The Production Effects, Diagnosis and Control Options for Maedi Visna in UK Sheep Flocks

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This article highlights the increasing importance of Maedi Visna (MV) within the national flock. MV is considered to be one of the 'Iceberg Diseases;' a group of infectious, production-limiting diseases which are endemic to the UK. Characterised by slow, progressive onset these diseases lie undetected and can have a large impact on flock efficiency. They also include Border Disease, Caseous Lymphadenitis, Ovine Johnes Disease and Ovine Pulmonary Adenocarcinoma. The prevalence and effects of these diseases within different UK flock types remains unknown.

Abstract

Maedi visna (MV) is an infectious, insidious production limiting disease of sheep. MV leads to a progressive loss of condition, reduced flock production and poor economic performance. The prevalence within the UK sheep flock appears to be rising. MV is transmitted between sheep and goats; once infected animals become lifelong carriers. The immune response may take up to several months, and the incubation period for the disease may take several years. Clinical cases may only become obvious when a significant proportion of the flock are infected; however subclinical signs appear well before this. The disease is incurable and progressive, but several control options are suggested.

What is Maedi Visna?

Maedi visna (MV) is a highly infectious disease of sheep caused by a non-oncogenic retrovirus, maedi visna virus (Figure 1) (Radostits *et al.*, 2007). It has a long incubation period ranging from several months to years (Asadpour *et al.*, 2014). MV leads to a progressive loss of condition, reduced flock

productivity and poor economic performance (Ritchie, Davies and Smith, 2012). Infected sheep will produce antibodies, however they are unable to eliminate the virus and so become life-long carriers of the disease (Ritchie, Davies and Smith, 2012). There is no treatment or cure for the disease and due to the nature of the disease there appears to be little chance of development of an effective vaccine.

Figure 1: Key facts relating to small ruminant lentiviruses (SRLVs):

- Maedi visna virus (MVV) is closely related to caprine arthritis encephalitis virus (CAEV).
- MVV and CAEV are a small ruminant lentiviruses (SRLVs) from the *Retroviridae* family (Iratxe Leginagoikoa *et al.*, 2006), and both may be transmitted between both species.
- SRLVs lead to slow, progressive and fatal lymphoproliferative disease (Berriatua *et al.*, 2003).
- Cases of MVV and CAEV infection present differently. Sheep infected with MVV primarily show respiratory signs and lose condition. They may also be affected by mastitis and show progressive neurological sings. Goats infected with CAEV commonly present with a polysynovitis-arthritis. Goats may also suffer with a loss of condition; poor hair-coat; respiratory signs and mastitis.
- The *Lentivirus* genus also contains human immunodeficiency virus (HIV), feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV) and equine infectious anaemia virus (EIAV) (Minguijón *et al.*, 2015).

Why is it important now?

MV appears to be widely dispersed in the UK flock. A study funded by the Agricultural and Horticultural Development Board and conducted by the Scottish Agricultural College (SAC) and Animal Health and Veterinary Laboratories Agency (AHVLA, now Animal and Plant Health Agency) (2012) using a random sample of UK flocks found that the prevalence of infected flocks appeared to have doubled between 1995/6 and 2010 (1.4% to 2.8%, p=0.015). Although the between flock prevalence appears to be relatively low, the rate of increase is alarming; some UK flocks have found the within flock prevalence to reach 85% (Ritchie, Davies and Smith, 2012; Priestley, 2016). Six years ago it was estimated that 100,000 ewes within the national flock could be infected with MVV (Ritchie, Davies and Smith, 2012) and the rate of increase is likely to be exponential. The apparent

increasing prevalence of MV within the UK means that understanding the effect of the disease are increasingly relevant.

How does MV impact on flock production?

Only partial data on productivity losses associated with MV infection are available for UK flocks at present. The financial costs may be influenced by several factors (Figure 2). In flocks with clinical MV, the within flock prevalence is often identified between 20 and 60%. A lag period of several years appears to be seen from initial flock infection to diagnosis due to clinical signs or production issues; this is a classic characteristic of an iceberg disease.

