A case control study of orf in pre-weaned lambs

Dissertation for the
RCVS Diploma in Sheep Health and Production

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Abstract

Orf, a viral disease which causes proliferative skin lesions around the mouth of lambs and on the teats of ewes, has long been assumed to have production limiting consequences. This case-control study collected data from naturally occurring outbreaks of orf in young lambs on eight commercial farms in north-east England. Measurements of weight and condition score were taken and orf lesions were scored on a numerical scale. Data from corresponding ewes were available on five farms. Forty four orf-affected lambs were matched to unaffected controls within the same groups. Paired t-tests showed that affected lambs weighed approximately 10% less than their unaffected controls for a period of at least five weeks following the start of the outbreak. The effects were highly significant whether the orf lesions affected the mouth or were elsewhere on the body. If a lamb had orf then there was a 82% chance that its mother also had orf on her udder or teats. The financial consequences of orf in young lambs were estimated using average UK figures and some conservative assumptions based on the results of this study.

Introduction

Orf (contagious pustular dermatitis, contagious ecythema, scabby mouth, sore mouth) is an eruptive skin disease of sheep caused by an epitheliotropic DNA parapoxvirus with a worldwide occurrence. It has been reported often that orf has a negative effect on lamb growth rates and causes secondary mastitis in ewes (Robinson and Balassu 1981; Meynink et al. 1987; West et al. 2002; Sargison 2008; McInnes 2009). Consequently it is considered to cause major economic loss to the sheep industry (Reid 1994; Bennett and IJpelaar 2003).

However, to date, there appears to have been only one study (Bennett 2003a) of the actual cost of the disease in the UK within a project which used computer modelling to evaluate the cost of eight sheep diseases (including pneumonia, enzootic abortion, toxoplasmosis, fly strike, pulmonary adenomatosis, scrapie and maedi-visna). Of all these diseases, orf was found to have the greatest impact on sheep welfare in Great Britain, due primarily to the large numbers of affected sheep. Its annual financial cost was estimated to be £10M (range £3.1M to £28.3M), less than enzootic abortion and approximately equivalent to toxoplasmosis and enzootic pneumonia. However, this study relied on a number of assumptions about incidence, prevalence and costs which were largely based on an unpublished case-study of 49 flocks, four of which had reported orf in the lambs (Bennett 2003a; Bennett 2003b).

As a poxvirus, the intracellular phase of the orf life cycle takes place within the host cell cytoplasm. There is an ordered cascade of viral gene expression so that early genes encode factors which regulate the expression of later viral genes (Haig and Mercer 1998). Infection with orf virus in sheep causes vigorous antibody and cell-mediated immune responses as well as an apparently normal inflammatory response. Yet, despite effective host-acquired immunity in limiting the extent of virus replication, this immunity does not prevent reinfection, apparently due to a number of virulence and immuno-modulating proteins that are encoded by the virus early in infection (Haig and Mercer 1998; Haig and McInnes 2002) (see appendix).

Typically, orf in lambs occurs in two peaks: one immediately following lambing and another in 3-4 month old lambs (Reid and Rodger 2007). The incidence of orf within

a typical group of sheep is often over 50% (Sargison 2008) and may approach 100% (Lewis 1996; Reid and Rodger 2007). The range of severity of outbreaks varies from those with virtually undetectable lesions to severe cases with very high associated mortality (Darbyshire 1961). Outbreaks last six to eight weeks and generally do not reappear until there is a fresh crop of susceptible lambs (Reid and Rodger 2007). In primary infections, there is a period of time before the host mounts an effective immune response, in which the virus can both replicate and produce immuno-modulating and virulence proteins, so that the lesions usually last for four to six weeks. Re-infections are less severe and only last for two to three weeks due to an accelerated immune response (Haig and McInnes 2002; McInnes 2009).

This project aimed to quantify the effect of natural outbreaks of orf on growing lambs by conducting a case-control study. The target population was pre-weaned lambs born in 2010 and 2011 and the study population comprised lambs belonging to farmers who volunteered for inclusion in the study. Young unvaccinated lambs were selected to ensure that each case was a primary infection of orf. Groups of lambs reared off their mothers usually experience rapid spread and high morbidity (eg. Meynink et al. 1987) and therefore no orphan or pet lambs were included in this study due to a lack of unaffected controls.

Materials and Methods

Commercial farms in north east England were recruited via their veterinary practice newsletter, posters and local media. Data were collected from seven farms between March and July 2010 and one farm in March 2011.

