deployment of a carrier test for FIS. This new diagnostic veterinary tool for risk-free breeding was immediately offered to owners of the two most at risk breeds (fell and dales ponies) and led to rapid reductions in FIS rates. In addition, the screening programme unexpectedly identified the spread of the disease in two further breeds: coloured ponies and cob ponies. Since its introduction, the test has led to a dramatic reduction in the number of FIS foals born, with only one FIS foal born in 2012. The screening programme has benefited vets, owners and breeders and the entire equine population through reduction in incidence and spread of this fatal disease.
Commission was satisfied that the science did justify the proposed ban on conventional cages.

The resultant European Directive took effect in January 2012. It prohibited the use of conventional battery cages for laying hens and introduced replacement enriched cages. This had a major impact on chicken welfare and was significantly influenced by Bristol research. The new directive increased the size of a cage to 750 cm² per bird, with provision for nest, litter and perches.

After the traditional cage was banned, the number of hens in enriched cages was reported to be 210 million birds in 2012 (42% of EU production). Bristol research contributed directly to both the content and implementation of the directive, in turn impacting on production systems and welfare. Following this, New Zealand has also banned conventional battery cages from 2022 (with expertise and advice provided during the process by the University of Bristol). Other countries, US states and international retailers are now in the process of phasing out battery cages.
Improving welfare for farm animals in closed confinement

**Researchers:**
Broom and team

In recent decades, intensive animal farming methods have been used in an attempt to increase production at relatively low costs. This type of farming usually involves keeping livestock in confined settings such as battery cages, gestation crates, and veal crates.

A major strand of the research carried out at the Centre for Animal Welfare and Anthrozoology (CAWA) at the University of Cambridge has been regarding the welfare of farm animals in close confinement, with a particular focus on the conditions of sows, calves and laying hens. Researchers studied how sow welfare was poorer when confined in stalls than loose-housing systems, and built a body of evidence to demonstrate this to policy makers. They did the same for veal calves by identifying many negative physical and psychological effects on calves that were housed in small crates. This included abnormal physiology as well as increased incidences of repetitive behaviours. CAWA’s research on laying hens presented evidence that linked osteopaenia and bone weakness to the use of battery cages. This would then lead to increased numbers of painful bone breakages during the commercial handling of hens.

The impact of the team’s work throughout the EU has been substantial. The research has led to new legislation, binding codes of practice and changes in animal production methods in both the UK and countries around the world. CAWA research, together with similar work by others, led to a ban on the use of stalls and tethers for pregnant sows and has resulted in a major change in conditions for the 13–14 million sows in the EU. The work has been quoted in reports that have led to similar impacts in Norway, New Zealand, Australia and nine states in the USA.

The CAWA team’s work on calves led to banning the use of small crates for calves after eight weeks. This had to be implemented on all farms by 1 January 2007 with the number of calves affected in the EU being 26 million per year. CAWA publications were also quoted in EU scientific reports which initiated a ban on the use of battery cages in the EU. Similar legislation referring to CAWA research has now been passed in New Zealand and some US states. Furthermore, the work carried out by the CAWA team was used in formulating the UK Animal Welfare Act (2006) as well as many EU reports.
Transforming feline health through pioneering PCR assays

Researchers:
Helps, Tasker and team

Accurate diagnosis of infectious and genetic diseases is important for the treatment and management of cats by vets, as well as to inform breeding policy to reduce the prevalence of inherited genetic diseases. Infectious agents result in serious and welfare-compromising clinical signs in cats, which can be fatal if not detected and not treated appropriately.

University of Bristol’s School of Veterinary Sciences was the first UK centre to develop and commercially offer quantitative polymerase chain reaction (PCR) assays, a method used to amplify DNA or RNA, to detect a range of feline infectious and genetic diseases. Early studies resulted in the development of PCR assays for detecting feline herpesvirus, feline calicivirus, Chlamydia felis and Bordetella bronchiseptica. These were initially used in samples from over 1,700 cats from 218 European catteries. Subsequent research led to the development of PCR assays to detect feline haemoplasmas, feline immunodeficiency virus and feline leukaemia virus. To date, 12 PCR assays have been developed for a range of important feline infectious diseases and more than 10 PCRs have been developed to detect a range of genetic diseases.