Figure 2: Factors influencing financial costs associated with MVV infection within a sheep flock:

- Clinical MVV disease develops slowly
- 30% of infected animals develop clinical signs
- The rate of transmission is influenced by flock prevalence and management factors
- Host and viral genetics influence the extent of the disease
- Concurrent disease will influence disease signs (Gonzalez *et al.*, 1993)

(Peterhans *et al.*, 2004)

Some of the production effects and associated financial implications of MV infection within a flock have been calculated (Table 1). Although these figures may not be representative of all flocks or systems, it goes some way to identify the potential economic losses associated with prolonged MVV infection within a flock. Further studies are needed to quantify additional effects of subclinical disease such as on-going transmission within infected flocks and how this relates to different flock types and management systems where transmission dynamics differ (I. Leginagoikoa *et al.*, 2006).

Table 1: Production effects and financial implications associated with MV infection within a flock.

Physical Performance	Baseline (disease free)	**Impact of Maedi Visna (at 20% prevalence based on ELISA seropositivity)**	
Scanning rate - ewes (%)	200	200	
Scanning rate - ewe replacements (%)	160	160	
Empty rate - ewes (%)	4	8.4	Estimated 9% reduction in conception rates*
Empty rate - ewe replacements (%)	7	7	
Total flock scanning rate (including empty) (%)	182.9	174.5	
Stocking density (ewes/ ha)	10	10	
Total lamb mortality (scanning - sale) (%)	12	13.2	Estimated 10% increase in lamb mortality*
Rearing rate (%)	161.0	151.5	
Live weight (kg)	40	40	
Cull ewe value (£)	50.00	40.00	Estimated 20% reduction in cull ewe value due to chronic wasting*
Replacement rate (%)	21	25.2	Estimated 20% increase in forced culling/replacement*
Replacement female purchase cost (£)	120.00	120.00	
Finishing rate (%)	140.0	126.3	
Killing out rate (%)	45	45	
Carcase weight (kg)	18	18	
Price per kilogram dead weight (£/kg dw)	4.00	3.95	Estimated 6% lower milk yield = 6% lower DLWG in 20% of lambs suckling MV infected ewes = reduced mean market price achieved
Variable Costs (£/lamb)	**51.14**	**56.69**	

Variable Costs (£/kgdw)	**2.84**	**3.15**	

**Estimates are conservative estimates based on expert opinion*

Clinical Disease:

Cases of MV may be difficult to identify due to the long incubation period of the disease; non-specific clinical signs; and the susceptibility of infected sheep to concurrent diseases (Iratxe Leginagoikoa *et al.*, 2006; Ritchie, Davies and Smith, 2012). Clinically infected sheep may present with one of two disease forms- 'maedi' or 'visna': both have been documented in the UK and are produced by infection with the same maedi visna virus (Ritchie, Davies and Smith, 2012).

- Maedi:

The more typical presentation within UK flocks is a chronic, progressive pneumonia in older sheep, typically over 3 years old (Winter and Clarkson, 2012). This interstitial pneumonia leads to a loss of condition, difficulty breathing and is eventually fatal (Winter and Clarkson, 2012). Post mortem examination of such affected sheep would show markedly enlarged and heavy lungs with a grey discolouration and obvious impression of the ribs (Minguijón *et al.*, 2015) (Plate 1). Enlarged mediastinal lymph nodes are usually noted and MV cases are commonly associated with secondary bacterial infection, particularly pneumonic mannheimiosis. Concurrent cases of ovine pulmonary adenocarcinoma (OPA) have also been reported (Baird, 2010).

- Visna:

The neurological form of the disease is a slowly progressive disorder with weight loss in older sheep. This may progress from a unilateral conscious proprioceptive deficit in one hind limb to toe dragging (Photo 1) and hind limb paralysis (Winter and Clarkson, 2012).

