# Factors associated with the clinical diagnosis of foot and mouth disease during the 2001 epidemic in the UK

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**Abstract**

The purpose of this investigation was to identify factors associated with the clinical diagnosis of foot and mouth disease during the 2001 epidemic in the United Kingdom. Using logistic regression, we compared: (1) reports of suspect disease that resulted in the declaration of FMD to reports that did not, and (2) laboratory-positive cases to laboratory-negative cases.

From 6801 reports of suspect disease, 2026 cases of FMD were identified. Suspect cases were more likely to become clinical cases if: (1) the report originated from the disease control authorities ('active surveillance') rather than the public, usually farmers ('passive surveillance'); (2) cattle were the species suspected of disease, as opposed to sheep; (3) the report was filed during the peak of the epidemic; (4) the reporting premises was within 3 km of an FMD case detected within the previous 2 weeks; or (5) the report originated from certain local disease control centres. There were significant two-way interactions between: type of surveillance and species suspected of disease, type of surveillance and proximity of other infected premises, species suspected and time in the epidemic, and time in the epidemic and proximity of other infected premises.

Clinical cases were more likely to be laboratory positive if: (1) they were found by passive versus active surveillance, (2) cattle were suspected of disease (versus sheep), (3) oldest lesions were less

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than 3 days, (4) the report was filed at any time other than the peak of the epidemic, or (5) the report originated from certain local disease control centres. Significant two-way interactions were found between: type of surveillance and species suspected of disease, and type of surveillance and time in the epidemic.


*Keywords:* Foot and mouth disease; Logistic regression; Risk factors; Clinical diagnosis; Interaction; Animal disease surveillance

## 1. Introduction

In 2001, the UK experienced a large epidemic of foot and mouth disease (FMD) that resulted in the identification of 2026 infected premises in Great Britain (England, Scotland, and Wales) and four in Northern Ireland. The rapid detection and subsequent removal of infected animals remains the foundation for the control and eradication of FMD. Failure to identify and destroy stock on infected premises permits ongoing viral shedding, and thus contributes to the further spread of infection. However, if premises are wrongly declared infected the consequences can be severe, both economically, related to resultant restrictions and compensation, and socially, due to public aversion to the destruction of healthy animals.

During the 2001 epidemic in the UK, the identification and ensuing destruction of stock on infected premises was based almost entirely on clinical presentation because laboratory testing could take up to 5 days, too long to leave potentially infected animals shedding virus (Anderson, 2002). The system in place to diagnose FMD is described thoroughly in McLaws et al. (in press). Suspect cases of disease were identified either by the public (primarily farmers), or by the disease control authorities in the course of their activities (patrols, tracings, and culls of susceptible stock on premises deemed at high-risk of disease). Upon receipt of a report of suspicion, a veterinarian from the nearest local disease control centre examined the relevant animals and described the clinical findings by telephone to another veterinarian at the national disease control centre. On the basis of the clinical description, veterinarians at the national disease control centre decided whether or not to declare the premises a case of FMD (commonly referred to in the literature and during the epidemic as an ''infected premises''). Subsequently, samples were submitted to the laboratory for confirmation.

Internationally agreed laboratory procedures, as described in the OIE Manual of Standards for Diagnostic Tests and Vaccines (Kitching et al., 2000), were used during the epidemic (Royal Society of London, 2002; Department for Environment Food and Rural Affairs, 2002). An antigen detection enzyme-linked immunosorbent assay (ELISA) was performed immediately. Samples negative to the ELISA were subjected to the more sensitive virus-isolation test (Royal Society of London, 2002). A case was deemed laboratory-positive if *either* the ELISA or the virus-isolation test was positive, and laboratory-negative if *both* tests yielded negative results. A number of clinically positive animals were laboratory test negative; because 100% specificity of clinical diagnosis is unrealistic, this is not unexpected. Some cases of FMD were found as a result of routine serological testing rather than on the basis of clinical signs; we did not consider these to be 'clinical cases' of FMD.