A minimum of three cases of orf in lambs qualified the farm for a veterinary visit (denoted visit one) to confirm the diagnosis based on clinical signs. Ear tags were applied, the orf lesion was scored (table 1) and the lambs were condition-scored (MAFF 1994) and weighed.

For each orf-affected case that was assessed, at least one, or preferably two, unaffected lambs in the same group were ear-tagged, weighed, condition-scored and orf-scored. The udders and teats of the mothers of both cases and controls were

checked and scored (table 1). At all stages of examination disposable gloves were worn by the vet and these were changed between each lamb.

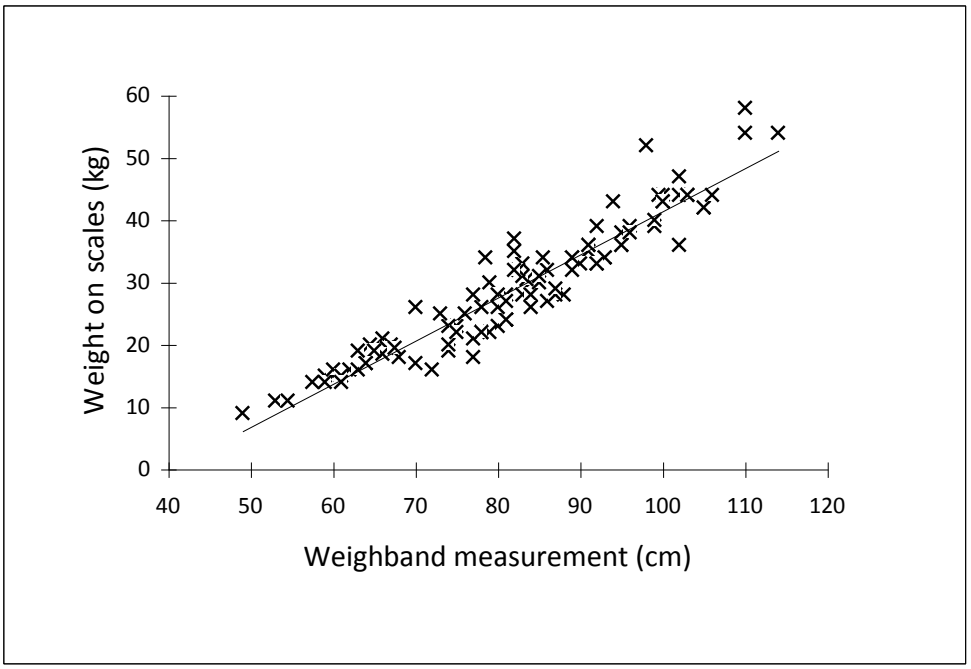
Table 1: Scores for orf lesions.

Lamb Orf Score	
0	No sign of orf lesions.
1	External orf lesion(s) of total area less than 50p coin. No lesions involve the mouth. No obvious secondary infection.
2	External orf lesion(s) of total area greater than 50p coin. No lesions involve the mouth. No obvious secondary infection.
3	External orf lesion with obvious secondary infection. No lesions involve the mouth.
4	Orf lesions involving the mouth but no obvious secondary infection.
5	Orf lesions involving the mouth with obvious secondary infection.
Ewe Udder Score	
0	No sign of teat/udder lesions.
1	Wound/bruising on teat/udder but no orf. No clinical mastitis.
2	Orf lesions on teats/udder. No clinical mastitis.
3	No lesions on teats/udder. Clinical mastitis
4	Orf lesions on teats/udder. Clinical mastitis.

The clinical cases and controls were checked after two weeks, with weight, orf score and condition score recorded, and the udders and teats of the mothers were again scored. If orf had developed in the controls, they were designated as new cases and further controls were found.

All lambs were measured around the thorax with a weighband, and on 107 occasions, lambs were weighed by scales as well. Measurement with the weighband (WB) was highly correlated with actual weight (R-squared = 0.90) so that weight (in kg) = 0.692WB – 27.76. All the lambs were measured with the weighband and so these data were used in the comparison, though the figures were converted back to weights in kilograms to make the results more accessible. This linear conversion scale could not be used with confidence for lambs of weighband measurement less than 50cm (fig 1). At visit one, there were nine controls and 13 cases which measured less than 50cm around the thorax and two such cases by visit two. These small lambs and their controls were excluded from the weight comparison.

Figure 1: A graph to show the weight on scales (kg) compared to the weighband measurement (cm).