The success of the PCR assays developed by the group has led to significant commercial activity with Langford Veterinary Services, with revenue in excess of £1.7m to date, which has helped fund further research. Consequently, these PCR assays are now offered to vets and cat breeders throughout the UK and Europe. Between 2002 and 2013 more than 53,000 PCR tests had been performed on over 40,000 cats. This has led to improved health outcomes for cats with infectious diseases due to more accurate diagnosis and treatment, and prevention of infection transmission with appropriate management.

Furthermore, there has been a 90% reduction in the number of cats testing positive for the polycystic kidney disease mutation over the eight years the researchers have been running the test. This is due to more effective screening, using the genetic test, and subsequent breeding.

An ever increasing number of vets and breeders are using the PCR testing service. Since 2009, 705 veterinary practices and 30 referral and university diagnostic laboratories, both in the UK and Europe, have submitted samples for feline infectious disease PCR testing. In addition, over 1,900 cat breeders across Europe have used the genetic testing service since 2005. Through sharing reagents derived from the PCR assay development, a number of other international laboratories are now offering infectious disease testing by PCR, enabling cats worldwide to be tested for infectious diseases.
ACHIEVING ONE HEALTH

The German pathologist Rudolf Virchow, often cited as an originator of the One Health concept, believed there to be no dividing line between animal and human medicine; instead, the two are interconnected.

The One Health initiative recognises this relationship between animals, humans and their ecosystems and works to ‘improve the lives of all species through the integration of human medicine, veterinary medicine and environmental science’. Though the concept has many definitions, a key feature of One Health is the promotion of collaboration between all sectors, locally, nationally and globally.

Animals share many common features with humans and experience similar chronic illnesses. This has allowed research into comparative medicine which uses animal models to help further our understanding of both animal and human disease. Researchers in this field have encompassed One Health ideas by collaborating with colleagues across the human and animal spectrum of medicine.

The One Health initiative is also viewed as essential in developing best practice in the fight against zoonoses – infectious diseases in animals that can be passed on to humans. This is a significant and global problem, with the World Health Organisation reporting that 75% of all diseases discovered during the last twenty years have had zoonotic origins. This is due to more efficient and economical travel, increased food production and expanded trade agreements, making transmission of zoonoses easier. Zoonotic diseases not only pose a threat to public and animal health, but they are also known to have devastating impacts on economies, particularly in developing nations. One Health has encouraged a new approach in responding to these infectious diseases which involves cooperation between physicians, veterinarians, governments and other professionals in the social and environmental field. This has led to joint efforts in diagnosis and prevention measures as well as improved communication to ensure greater control of disease.

The case studies that follow demonstrate many examples of the One Health approach. They emphasise Virchow’s belief in the interconnectedness of animal and human health by showcasing the impact that animal wellbeing has on public welfare. This includes examples of comparative studies that have furthered our knowledge of non-communicable disease to control measures and vaccination programmes which are helping combat emerging infectious diseases, particularly in the developing world. Therefore veterinary research, aided by One Health methods, continues to play a crucial role in protecting the future of public health.

Osteoarthritis is a degenerative joint disease which mainly affects the articular cartilage. It is associated with ageing and affects the knees, hips, fingers, and lower spine region. Worldwide estimates are that nearly 10% of men and 18% of women aged over 60 have symptomatic osteoarthritis (OA). The World Health Organisation estimates that 80% of those with OA have limitations in movements and 25% cannot perform major daily activities. The majority of OA patients receive periodic knee joint injections of steroids and/or hyaluronic acid (used to help lubricate joints), but the benefits are short-lasting and pain relief is limited. There are also some potential side-effects of steroids. Therefore there is a clear alignment of unmet clinical and commercial needs in seeking novel formulations.