McLaws et al. (in press) demonstrated that both routine monitoring for suspected disease and the declaration of FMD cases at the national disease control centre were highly sensitive and specific diagnostic tests. Both tests relied on clinical signs for the diagnosis of disease. Therefore, the outcome of the tests might have been affected by factors such as the origin of report (i.e. who reported the initial suspicion of disease), the species suspected of disease, the location of the suspect premises in relation to previously identified infected premises, the nature of the lesions in question, the time of the outbreak in relation to the epidemic curve, and the local disease control centre involved. In this paper, we examined each of these factors and their relationship to the clinical diagnosis of foot and mouth disease. Multivariable logistic regression models were developed to explore the association of these factors with the decision to declare suspect premises infected with FMD, and with the laboratory results.

## 2. Materials and methods

Premises were categorized into four hierarchical classes as: (1) disease never suspected, (2) suspect cases, (3) clinical cases, and (4) laboratory-verified cases. Following a report of suspected disease, the premises in question became a 'suspect case'. If a suspect case was declared infected with FMD, it was termed a 'clinical case'. Laboratory testing was usually performed subsequent to a positive clinical diagnosis, distinguishing between 'laboratory-positive', 'laboratory-negative', and 'laboratory-untested' clinical cases.

For reports of suspect disease that did not result in the declaration of FMD (''negative report cases''), the date of report, origin of report (farmer, patrol, etc.), local disease control centre involved, species suspected of disease, and the XY geographical coordinates of the premises were obtained from the Department for Environment, Food and Rural Affairs' Disease Control System. This database was created during FMD outbreak to be used as a management tool, and has been described previously (Gibbens et al., 2001).

Information about the species suspected of disease was recorded for only 328 of the 4775 negative report cases. To provide a better estimation of the total number of each species suspected of disease, 366 reports were randomly sampled from the negative reports that did not have species recorded. This sample was selected using a random number table, and was stratified by local disease control centre with proportional allocation. On this subset, the species suspected of disease was obtained from the telephone report forms completed by the veterinary official at the time of initial reporting. With the prior assumption that approximately 50% of report cases concerned suspect disease in cattle and 50% concerned sheep, the sample size allowed for an estimate of the true proportions with an allowable error of 4% (Dohoo et al., 2003, p. 41). Sheep and goats were categorised together, however approximately 99.5% of premises in this category possessed only sheep, and thus we refer only to sheep in the remainder of the paper. The total number of negative reports for each species was extrapolated from the sample (Table 1); exact 95% confidence limits were determined using the hypergeometric distribution (these calculations were performed with the in-house statistical program 'Distrib', developed by William Sears, Dept. of Population Medicine, University of Guelph).

Table 1
Species suspected of disease during the 2001 epidemic of foot and mouth disease in the UK

| Species | Negative report cases | | Total reports | | %Reports became clinical cases (95% CI) |
|---|---|---|---|---|---|
| | Frequency | | Frequency | | |
| | # (95% CI) | Column% (95% CI) | # (95% CI) | Column% (95% CI) | |
| Cattle | 1493 (1341–1652) | 31 (28–35) | 2555 (2403–2714) | 38 (35–40) | 42 (39–44) |
| Sheep | 2965 (2800–3126) | 62 (59–65) | 3798 (3633–3959) | 56 (54–59) | 22 (21–23) |
| Pigs | 138 (94–214) | 3 (2–4) | 156 (112–232) | 2 (1–3) | 12 (8–16) |
| Deer | 28 (5–57) | 0.6 (0.1–1.2) | 28 (5–57) | 0.4 (0.1–0.8) | 0 |
| Cattle and sheep | 151 (99–222) | 3 (2–5) | 225 (173–296) | 3 (1–3) | 33 (25–43) |
| Total | 4775 | 100 | 6762 | 100 | 29 |