A maximum of five visits was undertaken, with a minimum period of two weeks between each visit. The numbers of lambs in the study diminished significantly by the fourth visit, either due to the development of orf in controls or due to the illegibility of the numbers on the tags. For this reason only data from the first three visits were used in the analysis.

For the purpose of analysis, each case was matched with one control from the same farm so that a single lamb was always matched with a single and a twin with another twin. Once these criteria were met, the controls were convenience-chosen though, as far as possible, they were matched by age, sex, breed and group within the farm.

Results

The following breeds were represented in the study: Texel, Suffolk, Charollais, Beltex, Vendeen, Masham and Mule, with both pedigree and crossed lambs represented. Measurements were taken from 65 cases of orf and 86 controls. Three of the orf cases (4.6%) and one of the controls (1.2%) died during the course of the study though this difference was not significant. On one of the farms, orf developed

in 23 of the 24 twin lambs so much of this data could not be used due to a lack of controls.

At visit one, most of the lambs were three weeks old (median 21 days; range 14 to 35 days). 44 cases of orf were matched to a suitable control and of these, 30 were cases that involved the mouth. At visit two the lambs were five weeks old (median 35 days; range 27 to 49) and 20 cases still had orf. At visit three, the lambs were seven weeks old (median 52 days; range 41 to 70) and there were only six cases that still had orf. The analysis involved paired t-tests comparing the mean weights of each of the pairs of cases and controls (table 2).

*Table 2: Comparison of weights of lambs (converted to kg from weighband measurements) between controls (orf score 0) and lambs with lesions (orf score 1-5) with the lightest lambs (thorax <50cm) excluded. Significance is shown by ** at level p<0.01 and * at level p<0.05.*

	Visit 1		**Visit 2**		**Visit 3**	
	Controls	**Orf**	**Controls**	**Orf**	**Controls**	**Orf**
N	30	30	41	41	35	35
Mean weight (kg)	18.56	17.61	20.31	18.51	24.53	22.32
St Dev	7.16	6.18	8.67	8.04	8.96	8.55
Difference in mean weight (kg)	0.95		1.81		2.20	
T Statistic	1.68		3.07		2.98	
P	0.052		0.0019		0.0027	
Significance	ns		**		**	

A comparison was also made between cases with orf that involved the mouth with unaffected controls. At visit one, there was no significant difference (n=22; T = 0.97, p=0.17) between the mean weight of cases (18.30kg) and controls (19.45kg). At visit two, the mean weight of the cases (19.82kg) was significantly less than the controls (21.74kg; n=28; T= 1.77; p=0.044). At visit three, the mean weight of the cases (24.02kg) was significantly less than the controls (26.58kg; n=28; T= 2.22; p=0.018). On each visit, the actual difference in the weight difference between cases of orf

involving the mouth with their controls was greater than the weight difference between cases of orf anywhere on the body compared with their controls though this difference was not significant.

Average weight gain per day was estimated for the periods between visit one and visit three, though with a degree of inaccuracy because this calculation included lambs of thorax <50cm. At the earlier stage of the disease, between the first and second visits, the orf cases grew at a mean rate of 327g per day compared to their controls which grew at 379g per day (n=43; T=1.72; p=0.046). There was no significant difference in the growth rate of the orf cases compared to controls at the later stages of clinical disease (between the second and third visits) or over the month period between visit one and visit three.

Lambs were condition-scored (CS) on a scale of one to five (MAFF 1994) at each visit. At visit one, 9.1% of orf cases had a greater CS than their controls and 29.5% had a lower CS. A one sample t-test between proportions was performed (t = 2.3; df = 43; p=0.026). At visit two 9.3% of orf cases had a greater CS than their controls and 37.2% had a lower CS (t = 2.94; df = 42; p=0.0053). There was no significant difference between the condition scores of cases and controls on visit three.

On visit one, there were data on ewes from five farms (all lowland-type conditions) that could be correlated with their lambs (34 orf cases and 47 controls). There was a highly significant correlation between orf in the mother and orf in the lambs (Chi-squared test p<0.0001) (table 3). If a lamb had orf there was an 82% chance that its mother also had orf on her teats or udder. If a ewe had orf on her teats or udder, there was a 78% chance that her lamb also had orf but this lesion only affected the mouth of the lamb in 75% of these lambs.

Table 3: Correlation of ewes, affected or unaffected with orf, with their lambs.