The Science Foundation Ireland-funded Centre for Research in Medical Devices (CURAM) was established in 2015. One of its current projects led by the University College Dublin School of Veterinary Medicine focuses on nanomedicine, a form of drug delivery that allows the targeting of specific cells through materials with sizes in the nanometre range. The research team discovered that the peptide, calcitonin, had anti-inflammatory actions (in addition to its known benefits in osteoporosis) and hypothesised that a direct injection into the knee joints in nanocomplexes with hyaluronic acid might help reduce arthritic inflammation. Next, a delivery system had to be developed that allowed optimum exposure of the compound to the target area for a decent period. It is important to note that the hypotheses of the idea and development of the subsequent delivery system were collaborative efforts with other key colleagues from University College Dublin and Trinity College Dublin.

The new treatment developed by the team showed a marked decrease in indicators of inflammation following a single injection into joints of a mouse model. The patent application had inventors from University College Dublin and Trinity College Dublin and was written shortly after. The team is currently working on another collaborative project focusing on joint delivery to sport horses, as competition animals are not allowed steroids. Therefore the research carried out by the multidisciplinary University College Dublin team, as well as their collaborators, has worked to improve the health and standard of care for sufferers of this long term condition in both humans and animals.
Discovering a new MRSA emerging in human and bovine populations

Researchers:
Holmes and team

Methicillin-resistant *Staphylococcus aureus* (MRSA) causes a wide range of diseases in both humans and animals, including bovine mastitis, which is a very common and economically significant disease of dairy herds. It is distinguished by the fact it contains a gene which encodes a particular protein with low affinity for antibiotics. This allows resistance to these antibiotics, including the commonly used methicillin.

Researchers at Cambridge identified a novel variant of MRSA in livestock representing a previously unidentified reservoir of infection. The novel isolate of *S. aureus* was identified as being resistant to certain antibiotics in a way that would normally identify it as MRSA. However, established tests were negative for the gene which was understood to cause the identified resistance. Further research culminated in whole genome sequencing of this isolate, which found that the genetic basis for the resistance was a different, previously unclassified gene.

The failure to detect this new gene using a screening standard method (polymerase chain reaction) led the team to adapt the method so as to detect this new MRSA. Following this, the screening of the new MRSA isolates in humans, and comparing with bovine isolates, revealed an apparent clustering by geographical region. All the isolates obtained from human samples were animal associated.

Prior to this research, patients presenting with MRSA which was positive for the newly classified gene were wrongly diagnosed as carrying ‘methicillin-susceptible’ *S. aureus* rather than ‘methicillin-resistant’ *S. aureus* – a crucial difference when allocating treatment. The importance of the research was highlighted by the immediate adoption of the group’s adapted screening method for MRSA detection in laboratories in the UK and across Europe. UK Department of Health and international microbiology reference laboratories have now developed a number of further tests to identify the newly classified gene for clinical laboratory use as well as to better detect accurate diagnosis of MRSA in infected patients. In hospital settings, there is increased use of automated polymerase chain reaction-based screening, and the test equipment is being updated to make provision for screening for the newly classified gene among patients presenting with MRSA. Additionally, the discovery of the new gene has been used to inform policy decisions at a governmental level in the UK, Europe and in the USA.
Driving the One Health response to the threat of avian influenza

Researchers:
Pfeiffer and team

Highly pathogenic avian influenza (HPAI), commonly called bird flu, is a highly transmissible disease of poultry, with a flock mortality approaching 100% in vulnerable species. Since its emergence in 2003, 63 countries have reported outbreaks of HPAI subtype H5N1 in domestic and wild birds. In Southeast Asia alone, virus outbreaks have caused the destruction of 140 million birds, equating to losses of around $10bn and putting low income families’ livelihoods at risk. The virus also constitutes a major public health risk: nearly 600 human infections have been reported, with a mortality of 60%.