- MV-related death and culling:

Despite MVV targeting several organs, only the respiratory and neurological forms of the disease appear to lead to cachexia and death: viral strains targeting the mammary gland and joints may lead to premature culling due to poor performance (Minguijón *et al.*, 2015). Mortality associated with small ruminant lentivirus (SRLV, Figure 1) infection is thought to be low in endemic areas, but is strongly influenced by concurrent disease, husbandry, nutrition and environmental factors (Peterhans *et al.*, 2004). Such high rates of mortality in newly infected animals as documented during the Icelandic epidemic (Sigurdsson, Grímsson and Pálsson, 1952; Sigurdardóttir and Thormar, 1964), have not been repeated: evidence suggests that the native Icelandic breed were highly susceptible to MVV infection. However whole flock culls due to poor performance associated with MVV infection have been documented in the UK (Priestley, 2016).

PLATE 1: PATHOLOGY SAMPLES FROM MV INFECTED SHEEP:

Photo source: Dr P. Davies, Pro Ovine Ltd.

Photo (above) showing two pairs of lungs from 3-year-old Texel rams. Unaffected lungs on the left (from a clinically well, MV negative ram) deflated on removal from the thoracic cavity and placement on the table reveals the heart. In comparison, the affected lungs (taken from an MV positive ram; right) failed to collapse when the chest was opened, have a firm-rubbery texture and are diffusely pale. The interstitial pneumonia in the MV animal causes the lungs to appear swollen, which obscures the heart in the photo.

Photo (below) showing a lung infected with MV. On cut surface the parenchyma of the caudal lobe shows multiple coalescing grey and firm foci.

Gross post-mortem findings cannot be relied on for confirmation of MV. Further diagnostic tests are required:

- Histology may be performed on formalin fixed samples of lung, bronchial lymph node, mammary gland, synovial membrane and brain.
- Heart blood serum may be collected for serology.

(Radostits *et al.*, 2007).

Photo source: Ben Strugnell, Farm Post Mortems Ltd.

Sub-clinical Disease:

- Ewe health and production:

Many studies have identified production limiting affects in sub-clinically infected flocks. MVV infection is suggested to decrease the average lifespan of infected animals: they may be culled at least a year earlier due to reduced productivity (Peterhans *et al.*, 2004).

Infected ewes were found to have a reduction of 9% in conception rates compared to uninfected ewes and a 6% reduction in milk yield in dairy ewes of similar ages within the same flock (*P. Davies, unpublished data collected from a flock of UK dairy ewes, based on cumulative milk yields; corrected days in milk; parity and serological MV diagnosis on milk ELISA.)* Indurative mastitis may be found in infected ewes which inhibits the flow of milk throughout the mammary gland thus reducing milk yield (Snowder *et al.*, 1990). Clinical examination of the udder may be unremarkable, and milk remains normal in appearance (Asadpour *et al.*, 2014). High levels of bacterial and indurative mastitis have also been reported in clinically affected flocks in other studies (Pekelder *et al.*, 1994; Ritchie, Davies and Smith, 2012).

- Lamb performance:

The effects of reduced milk yield due to MVV associated mastitis and induration on lamb production has not been accurately assessed within a UK setting. It is plausible that lambs nursing ewes with a high degree of induration and subsequent lower yield may lead to reduced survival and poor lamb growth. In other countries MV seropositivity has been associated with increased pre-weaning mortality (Arsenault *et al.*, 2003). The effects of MV infection appear to be more marked with increasing ewe age: Dohoo *et al.* (1987) found that the birthweight of lambs born to 3-4 year old

seropositive ewes were 3-6% lower than those born to non-infected ewes of the same age. The weaning weight of lambs born from seropositive ewes ≥ 4 years old was associated with a reduction of 0.94kg (Arsenault *et al.*, 2003). These effects may be especially felt in medium or high prevalence UK flocks that aim to attain the higher sale prices associated with early lamb sales.

How is MV transmitted?

MV may be transmitted in a number of ways, although the chief route (vertical or horizontal) is unclear. MVV is spread via pulmonary secretions and milk containing infected macrophages, thus the respiratory route and the ingestion of infected milk and colostrum, known as lactogenic transmission, form the basis for natural MV transmission (Berriatua *et al.*, 2003; Iratxe Leginagoikoa *et al.*, 2006; Radostits *et al.*, 2007). Successful eradication programmes focusing on the removal of lambs at birth and rearing on artificial milk and colostrum (Houwers *et al.*, 1987), appear to demonstrate that in utero and intrapartum transmission are of little consequence (Cutlip, Lehmkuhl and Jackson, 1981). The virus can also be found in semen, saliva and urine (Houwers, 1990; Berriatua *et al.*, 2003; Ritchie, Davies and Smith, 2012).