	Lamb - orf on mouth (score 4 or 5)	**Lamb – orf not on mouth (score 1,2 or 3)**	**Lamb – no orf (score 0)**
Ewe – orf (score 2 or 4)	21	7	8
Ewe - no orf (score 0, 1 or 3)	5	1	39

Of the eight lambs that did not have orf at visit one despite their mothers having orf, five (62.5%) had clinical orf at subsequent visits. Of the 39 lambs in which neither themselves nor their mothers had orf at visit one, nine (23%) lambs had orf at subsequent visits. There were four cases of mastitis (8.9%) amongst the 45 ewes that showed no clinical signs of orf and five cases of mastitis (13.9%) amongst the 36 ewes that had clinical signs of orf on their teats or udder. There was no significant difference in these levels of mastitis when tested under the Fishers Exact test.

Economic analysis

The economic effect of hypothetical outbreaks of orf were calculated using average farm figures (EBLEX 2011), a spreadsheet to calculate unit cost of production (after Stubbings 2007) and figures obtained from this study (tables 4 & 5). Average profit margin for a ewe in a lowland breeding flock in 2011 was £0.14 (EBLEX 2011) which suggests the average unit cost of production was 338p/kg carcase. Average profit margin for a ewe in a breeding flock in a less favoured area (LFA) in 2011 was £7.83 (EBLEX 2011) which suggests the average unit cost of production was 317p/kg carcase.

For the purpose of the cost of production calculation, three components of the ewe variable costs (feed, veterinary and miscellaneous) were sub-divided so that estimated ewe and lamb costs could be considered separately. In the figures, non-cash costs (such as family labour, rental value of owner-occupier land and interest on working capital) were not included. For this reason, the cost of additional labour required to deal with an outbreak of orf, though sometimes considerable, has not been included in the cost calculations.

In an average flock, 20 ewes are replaced annually for every 100 ewes in the flock so the replacement cost per ewe = $(ry/5 – c(y/5-my/100))/y$ where y is the number of ewes in the flock, r is the cost of a replacement ewe, c is the value of a cull ewe and m is the ewe mortality (%). In an orf affected flock, there would be a percentage of involuntary culls (i) due to the extra cases of mastitis (e) though $i=4e/5$ to account for those cases that would have already been due for culling. In an orf-affected flock, replacement cost per ewe = $(r(y/5+iy/100) – c(y/5-my/100+iy/100))/y$.

Table 4: Example of calculation of unit cost of production and profit per ewe for average breeding flocks in lowland and LFA areas (after Stubbings 2007; EBLEX 2011). Increased costs have been added following hypothetical outbreaks of orf using figures derived from this study.

	Average Lowland figures		**Same figures for lowland flock with orf in 40% of lambs**		**Average LFA figures**		**Same figures for LFA flock with orf in 40% of lambs**	
Lambing Index (lambs reared/ewe)	1.59		[1]1.57		1.44		[1]1.42	
Average carcase weight (kg)	19.8		19.8		19.4		19.4	
Production Level (kg carcase/ewe)	31.5		31.1		27.9		27.5	
Unit cost of Production (p/kg carcase)	338		355		317		325	
Output (per ewe)	*£*	*p/kg carcase*	*£*	*p/kg carcase*	*£*	*p/kg carcase*	*£*	*p/kg carcase*
Lamb output after valuation changes	105.48	335			95.23	341		
Wool sales	1.19	4	1.19	4	1.25	5	1.25	5
Variable costs (ewe only) per ewe								
Replacements	14.78	47	[2]17.44	55	12.66	45	[2]13.64	49
Feed	8.00	25	8.00	25	8.07	29	8.07	29
Other Feed	1.50	5	1.50	5	2.22	8	2.22	8
Forage	4.89	16	4.89	16	4.36	16	4.36	16
Vet & Med	6.00	19	[3]6.30	20	5.50	20	[3]5.63	20
Bedding	1.20	4	1.20	4	0.70	3	0.70	3
Other costs	2.80	9	2.80	9	3.00	11	3.00	11
Total	39.17	124	39.95	134	36.51	131	37.62	135
Variable costs per lamb								
Feed	2.65	13	[4]3.93	20	1.38	7	[4]1.92	10
Vet & Med	0.86	4	[5]0.96	5	0.81	4	[5]1.04	5
Other costs	1.53	8	1.53	8	0.70	4	0.70	4
Total	5.04	25	6.43	32	2.89	15	3.66	19
Total variable costs per ewe	**47.18**		**52.23**		**40.67**		**42.81**	
Total fixed costs per ewe	**59.35**	189	**59.35**	189	**47.98**	172	**47.98**	172
Break-even unit cost (p/kg carcase)		335		351		313		319
Assumed market price (p/kg carcase)		335		[6]335		341		[6]341
Profit margin (p/kg carcase)		0.4		-16		28		22
Profit margin £ per ewe	**0.14**		**-4.97**		**7.83**		**5.54**	

