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Control of Animal Disease, Exemplified by Vaccination against Bluetongue in Ruminants

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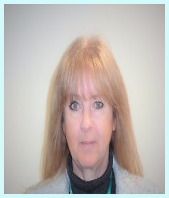
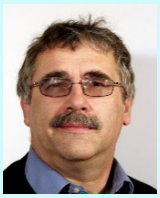


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COLUMN ARTICLE

Climate change and environmental degradation, along with an increasing human population that is predicted to reach 9.6 million by 2050, are putting enormous pressure on global food production and supplies. To meet these increasing demands, an intense international effort has been implemented and is beginning to gain traction, to change farming methods and improve the quality and sustainability of farmed crops and livestock.

With global demand estimated to increase by 70%, over the next 30 years, livestock will continue to be an important food and product resource. Livestock are not just an important source of food, they also represent a vital source of income both in the richer developed countries, as well as for ~1 billion people that live in poverty worldwide, mainly in developing countries (http://www.fao.org/livestock-environment/en/). However, livestock are heavy users of land, water and crop resources and contribute to climate change. For these reasons, organisations such as the FAO are committed to facilitate the 'sustainable development' of livestock, contributing to food security and poverty alleviation, while reducing their environmental footprint and use of resources (www.livestockdialogue.org).

One of the most important ways to increase livestock productivity and quality is to prevent losses due to disease. Infectious diseases of livestock are a serious threat to animal welfare and productivity [1]. As a result of climate change, environmental degradation and habitat loss for wild animals, as well as increased international travel and trade, farmed animals worldwide are experiencing multiple outbreaks of emerging and re-emerging diseases. Some of these diseases particularly those caused by viruses are zoonotic and are capable of infecting and spreading to the human population. The pandemic Influenza outbreak of 2009 was caused by influenza virus that had altered its genetic properties in pigs and subsequently jumped to the human population [2].

Another consequence of climate change is an increase in the seasonal and geographic distribution of insect or arthropod vectors. This can also lead to incursion of diseases into areas that were previously clear of infection. In humans, malaria caused by plasmodium unicellular parasites that are transmitted by mosquitos is one of many examples.

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There are several examples of current, or recently emerging arboviral diseases of livestock, including African swine fever virus [3], bluetongue virus (BTV) in ruminants [4] and African Horse sickness virus [5].

Along with good animal husbandry, the best way to prevent infectious disease is by vaccination. We are currently involved in a large multinational consortium funded by the European Union, that includes19 partners, spread across 11 different countries in Europe, North Africa and the Middle East, that is led by the University of Nottingham (PI, Professor Peter Mertens) to understand pathogen, livestock and environmental interactions involving bluetongue virus (PALE-blu). Bluetongue virus (BTV) is one of the most economically important livestock pathogens worlwide, capable of infecting all domesticated and wild ruminant species (as well as some large carnivores), causing severe clinical disease (including fatalities) primarily in sheep and some deer species, as well as reduced productivity and reproductive performance in other ruminants (e.g. cattle). The virus is usually transmitted by Culicoides biting midges and was previously confined to tropical and sub-tropical regions but is now endemic in many southern and central European countries. Epidemiological studies and phylogenetic analyses (primarily by members of the PALE-Blu consortium) have identified new introductions of the virus into Europe each year since 1998. The continuing arrival of new 'exotic' strains from neighbouring regions, suggests that incursions by BTV (and possibly by related orbiviruses, or other arboviruses) are likely to continue in Europe for the foreseeable future.

With recent advances in diagnostic and gene sequencing technologies the number of different BTV serotypes that have been recognised in current circulation globally, has increased to 32. Animal hosts can become infected with more than one serotype of BTV (dual or multi serotype infection), particularly in areas where multiple serotypes are endemic and frequently co-circulate. The segmented nature of the BTV genome (10 segments of double stranded RNA) facilitates the exchange or 'reassortment' of genome segments between different 'parental' BTV strains, generating new and variant 'progeny' viruses that may have distinct biological properties and may represent additional threats to animal health. Within the overall PALE-Blu programme, the authors are particularly interested in developing new vaccines and vaccination strategies for bluetongue that will protect against multiple variants (serotypes) of the virus.

The commercial BTV vaccines that are currently available, contain either live-attenuated strains, or inactivated 'whole virus' antigens derived from specific BTV serotypes and induce BTV serotype-specific protection. Polyvalent vaccines containing antigens from several different BTV serotypes can be used to widen the protection induced against multiple, or additional BTV serotypes, but their design requires a knowledge of which viruses represent a threat or are in local circulation.

Although effective the currently available BTV vaccines generate an immune response against all of the BTV proteins and therefore are not compatible with serological tests to discriminate between infected and vaccinated animals (DIVA). However, BT virus particles have hemagglutination activity that allows them to adhere to circulating erythrocytes, leading to a positive signal for viral RNA in post infected animals, but not in animals that have only received the inactivated vaccines.

Vaccinated ruminants are protected from bluetongue disease by generating both a cell mediated immune response and producing virus-neutralising antibodies against the outer capsid VP2 protein of the virus. This not only protects the individual vaccinated animal against clinical disease, but also suppresses the level of viraemia if the animal does become infected, reducing the chances of transmission to and infection of additional vector insects during subsequent rounds of feeding. Vaccination therefore also helps to control the spread of an outbreak.

The BTV VP2 protein determines serotype specificity. We are studying mice, sheep and cattle immunised with purified, plant-expressed recombinant VP2 proteins from different BTV serotypes, to identify cross-serotype neutralising antibodies that could be preferentially targeted in an immunisation/vaccine strategy. We are also testing the expression of the VP2 proteins using adenovirus vectors, a promising way to deliver vaccines that is being developed by the Jenner Institute in Oxford [6,7] and in Pischia pasto-

ris (yeast) by a partner group in Tunisia [8]. Another strategy for cross-BTV serotype protection is being tested by other PALE-Blu partners, using BTV non-structural protein (NS1) to induce cell-mediated immunity (CMI) that is cross-BTV serotype protective [9]. Using the combination of VP2 and NS1 in AdV will be tested for cross-serotype protection in sheep.

Another approach that is being developed by our partner in the Netherlands is to use genetically engineered BTV that lacks virulence proteins but expresses both VP2 and NS1 antigens within the vaccinated host [10]. If successful, the project will lead to a strategy for the control of Bluetongue that can be rapidly deployed, is specific for local circulating virus serotypes and is DIVA compliant.

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