The role of post-natal maternal transmission to offspring is of importance although the primary route of transmission (respiratory or lactogenic) remains unclear. The rate of transmission within a flock appears to be related to management procedures and MV flock prevalence. Although intensively farmed flocks appear to have higher prevalence (Iratxe Leginagoikoa *et al.*, 2006) thus assuming transmission due to repeated close contact with infected sheep, studies have shown high rates of transmission in flocks with clinically healthy ewes with high MV prevalence, managed under extensive conditions (Pekelder *et al.*, 1994).

The genetics surrounding the susceptibility of SRLV infection have been explored; some animals appear to be resistant despite repeated exposure to infection (Berriatua *et al.*, 2003; I. Leginagoikoa *et al.*, 2006; Heaton *et al.*, 2012). Genetic selection for MVV resistance should be regarded cautiously: viral strains undergo frequent antigenic drift and so virus adaptation may diminish the benefit of previous genetic selection (Minguijón *et al.*, 2015).

It has been suggested that eradication programs, involving the removal of lambs at birth for artificial rearing, may fail due to poor hygiene and disinfection procedures (Houwers *et al.*, 1987). Indeed, fomites are an important consideration during MV eradication even if survival outside the host is limited.

Diagnosis of MVV Infection

Although there is no universally accepted 'gold standard' to determine sensitivity and specificity of tests used for MV infection, successful control programs indicate that the tests available are useful in reducing prevalence of infection (Peterhans *et al.*, 2004). Serological diagnosis used to detect MV antibody in infected animals is considered the most convenient diagnostic method. However, the time from infection to seroconversion can vary from a few weeks to several months (de la Concha-Bermejillo, 1997; De Andrés et al., 2005). Repeated testing during diagnosis and eradication programmes are necessary (De Andrés *et al.*, 2005) as animals with low antibody titres may become transiently seronegative despite latent infection (Houwers and Nauta, 1989), and it has been suggested that some carrier ewes may not test positive on the ELISA due to a disrupted immune response in some infected individuals (Gayo *et al.*, 2017).

The most commonly used laboratory techniques used in the UK for MV diagnosis are the agar gel immunodiffusion test (AGIDT) and enzyme-linked immunosorbent assay (ELISA). The AGIDT is highly

specific but less sensitive than ELISA (Synge and Ritchie, 2010): it was found to be 76% sensitive and 98% specific when compared to ELISA (De Andrés et al., 2005). Therefore, due to its high but subjective specificity and low sensitivity, the AGIDT is used mostly for confirmation of more sensitive ELISA results.

ELISAs are suitable for screening large numbers of animals; are more sensitive than the AGIDT; and are quantitative allowing for computer-based analysis of raw data (Peterhans et al., 2004). Commercial ELISAs have been reported with a claimed sensitivity and specificity of 99.4% and 99.3%, respectively. However apparently high number of false positives have occurred when screening certain UK flocks, thus suggesting a lower specificity under some circumstances. To overcome this, the routine confirmatory testing of positives is recommended using alternative assays.

Milk and bulk milk samples have been tested against SRLV for use and ease in dairy breeds (Minguijón et al., 2015). There is an agreement of 90% between ELISA used for blood and milk therefore milk samples may be preferable to serology in milking flocks and potentially meat flocks during lactation as they are easier and cheaper to obtain. MVV infection may also be identified from post mortem sampling (Plate 1).

In summary it is vitally important to establish which tests are appropriate for the desired level of confidence and to select the appropriate type (Figure 3- see attached schematic) and number of animals to make flock screening valid and robust. Typically, this can be summarised as using a high-sensitivity ELISA for screening followed by a high-specificity ELISA or AGIDT for any resulting positive samples generated. To establish flock status, i.e. for flock-screening tests, the highest risk sheep which are most likely to have antibodies should be selected, typically thin, older ewes who are more likely to have encountered the disease and sero-converted.