Notes for table 4:

[1]Assumed that mortality in orf-affected lambs is increased by 3% (this study) and a further 0.5% in LFA flocks due to increased time on farm (EBLEX 2005b; EBLEX 2005a)

[2] For every lamb with orf it was estimated that there was an 82% chance that its mother would also have orf (this study). In the lowland situation, it was assumed that the orf-affected ewes had a 14% incidence of mastitis (this study). In LFA flocks, the number of cases of mastitis per ewe with orf was estimated at 5% (compared to an expected level of 1% in hill flocks (Winter 2001)). It was estimated that ewe mortality increased by 0.1% for every extra ewe with mastitis and that a mastitic ewe that survived would be culled. For calculation of replacement costs see text.

[3]Assumed cost of drugs for each mastitis case of £6.50 for antibiotic and anti-inflammatory drugs at 2011 prices.

[4]Assumed orf lambs on average 2.2kg lighter than unaffected lambs at end of orf outbreak (this study) and that they maintained this discrepancy up to weaning. Assumed concentrate cost £229 per tonne (EBLEX 2011). In a lowland flock, estimate two extra weeks to finish and 1kg concentrate consumed per day (after Stubbings 2007). In LFA flock, estimate that once weaned, unaffected lambs (equivalent to short-keep stores at 34kg) finish in six weeks by gaining 1kg a week off grass with 1kg of concentrate a week (EBLEX 2005b) and affected lambs (equivalent to medium-keep stores at 32kg) finish in twelve weeks by gaining 0.7kg a week off grass with 1 kg of concentrate a week (EBLEX 2005a).

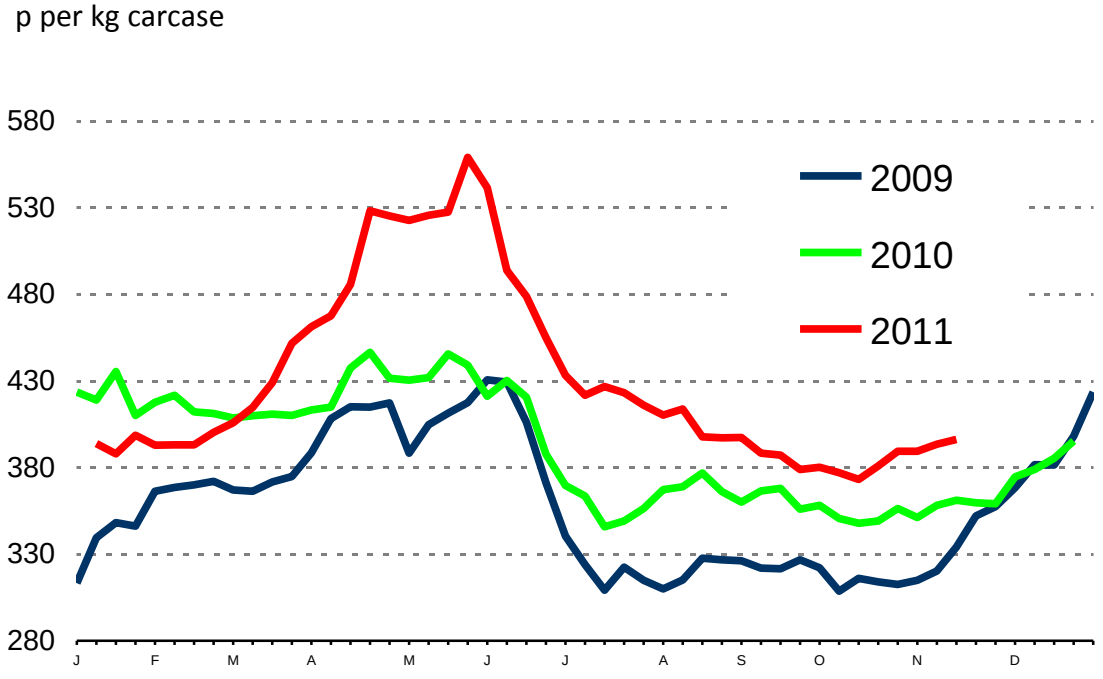
[5]Assumed every orf-affected lamb treated with topical antibiotic spray so that 30 lambs treated per can at a cost of 20p per orf lamb. Assumed that 10% of orf lambs are given an antibiotic injection (£0.60) to treat secondary infection. For LFA flock, estimate additional £0.30 cost for medium-keep compared to short-keep store lamb (EBLEX 2005a; EBLEX 2005b).