The Royal Veterinary College’s Veterinary Epidemiology, Economics and Public Health team embarked on a series of studies, research and data analysis to inform and help governments and global health authorities to respond quickly to an outbreak of the disease. The RVC team took an interdisciplinary approach to their research, working alongside their overseas colleagues and other UK higher education institutions. This collaboration is a key aspect of the One Health response.

The group’s research showed that farming systems in Asia’s Mekong Delta, involving domestic water birds and rice production, represented ideal conditions for the spread of infection. Analysis also suggested that vaccination campaigns in countries such as Vietnam contributed to transmission of infection. This was due to either ineffective vaccination or via the people administering the vaccinations.

Collaborative work in the UK has shown that planned interventions based on movement restrictions would control the majority of outbreaks – neither localised reactive vaccination nor culling were likely to have a substantial impact. Globally, the Royal Veterinary College team demonstrated that confined food animal production systems can increase animal and public health risks, thus geographical variations in poultry density and production systems must be taken into account to inform preventative measures.

As a result, the Royal Veterinary College team’s research has had a substantial international impact on global disease control policy. The group’s studies were closely aligned with policy resulting in the rapid translation of programme findings into risk management strategies. Consequently, governments have been able to tailor control measures for high-risk areas, adapt vaccination campaigns to minimise risk of infection and safeguard traders’ livelihoods. Thailand, Vietnam and countries in Africa have now modified their control strategies, with more focussed vaccination and culling campaigns. The work has helped improve surveillance for HPAI in endemic and disease-free countries, and improved international coordination of national surveillance and control efforts. The introduction of rest days for live bird markets provided a low-cost disease-control approach that would be accepted by local communities. In Europe, risk assessments relating to HPAI involving the RVC team have shaped guidelines contained in a series of Scientific Opinions issued by the European Food Safety Authority. Both the research findings and Royal Veterinary College’s expertise in this field continue to impact upon policy discussion in the UK and internationally.
This programme covers the entire spectrum from social studies, for understanding the prescription behaviour of vets and physicians, to the development of crystal structure-based multivalent vaccines against emerging viruses. An important aspect in the group’s work is the intense interdisciplinary collaboration between fundamental and applied research investigators in the veterinary and human field. The common problems associated with antimicrobial resistance and emerging infections, and the synergy resulting from the teaming up of veterinary and human medicine, are major pillars of the Utrecht University One Health programme.
Musculoskeletal health from the One Health perspective – human and veterinary patients benefit from each other

Researchers:
Meij, Tryfonidou, van Weeren and team

Two major musculoskeletal disorders are commonly encountered in both human and veterinary patients: back pain and osteoarthritis. Back pain is the most common type of pain restricting daily activity and the most common first cause of years lived with disability in humans. In dogs, young adults are commonly affected with neurologic deficits due to herniation, with 30% mortality, whereas prevalence of back pain in large breed dogs is 50%. Osteoarthritis affects 10% of men and 18% of women aged greater than 60 years, but also 20% of adult dogs and 80% of the geriatric canine population (greater than eight years). In horses aged greater than 15 years, 84% suffers from OA. Medical and physical therapies for back pain and osteoarthritis alleviate pain and delay the time to surgical treatment, but patients with late-stage disease can only be treated surgically, demanding extended hospitalisation and revalidation and incurring high costs. Musculoskeletal diseases therefore result in disability and decreased quality of life with severe socio-economic effects.

Biologic repair of diseased joints is the challenge. As an integral part of the Regenerative Medicine Centre Utrecht, the companion animal and equine clinics of Utrecht University’s Faculty of Veterinary Medicine develop strategies based on biomaterials, cells and bioactive substances, alone or in combination, aiming at biological and functional repair of the degenerated tissues. These are tested in either pre-clinical studies or in relevant patients from the large clinical caseload. Biomarker analysis enables characterisation and quantification of joint homeostasis and facilitates early diagnosis and follow-up of the regenerative strategies. Pre-clinical studies have shown the advantages of modification of joint homeostasis via controlled release systems in both dogs and horses. The first-in-dog studies have recently been completed and reveal promising results with significant improvement of quality of life without adverse effects.