MVV Control Options

Due to the long course of MVV infection control methods may span several years and so selecting the right plan is crucial to maximise compliance and plan success. MV control for an infected flock can either be via eradication or by conservative management. Many factors may influence the choice of plan including flock prevalence; farming production objectives; cost-benefit analysis; animal health and genetics (Minguijón *et al.*, 2015). Analysis of flock production data may allow the effects of MV infection to be seen, for example assessing ewe longevity and lamb performance may address likely cost-benefit analysis of disease control. Flocks seeking full eradication must ensure that both vertical and horizontal routes of transmission are targeted (Minguijón *et al.*, 2015).

An overview of several control strategies has been provided by Minguijón *et al.* (2015): a flow diagram (Figure 4- see attached file) and several control strategies are outlined (Table 2).

Table 2: Summary of MV Control Options

Control Option	Advantages	Disadvantages
1. Depopulation and repopulation ***Level of control:*** *eradication* The entire flock is culled and restocked with accredited or monitored MV free sheep.	Works well for smaller flocks of low genetic value. Can quickly eliminate the disease if sufficient appropriate stock can be sourced	Large financial implications associated with whole flock culling. Loss of genetics.

	Very successful method in Iceland (Pétursson, 1994).	Needs ready availability of disease-free stock for restocking
2. <u>Selective culling of infected animals +/- their progeny</u> ***Level of control:*** *eradication* Repeated testing and culling of all stock >12 months old. This method uses high sensitivity ELISA and AGIDT, outlined in Figure 3. All sheep on farm are routinely tested twice a year. Flocks frequently cull progeny (< 1 year old) of infected animals as well (Houwers *et al.*, 1987; Williams-Fulton and Simard, 1989; Radostits *et al.*, 2007). Replacements are sourced internally from seronegative mothers, ideally these should be older ewes which may be virus free and transmit resistant genes to their offspring (Berriatua *et al.*, 2003; Radostits *et al.*, 2007),	May be useful in flocks with low to moderate prevalence; allows rapid reduction in seroprevalence (Reina *et al.*, 2009). The diagnostic tests are sufficiently accurate to allow fairly rapid eradication. Culling progeny of infected ewes may reduce vertical transmission and inherited susceptibility (Reina *et al.*, 2009).	Flocks with high prevalence may see flock size reduce if culling is greater than the normal culling rate (Reina *et al.*, 2009). Expensive in terms of diagnostics and high flock replacements costs

or from MV-free monitored or accredited flocks. Eradication can be achieved in 1-3 cycles.		
3. <u>Artificial rearing of lambs:</u> ***Level of control:*** *eradication* • Lambs are snatched from their dams at birth; reared on bovine/ alternative milk and colostrum (Houwers *et al.*, 1983; Williams-Fulton and Simard, 1989); <u>OR</u> • Lambs are fostered onto MV-accredited recipient ewes; <u>OR</u> • Embryo transfer (ET) into MV-accredited recipient ewes. Lambs must be kept separate from the rest of the flock to prevent future horizontal disease transmission (Reina *et al.*, 2009). On-going testing is necessary to ensure adequate hygiene measures are in place.	May be used on a larger scale. If thorough hygiene procedures are adhered to, can be very effective. ET may be advantageous and economically viable in flocks with high genetic merit.	Very labour-intensive approach. May be especially expensive if infected flock is not retained, though their continued presence poses a significant risk of horizontal transmission (Radostits *et al.*, 2007). Lack of passive lamb immunity and artificial feeding may cause additional problems.

4. <u>Separation of flock into two separate flocks</u> ***Level of control:*** *conservative* The whole flock (>12 months old) is tested and separated according to infection status. The seronegative group must be kept isolated from the seropositive group and strict hygiene must be adhered to. Repeated testing continues on the seronegative group and any returning seropositive are immediately moved into the seropositive group. Replacements are sourced as of option 2.	Works well for moderately/highly infected flock. Eliminates drastic culling procedures - keeps more stable flock numbers and may be more economically stable than culling positive animals/entire flock (Reina *et al.*, 2009; Pérez *et al.*, 2013).	Requires strict internal hygiene over 3-5 years, very difficult to maintain, especially around grazing and flock handling. Increased labour, large degree of planning. May have to increase farm facilities to maintain separate flocks - increased costs associated with this.
5. <u>Young flock, early culling:</u> ***Level of control:*** *conservative* This method includes keeping a younger flock; increasing replacement rate and	May reduce some effects of MV.	The cost of keeping a younger flock with increasing culling and replacement rates may well outweigh the cost of disease eradication