[6]In this example, the average market price has been not been altered for the orf affected farms.

Table 5: Comparison of the profit margins for an average lowland breeding flock and an average breeding flock in a less favoured area (LFA), based on EBLEX average 2011 figures, for different incidences of orf in lambs. In column 3 & 6, it was assumed that the average price per kg remained constant despite delayed marketing of the orf-affected lambs. In column 4, it was assumed that the marketing price fell by 10p per week that marketing was delayed.

Lambs with orf (%)	Lowland breeding flock			LFA Breeding flock	
	Unit cost of production (p/kg carcase)	Cost of lost profit margin per ewe due to orf in the flock (fixed marketing price) (£)	Cost of lost profit margin per ewe due to orf in the flock (marketing price altered) (£)	Unit cost of production (p/kg carcase)	Cost of lost profit margin per ewe due to orf in the flock (fixed marketing price) (£)
10	343	1.29	1.92	319	0.58
20	347	2.57	3.82	321	1.15
30	351	3.84	5.71	323	1.72
40	355	5.11	7.60	325	2.29
50	359	6.37	9.47	327	2.86
60	363	7.62	11.33	329	3.42
70	367	8.86	13.17	331	3.97
80	371	10.09	15.01	333	4.53
90	375	11.32	16.83	335	5.07
100	379	12.54	18.65	337	5.62

Figure 2: Great Britain deadweight prices (p per kg carcase) per week for 2009-2011 (Source: EBLEX/AHDB Market Intelligence)



A change in the market price of lowland lambs was estimated based on a fall in price of £0.10 per week through September which was the assumed time of marketing of these lambs. No attempt was made to predict a change in the market price for the LFA lambs as it was estimated that the orf-affected lambs would remain on farm for an extra six weeks. Generally the price is at its lowest in October, after which it usually rises, so it was not possible to predict a price change over a six week period from September to early November which was the estimated marketing time for these lambs (figure 2).

Discussion

Given the nature of this study, in which data were collected from commercial farms during a busy time of year, it was not possible to weigh each lamb on scales. Weighbands are calibrated for use in cattle and pigs, which are not only different species but also much larger animals than young lambs. However, this study has shown a highly significant correlation between a weighband measurement and a weight in kilograms for lambs with a thoracic measurement above 50cm.

At both the first and second visits the lambs with orf lesions had significantly lower body condition scores than the controls, but by the third visit there was no difference in body condition score. The measurement of body condition score (Jefferies 1961; MAFF 1994) has been widely used, though generally in the management of adult ewes rather than pre-weaned lambs. It is a subjective measure and there are few published data on the repeatability between observers. It is accepted that for this study, which was not blind, there may have been observer bias so that lower condition scores may have been sub-consciously allocated to the orf lambs due to their otherwise diseased appearance at visits one and two.

Although the difference in the weight of the cases and controls at visit one was not significant, there was an indication that the cases were lighter even at this stage. Orf pustules rupture about eight days after infection to form scabs and the typical hyperkeratosis and proliferative lesions form as keratinocytes proliferate during the repair process (West et al. 2002). This suggests that orf had been established in the

groups of lambs for at least one week by the time of the first visit. For this reason, the data recorded at visit one cannot be considered a baseline measure.

The possibility that orf affects lambs that are already lighter cannot be completely ruled out as no pre-infection weight data were collected. However, there were strong indications that the lower weights recorded were due to orf as there was an increase in the weight difference as the study progressed and a significantly lower weight gain per day in the orf cases between visit one and two. The weight gain per day in this study was comparable to a range of 280-350g/day that might be expected for pre-weaning lambs on other commercial farms in the UK (Sargison 2008).

With the introduction of widespread electronic identification of sheep, there will be increasing opportunities to weigh accurately large numbers of lambs at regular times during their growth. This would provide data for the period prior to the onset of clinical disease and also confirm whether the slower growth rate during clinical orf, identified by this study, leads to lambs that take longer to finish and are worth less at slaughter.

