Eradicating BSE in goats

Dr Jan Langeveld, acting coordinator of the GoatBSE consortium, and former coordinator Dr Alex Bossers discuss their plans for breeding goats which are insensitive to the infectious agents responsible for past epidemics of ‘mad cow disease’, namely the bovine spongiform encephalopathy agent and similar prions.

Could you outline the primary aims of your research?

Our consortium aims to generate data for human bovine spongiform encephalopathy (BSE) risk estimations related to the consumption of goat products. We will obtain an EU-wide insight into the characteristics and control of transmissible spongiform encephalopathies (TSEs, a generic name for prion disease like BSE and scrapie) in goats. Our field research collects national and regional information on TSE variants and the genetic background of susceptibility in animals from the main goat producing countries in Europe. The laboratory research will estimate the risk of disease transmissibility, especially between goats and humans.

Why is the field of TSEs so significant?

The BSE epidemic that started in the UK in the 1980s and subsequently spread through Europe provides the impetus for our research. The source of the epidemic remains unknown, but the most plausible explanations are either small ruminants such as goats that are known targets of this disease, or infected cattle that went unnoticed because infections were rare or because clinical signs appear late in the animal’s lifespan. The epidemic developed following the feeding of insufficiently inactivated ruminant-derived meat and bone meal rations to cattle. TSEs, especially the BSE crisis, have shown in a very costly way that certain infectious diseases are behaving as new agents, are difficult to pasteurise and have unpredictable epizootic and zoonotic behaviour (properties which mean animal diseases can affect other animal species including humans). BSE infected several hundred thousand cattle, and also a few hundred people suffered from the human variant that causes Creutzfeldt-Jakob disease. The disease in humans and animals is still incurable and untreatable, and involves progressive brain degeneration.

Eradicating TSEs in goats means no possibility of hazardous transmissions through the animal production sector or from animals to society.

Can you provide a summary of some of the techniques you are using in the project?

This approach combines many techniques: we are testing healthy and infected goats with prion protein (PrP) gene polymorphisms for their genetic susceptibility to infection; producing transgenic mice with goat PrP genes highly susceptible to the disease; in vitro PrP misfolding studies using specially designed PrP variants; and testing goats with different PrP polymorphisms for resistance to BSE and scrapie infection.

We are also analysing caprine TSE strain variations in seven EU countries (Greece, Cyprus, Italy, Spain, France, The Netherlands and the UK). Testing the infectivity levels of TSE-infected goat tissues using caprinsised and humanised transgenic mice, and testing for the potential survival of TSE infectivity in the cheesemaking process.

Why is it important to study samples from a large geographical range?

The PrP polymorphisms conferring resistance to TSEs are rare, so sampling many animals with a broad range of genetic diversity is important — data from many geographical locations and breeds of production goat are desired. Furthermore, different TSE strains are expected to occur at various geographical locations and these might have different geographical locations and hence different PrP-based genetic resistance profiles.

Can you detail some of the achievements of the project so far?

A very promising resistance allele has been detected in goats in Cyprus, though in most countries of Europe this is absent. This is already being used in a resistance breeding programme in Cypriot goats as European Food Safety Authority (EFSA) approved emergency action due to the very high scrapie incidence there. However, more experimental work is needed to confirm the effectiveness of this strategy. Another allele found at higher frequencies in the other EU countries has yet to be confirmed as a resistance allele, though we have a better experimental basis to start a breeding programme with this than we do with the allele identified in Cyprus.

Who will benefit from the project?

EFSA advocates our work for the promotion of safe food for consumption in the EU. Also, this work is of particular concern for producers of goat milk: their products are enjoying an increased appreciation throughout Europe.

Goat TSEs are a serious issue, since identifying one infected animal means a whole herd must be culled, which is unethical, economically difficult for farmers, and goes against public opinion if there are alternatives that could be developed. Although the BSE problem has subsided in cattle, goat TSEs still have a continuing impact on farmers who raise these animals.
Avoiding the cull

BSE, the prions responsible for epidemics of ‘mad cow disease’, have recently been identified in goats. In response, the GoatBSE consortium is examining the risk posed to humans, and hopes to breed disease-resistant animals.

The tolls of the BSE epidemics helped to spur on the formation of the European Food Safety Agency (EFSA) in 2002, which began actively surveying livestock other than cattle for various forms of BSE related transmissible spongiform encephalopathies (TSEs) in order to safeguard humans from new routes of infection through the consumption of small ruminants (sheep and goats).

In 2005, concerns about ulterior risks of TSEs grew when the EFSA reported the first case of a BSE infection in goats. In response to this, researchers convened to structure and stimulate goat TSE studies; this was initially executed under the EU-funded FP6 Neuroprion network. Subsequently, the GoatBSE project was commissioned to investigate the control of TSEs in goats and to estimate the risk of transmissibility of the agents, both between members of a herd and between goats and humans. Previous efforts to avoid future mass culls of infected livestock successfully led, in several EU regions, to the breeding of sheep that appear resistant to TSEs, and the European Commission has pushed for a repeat of such a breeding programme in goats.

However, as Dr Jan Langeveld – an acting coordinator of the GoatBSE consortium – explains, TSEs and BSE in goats have had a long history without much scrutiny: “For centuries, TSEs have been known as scrapie in sheep and goats but it only became apparent that the disease was transmissible in the 1930s,” he outlines. “TSEs are commonly recognised to cause three main forms of disease in small ruminants: classical scrapie, BSE, and atypical scrapie. BSE has recently been found in two goats to date (one in France and another in the UK), and while no cases have been reported in sheep thus far, both are susceptible to infection when fed brain tissue from infected cattle.”