From a market perspective, the global musculoskeletal disorders therapeutics market is forecast by GBI Research to grow to a record sales value of $54.8 billion by 2017. This growth is driven by new smart developments in the treatment of osteoarthritis and back pain. Hence the strategies which are currently being developed at the Faculty of Veterinary Medicine in close collaboration with academic partners and industry hold a future in this market. Successful implementation of the new therapies in back pain and arthritis patients will alter the standard of care of human, canine, and equine patients, and minimise the need for surgical treatments.

Reducing the cost of prevention, control and elimination of rabies

Researchers:
Cleaveland, Hampson, Lembo, Knobel and team

Rabies is a lethal infectious disease which develops in people who are bitten by animals (usually dogs) that are infected with the virus. If left untreated, rabies is fatal in essentially all individuals once symptoms appear. Preventative vaccination is almost 100% effective, as is post-exposure prophylaxis (PEP) treatment, but PEP must be administered within 24 hours of exposure to the virus. Despite successes in the control of rabies in Central and South America, the incidence of canine and human rabies in Africa continues to rise, killing around 24,000 people annually.

The control and elimination of rabies in Africa and Asia has been hampered by misconceptions about the epidemiology of the disease, the ecology of domestic dogs and the cost of prevention in humans. In particular, policy-makers have often opted for culling ‘stray’ dogs as the principal strategy for canine rabies control. Investigators at the University of Glasgow demonstrated that rabies transmission is not highly dependent on the density of dogs, therefore measures such as culling are not likely to be effective. Contrary to common perceptions, very few domestic dogs in Africa are ‘strays’ and the vast majority are accessible for vaccination. This research provided evidence for the feasibility of mass canine vaccination and, crucially, showcased this strategy as the most cost-effective way to prevent and eliminate human rabies in rural Africa.

Rabies PEP treatment is expensive and places a heavy economic burden on healthcare systems, particularly in low-income countries. In high throughput clinics, regimens that use injections into the skin (intradermal delivery) have been recommended as a cost-saving alternative to the conventional intramuscular injections. Yet these regimens were rarely used in Africa and had never been tested in its settings. The research team simulated different PEP regimens in a range of environments and identified the costs to both the health authority and the bite victims. They found that, irrespective of the type of clinic, a universal switch from intramuscular to intradermal regimens would reduce the amount of vaccine required, resulting in significant savings to public health budgets and helping to mitigate the vaccine shortages that occur widely in Africa.

The group’s work has had a strong impact in several African countries and at a global level. The research has led directly to major changes in policy, influencing decisions made by authorities in Tanzania and Kenya, including the development and adoption of national rabies control and prevention plans. The team also helped develop a cost effective proposal for sustainable canine rabies control at a WHO/Bill & Melinda Gates Foundation consultation. The consultation recommended a One Heath approach where solutions to rabies control are addressed as a joint concern of both veterinary and medical authorities. Since the publication of the group’s work in the Research Excellence Framework 2014, further advancements have been made in the fight against rabies helping to improve the lives of those most at risk to the disease.
Stamping out sleeping sickness in Uganda

Researchers: Welburn and team

Sleeping sickness is a disease transmitted by tsetse flies in sub-Saharan Africa. The disease is fatal if left untreated and diagnosis can be difficult and expensive. There are two forms of disease: ‘acute Rhodesian’ caused by T. b. rhodesiense and ‘chronic Gambian’ caused by T. b. gambiense. In Uganda, there are 32 high-risk districts with acute Rhodesian sleeping sickness threatening nine million people, mostly in poor, rural areas. Nine districts currently account for 80% of all reported Rhodesian sleeping sickness cases in Uganda.

Researchers at the University of Edinburgh provided the evidence base for a new approach to control sleeping sickness in Uganda and established a public-private partnership called Stamp Out Sleeping Sickness (SOS), a unique One Health solution. The work also involved collaboration with Makerere Veterinary School in Uganda.