It is well established that orf has a negative effect on lamb growth rates (West et al. 2002; Sargison 2008; McInnes 2009) though no field studies from commercial farms in the UK have been reported. In the only published quantitative study, computer modelling was used to estimate the cost of the disease. Estimates of losses due to increased mortality rates ranged from £2.70 to £4.00 per affected sheep, and estimates of liveweight losses ranged from zero to £0.08 per affected sheep (Bennett and IJpelaar 2003; Bennett and IJpelaar 2005), figures that are considerably lower than those found in this study.

At both the second and third visit (approximately three and five weeks after the start of the outbreak), the orf lambs weighed approximately 10% less than their controls. This compares with an estimated 12% loss in weaning weight for lambs born to ewes severely affected by Maedi-Visna (Pekelder 1994), 30% reduction in liveweight in lambs experimentally infected with sheep scab (Kirkwood 1980) and up to 37% reduction in growth rates in lambs experimentally affected by *Ostertagia circumcincta* larvae (Coop et al. 1985). A study of the effect of footrot in sheep found weight losses of 0.5 to 2.5kg live weight, although the lambs regained most of

this lost liveweight over a period of approximately ten weeks after the lesions had healed (Nieuwhof et al. 2008).

From this study it was possible only to estimate the ongoing effect of orf on the lambs as there were no data for the period after five weeks following the start of the outbreak. It would not be unreasonable to assume an ongoing discrepancy of 10% though to be conservative for the purposes of the economic estimate, the actual average weight difference at the time of the study (2.2kg) was used as the weight difference at weaning time. It has been established clearly that the shape of a lamb's growth curve determines the proportions and composition of the body and that, proportionally, bone develops first followed by muscle and then fat (Hammond 1952). Consequently, the significant growth check caused by orf that this study demonstrated, would have a detrimental effect on carcase composition such that at the same finishing weight, affected lambs would have a higher proportion of fat compared to their unaffected contemporaries. In the economic analysis, no attempt was made to allow for a lower price due to poorer carcase composition, though it is likely that the actual financial impact could be greater that that calculated.

The timing of this study was at the expected peak time for acute mastitis. However, despite this, the mastitis prevalence in both orf-affected (14%) and orf-unaffected ewes (9%) was high in comparison with other studies where the incidence of mastitis varied widely from, for example, 0.5% in 32 Irish flocks (Onnash et al. 2003) to 7% in a study of 920 Norwegian ewes (Larsgard and Vaabenoe 1993). An incidence of less than 5% is quoted often as average in UK lowland flocks (Winter 2001; Contreras et al. 2007). In this study there was no significant difference in the prevalence of mastitis between those ewes with orf and those without. However, as all the ewes in this study were within groups of sheep with active orf virus present, it is possible that some of the mastitic ewes had subclinical orf present, or had previously had orf following which the lesions had healed.

It has been suggested that there is a distinct progression of orf lesions from the teats of the ewes to infect the mouths of the sucking lambs (Lewis 1996). This observation is strengthened by the finding in this study that a number of the lambs that were unaffected on visit one despite their dams having orf, had developed orf by

subsequent visits. It is perhaps surprising that there were a number of ewes with orf-affected teats that had lambs affected on areas of the body other than their mouths.

There were insufficient cases within this study to determine whether the poor growth rates in the lambs occurred directly as a consequence of their infection with orf, or indirectly because of poor milk supply due to clinical or subclinical mastitis subsequent to orf in the dam. Whichever is the case, orf in the ewes was shown to have a large impact on the economic costs of an outbreak of orf due to the proportionally high costs of replacing ewes in the flock and the inevitable need to cull a ewe following mastitis.

Appendix - Pathogenesis of the orf virus in sheep

Trauma to the skin appears to aid the establishment of the orf virus. Once within the keratinocytes of the *stratum granulosum* and *stratum spinosum* (the granule and prickle cell layers), the virus is able to replicate rapidly. These epidermal cells undergo 'ballooning degeneration', a vacuolation and swelling followed by shrinkage of the nuclei. Within four days, cell necrosis occurs, at which stage inclusion bodies may be seen in the cytoplasm. Neutrophils infiltrate the dermis and this is followed by the development of lesions which progress through macule, papule and vesicle stages to pustules. The pustules rupture about eight days after infection to form scabs which are thickened by the presence of accumulated debris and microabscesses within the epidermis. The typical hyperkeratosis and proliferative lesions form as the keratinocytes proliferate during the repair process. This epidermal proliferation down into the dermal layers is called rete-formation. Damage to the scab leads to profuse bleeding and further proliferation of granulation tissue. Depending on the extent of secondary infection, it is expected that the virus-rich scabs are shed within a month, leaving no scar. (Robinson and Balassu 1981; Lewis 1996; West et al. 2002; McElroy and Bassett 2007)

Studies have shown that the sequence of histological changes are similar in both primary infections and reinfections. In both cases, there is an influx of neutrophils initially followed by an accumulation of T cells, B cells and dendritic cells below and adjacent to the orf-infected epidermis. Compared to primary infections, there is less virus replication and less evidence of rete-formation in reinfections (Haig and Mercer 1998).