Comprising of a consortium of 10 institutions in seven EU Member States and funded by the EU’s FP6 Food Programme and national governments, GoatBSE is now addressing the paucity of knowledge surrounding TSE infections in goats. An up-to-date website is available to inform scientists and stakeholders (www.goatTSE.eu).

TISSUE INFECTIVITY

The project has already made headway on several fronts. One of the primary aims of GoatBSE is the clinical investigation of the diseases in goats which are inoculated with – or orally exposed to – prions. The team is specifically looking at the infectivity distribution of BSE and TSEs in cells involved in the central nervous system or peripheral nervous and lymphatic tissues (which prions target), as well as tissues which may be more relevant to human consumption such as muscle, intestines and milk-based products. Screening tissues for the presence of infection, and for the presence of the malfolded protein PrPSc which is associated with disease status diagnostics, is conducted by testing in highly susceptible transgenic mice.

THE BOVINE SPONGIFORM encephalopathy (BSE) outbreaks in the 1980s led to the culling of several million cattle in the UK and Europe, and the infectious agents responsible – proteins called prions – grew in notoriety by crossing the species barrier to infect humans, causing around 200 cases of the fatal neurodegenerative condition Creutzfeldt-Jakob disease.

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To provide sound scientific information which can be used to quantitatively assess the risk of human exposure to BSE via goat milk, meat and products thereof. Such knowledge only can be usedfully obtained if scientific insights are gained into the control of TSEs in goats within EU Member States and regions.

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So far, clinical disease has been observed in brain tissue following the inoculation of goats with varying levels of natural resistance to TSEs offered by different prion protein gene (PrP) polymorphisms (gene characteristics which vary in populations). Some goats have shown BSE infection status in enteric nerve cells within a year of oral passage of the prion.

Further work to quantify the risk of transmissibility of diseases from animal to animal, and to humans via the consumption of infected meat or milk, is underway. “Concerns about milk consumption are warranted because, in sheep, milk from infected ewes can be involved in the transmission of TSEs to their lambs,” Langeveld points out. More understanding of the risks involved in consuming goat products will help to promote food safety in the EU Member States.

Understanding disease status also depends on surveying goat populations for different strains of TSEs across Europe. To do so, the GoatBSE consortium conducted a large study on the geographical distribution of the diseases in major goat-producing regions of seven EU Member States (Greece, Cyprus, Italy, Spain, France, The Netherlands and the UK). Biochemical analysis and determination of biological transmission characteristics in susceptible rodent models is ongoing, with more samples currently being collected from institutions outside of the consortium. Such efforts should serve to characterise the breadth of variation in strains of prions which infect goats locally and internationally.

Another line of enquiry for the team is to identify and determine the influence of genetic polymorphisms in PrP on the susceptibility of goats to infection by BSE and TSEs. This has been carried out by comparing the genes of scrapie-infected animals with those of their uninfected peers in the same herds. Initially, this involved analysing infected field herds where susceptibility appeared dependent on PrP polymorphisms. Subsequently, the team used various TSE inoculations to infect a series of goats with differing PrP polymorphisms, and also tested the transmissibility of infection between goats with different genetic variants using caprines transgenic mice or in vitro models. Useful PrP polymorphisms may be rare among goats, and the frequency of different alleles can vary across regional and/or national populations, so the project screened and genotyped goats for variation in the PrP gene in each of the seven countries involved.

The efforts have led to the identification of possible resistance polymorphisms which are present at low frequencies throughout the various European goat populations. Evidence confirms that the 146 mutation in the PrP gene offers a strong degree of resistance to TSE infection, but currently this is a very rare allele in goat populations outside of Cyprus. The 222 mutation is present at higher frequencies than 146 in other EU countries, and there is a stronger basis for it being used in breeding resistance, but work to confirm the level of resistance that it confers is ongoing. Further in vitro studies of prion protein malfolding in animals with the 222 mutation will help with this.

When suitable polymorphisms are found to have meaningful benefits for boosting resistance to prions in the animals, the next stage is to use breeding programmes to increase the frequency of these. Langeveld states the potential of such programmes: “There are very promising results from goat challenge experiments (with scrapie and BSE) that suggest breeding resistance to TSEs is possible. At this stage, little action has been undertaken to use breeding but it is a subject for new work and pilot field studies”.

All of these insights will contribute to a safer and more robust market for goat products in the EU. Though concerns about BSE epidemics in cattle have reduced recently, the risks of prion infections posed by the consumption of goat meat and milk have not been quantified. Some regions of the EU (such as Cyprus) currently have a high incidence of scrapie in goat herds, at a time when Europeans are increasingly consuming goat meat, milk and milk-derived products. These factors, along with new concerns about the rise of caprine BSE cases, suggest that assessing the transmissibility of these diseases from goats to humans is rightly deemed a priority for minimising health risks to consumers.

The developments made by GoatBSE will also facilitate the control of TSEs in goats. Scrapie and related infections of single animals currently necessitate the culling of entire herds, the results of which are extremely wasteful, evoke strong public outcry and severely damage the financial prospects of farmers. By reining in the impact of TSEs on goat populations through breeding programmes used to raise prion resistant animals, mass culls can be avoided. Thanks to GoatBSE, both consumers and producers will eventually benefit from healthier herds.