Previously, it was impossible to assess the risk posed by livestock carrying both T. b. rhodesiense, which is infective to humans, and T. b. brucei, which is not, that were indistinguishable. The team identified and validated a robust molecular marker for human infectivity in trypanosome, the microscopic parasite which carries the disease. This subsequently revealed that up to 40% of cattle in South-East Uganda carried T. b. rhodesiense. Further investigation showed that outbreaks of sleeping sickness were caused by importation of cattle from endemic areas. Using mathematical modelling, the researchers predicted that treating more than 86% of cattle would control the spread of disease. The model was tested in Uganda by mass chemoprophylaxis of cattle to remove parasites from the reservoir hosts and by applying insecticide to cattle to prevent reinfection by tsetse. It was shown that a single round of treatment could eliminate human trypanosomes in the cattle reservoir and a monthly application of insecticide to cattle could limit reinfection.

Stamp Out Sleeping Sickness was created to ensure the mass treatment of cattle in the five districts of the disease overlap zone, maintain compliance with government policy to treat cattle at markets, establish veterinary businesses to deliver a cattle-spraying service and to tie in with Ugandan Ministry of Health screening activities to coordinate treatments.

The impact of applying SOS has been vast. It has affected public policy in Uganda and the model for sleeping sickness control is now promoted by the WHO and donor agencies. As a result of the initiative, the prevalence of trypanosome has been reduced by 75% and sleeping sickness cases have fallen consistently since SOS was established. Uganda has also received a cost benefit of between US$125 and $400m in human health care costs plus an estimated $25 per head of cattle per year increased productivity from improved animal healthcare provision in its poorest communities.
Supporting the role of early life nutrition

Researchers:
Langley-Evans, Gardner, McMullen, Sinclair and team

Research in the field of Developmental Origins of Health and Disease (DOHaD) has shown that the risk of non-communicable disease in adulthood is partly determined by maternal diet during pregnancy and nutrition during early infancy. An individual born relatively small or relatively large has a two-to-eight-fold greater risk of dying due to ischaemic heart disease or type 2 diabetes in middle age. The DOHaD phenomenon therefore has broad implications for public health and the national economic spend on health-related morbidity for generations to come.

Initially, epidemiological studies in human populations received heavy criticism for ascribing cause-and-effect by association and inappropriate adjustments for potential factors such as current lifestyle and ethnicity. Hence, suitable animal models had to be developed to test DOHaD prospectively and in a controlled laboratory environment. Investigators at the University of Nottingham initiated and subsequently developed the experimental research that confirmed the biological plausibility of DOHaD and offered insight into a mechanistic pathway. The team created the first nutrition-related animal model of DOHaD in which pregnant rats fed a low protein diet (commonly associated with low birth weight in populations with a high prevalence of protein-energy malnutrition) gave birth to smaller offspring. The offspring would develop high blood pressure and showcase an increased propensity to other non-communicable diseases. This was followed by further investigation using large animal models of DOHaD.

The Nottingham researchers are among a number of prominent UK groups that take a lead role in studying the early life programming phenomenon and shaping the positions and policies of public health bodies. The team’s work has helped strengthen the current evidence base in favour of developmental programming effects upon adult health and disease. The total body of UK and international work, including the research completed at Nottingham, has prompted several expert committees, global organisations and high-impact journals to make specific recommendations about maternal and infant health. This included the British Medical Association, Nestlé and the Department of Health. The research also led to the World Health Organisation proposing global targets and recommendations for the nutrition of mothers, infants and young children in order to reduce the prevalence of low birth weight. As well as this, Nottingham researchers have contributed evidence that has challenged some of the prevalent views about childhood obesity.

This has had an international impact and has informed many governments’ strategies on economic spend on healthcare. The ultimate beneficiaries of the ongoing University of Nottingham contribution to global research in this area are pregnant women and their children throughout the world, as the research is a springboard for policy changes that will benefit health across generations.