Orf infection is localised with no evidence of viraemia. To clarify the details of the host immune response to orf, the contents of afferent and efferent lymph draining the site of orf infections have been examined for cellular and cytokine content. There is a biphasic lymph response thought to be triggered initially by orf virus antigen and later due to replicating virus. Host partial protection against infection is undertaken primarily by CD4+ helper T cells and interferon (IFN-γ) but with CD8+ cytotoxic T cells also playing a role. Orf-infected sheep do produce a number of antibodies but protective antigens have not been identified and there is rarely virus-

neutralising antibody present. Indeed lambs are not protected following the transfer of antibody-rich serum or colostrum (for original references see Haig and Mercer 1998; Haig and McInnes 2002).

Infection with orf virus in sheep causes vigorous antibody and cell-mediated immune responses as well as an apparently normal inflammatory response. However, despite effective host acquired immunity in limiting the extent of virus replication, it does not prevent reinfection. This appears to be due to a number of virulence and immuno-modulating proteins that are encoded by the virus early in infection (table 6).

In primary infections, there is a period of time before the host mounts an effective immune response, in which the virus can replicate and produce immuno-modulating and virulence proteins. Reinfections last for a shorter time period as the immune memory response allows for a quicker containment of the virus before it is able to evade the host immune response (Haig and McInnes 2002).

Table 6: A summary of virulence and immuno-modulating proteins encoded by the orf virus (Haig and Mercer 1998; Haig and McInnes 2002)

What is the normal function of some proteins within the cells of the sheep?	**Proteins produced by the orf virus**	**How do these proteins interfere with host immune and inflammatory responses?**
Ovine vascular endothelial growth factor (VEGF) mediates vascular permeability & angiogenesis & is involved in epithelial cell proliferation.	**vVEGF** - A virulence protein which is a viral orthologue of VEGF.	Orf virus vVEGF may stimulate epidermal keratinocyte hyperplasia & inhibit apoptosis - thus providing more target cells for virus replication.
Granulocyte-macrophage colony-stimulating factor (GM-CSF) is involved in the development & activation of neutrophils, macrophages, eosinophils & basophils and in the recruitment & development of dendritic cells in sheep skin.	**GM-CSF inhibitory factor (GIF)** inhibits the cytokines, GM-CSF & IL-2.	GIF inhibits GM-CSF production by infected keratinocytes - thus preventing accumulation & activation of immune & inflammatory cells & dendritic cells adjacent to the infection site.
Interleukin-10 (IL-10) is an immuno-regulatory, anti-inflammatory cytokine which inhibits the synthesis of a range of cytokines and down-regulates T-cell mediated immune response by altering the function of antigen-presenting cells.	**vIL-10** - an orthologue of mammalian IL-10.	Both ovine IL-10 and orf virus IL-10 inhibit TNF-α & IL-8 production from macrophages & keratinocytes and IFN-γ production from activated lymphocytes.
Interferon induces an 'anti-viral state' in cells (see below for more details)	**Interferon resistance factor (OVIFNR)** - An immuno-modulator protein which binds to viral dsRNA.	OVIFNR prevents the inhibition of protein synthesis by interferon hence OVIFNR may allow orf virus to utilise protein synthesis in the host cell and produce virions.
Interferon response to viral attack In the presence of certain patterns of molecules, such as double-stranded RNA (dsRNA), which are only present during pathogen infection, type I interferons (IFN-α & IFN-β) are released by both virus infected cells and specialist immune cells such as dendritic cells. Type II interferons (IFN-γ) are released by lymphocytes during the immune response. All types of interferon bind to IFN-receptors on uninfected cells and induce an 'anti-viral state' within the cell, primarily by up-regulating the expression of cellular genes which encode proteins with anti-viral action. Two such proteins are PKR-kinase which inhibits viral protein synthesis and encourages apoptosis (programmed cell death) and 2'5'oligoadenylate synthetase (2-5A) which inhibits viral protein synthesis and encourages the degradation of cellular and viral DNA. Both these proteins are activated by the presence of the dsRNA.		

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