increase culling based on BCS and ewe performance. Flock may be kept in age stratified groups, and replacements kept from younger ewes. Replacements are bought in from MV-accredited flocks and kept separate from older sheep. Batch testing of older and thin ewes is recommended.		in the medium /long term. Horizontal and vertical transmission will continue, and subclinical disease will continue to cause production losses.

Strict biosecurity procedures are necessary to ensure adequate control of MV infection or prevent re-infection in cases where eradication has been achieved. A single serological test may not be sufficient to determine the infection status of an individual animal due to differences in time to seroconversion (de la Concha-Bermejillo, 1997) and the immune response of infected individuals (Gayo *et al.*, 2017). Therefore replacement ewes and rams should be sourced from MV-monitored or accredited flocks (Radostits *et al.*, 2007) who have undergone multiple serological tests. As MVV has been found in the male genital system and viral shedding in semen has been shown, only certified MVV-free males should be used as semen donors for artificial insemination to avoid both horizontal and vertical transmission (Minguijón *et al.*, 2015).

Farmers selling MV seropositive stock must be strongly encouraged to sell either through the cull ewe market or direct to slaughter. Although there is the temptation to sell stock through other methods the moral duty to sell only healthy stock on to fellow farmers must be strongly encouraged.

UK MV Accreditation:

An MV accreditation scheme was introduced into Great Britain in 1982 and may be credited with limiting the spread of MV in the UK. The scheme parameters initially accredited participating flocks to have a MV prevalence of <2% with a confidence of 95%, tested on a biannual or triannual basis along with strict biosecurity precautions. Over 3000 flocks have participated in the scheme over the past 35 years.

The high uptake of the scheme amongst pedigree producers may have had an important effect of limiting transmission within the national flock as these flocks have the greatest 'contact' with other, commercial flocks, primarily via the sale of breeding rams. Several hybrid breeds are also subject to similarly rigorous testing to prevent transmission to client flocks independently of the scheme. The current scheme now sets a standard of <5% prevalence and 95% confidence in order to achieve accreditation. This compares to the previous standard of <2% prevalence. It is important for owners to appreciate the fact that accreditation does not guarantee disease freedom!

The uptake of the scheme has been minimal within the commercial lamb producing sector. Though the costs associated with testing may be high, the lack of clear cost benefits of disease freedom for commercial lamb producers is also a likely contributing factor.

Summary

Given that UK flock prevalence is rising and likely to accelerate, MV is destined to become a far more important problem for UK sheep industry. The effects may be increasingly felt within the lamb producing industry in the future. Perhaps consumer drive to ensure higher animal welfare may be

the turning point, or further research will underline how much MV is holding back the potential of UK sheep production. It is clear there is a need to engage a far larger proportion of flocks in disease screening and control if we are to avoid MV becoming a truly endemic disease in the UK as in countries such as Spain. Portugal or Canada where there are high numbers of infected flocks.

Legends:

Figure 1: Key facts relating to small ruminant lentiviruses (SRLVs)

Figure 2: Factors influencing financial costs associated with MVV infection within a sheep flock:

Table 1: Production effects and financial implications associated with MV infection within a flock.

Photo 1: Toe dragging in a ewe infected with MV

Plate 1: Pathology samples from MV infected sheep

Figure 3: Diagnostic options for MV investigation

Table 2: Summary of MV Control Options

Figure 4: Control strategies for MV infected flocks

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Peers Davies:

Dr Peers Davies graduated from Cambridge University Vet School in 2008. He worked in farm animal practice in Devon and North Wales. He founded Pro-Ovine Sheep Consultants in 2010 and was Clinical Lecturer in Sheep Health and Production from 2013-18. He is now Senior Lecturer in Livestock Health & Welfare at Liverpool University researching production limiting diseases of sheep.

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