For each case of FMD, the date of report of suspicion, date it was declared infected, origin of report, local disease control centre involved, age of oldest lesion, species infected, laboratory results, and XY coordinates were obtained from the database developed by the epidemiology team located at the national disease control centre headquarters during the outbreak. This database has also been described previously (Gibbens et al., 2001). Any incompatibilities in the data (for example if cattle were recorded as the species infected but it was not recorded that there were any cattle on the farm), or cases with missing data, were investigated using the 'Final Epidemiology Report' database. This database was compiled by the field epidemiology teams at each local disease control centre using information from the Disease Control System, forms completed at the time of investigation, and local knowledge. If more detailed information could be gleaned from this database that clarified the inconsistent entry in the epidemiology database, the record was adjusted.

For each case of FMD, information about the species suspected of disease was obtained from the Disease Control System. For 30 of the 34 premises where the species suspected of disease was not recorded, a single species was infected and assumed to be the species suspected of disease. On the four remaining premises, the species suspected of disease was inferred from the Final Epidemiology Report database.

We performed two logistic regression analyses. For the first, the outcome was whether a report of suspected disease resulted in the declaration of FMD (yes or no). The 39 cases detected as a result of serological testing were omitted because they were not subject to diagnosis on the basis of clinical signs. The model was built using all remaining suspect cases of FMD for which the data were complete (2635 observations). This analysis was repeated omitting species suspected of disease as a predictor variable, allowing 6261 of 6801 report cases to be used.

For the second analysis, the outcome was whether the laboratory result of FMD clinical cases was positive or negative. FMD cases discovered by serological testing were omitted from this analysis as well. The model was developed using all remaining cases that had laboratory samples submitted (1685 out of 2026 cases).

The predictor variables used in each analysis are described in the first two columns of Tables 2 and 3. Categorical variables were created for each model to represent the time period within the epidemic (First month, Peak, {End of Peak}, Tail).

Table 2
Univariable logistic regression analyses of all putative risk factors used in the analysis comparing report cases that resulted in the declaration of FMD to those that did not during the 2001 epidemic in the UK

| Predictor variable | Classification | #Suspected premises declared infected | #Suspected premises not declared infected | Crude odds ratio (95% C.I.) | $p$-Value[a] |
|---|---|---|---|---|---|
| Type of surveillance that detected report case | Active surveillance | 488 | 609 | 2.08[b] (1.81–2.39) | <0.001 |
| | Passive surveillance | 1494 | 3884 | 1 | |
| Report case within 3 km of an infected premise confirmed within the previous 2 weeks | Yes | 1344 | 1287 | 5.48 (4.88–6.15) | <0.001 |
| | No | 643 | 3375 | 1 | |
| Species suspected of disease | Cattle (or cattle & sheep) | 1136 | 240[c] | 2.53 (2.10–3.04) | <0.001 |
| | Only sheep or pigs | 851 | 454[c] | 1 | |
| Time of report case in relation to the epidemic curve | First month (19 February–19 March) | 391 | 1175 | 0.57 (0.49–0.65) | <0.001 |
| | Peak (20 March–19 April) | 1013 | 1728 | 1 | |
| | End of peak (20 April–25 May) | 230 | 1013 | 0.39 (0.33–0.46) | |
| | Tail (26 May–30 December) | 353 | 859 | 0.70 (0.61–0.81) | |
| Local disease control centre | 18 Dummy variables | – | – | – | <0.001 |

[a] For non-dichotomous variables, refers to the significance of the predictor represented by a group of dummy variables.
[b] OR of 2.08 indicates that the odds of a suspect case being declared a clinical case at the national disease control centre were twice as great when the case was detected by active surveillance, compared to cases detected by passive surveillance.
[c] Numbers reflect sample of species suspected.

Table 3
Univariable logistic regression analyses of all putative risk factors used in the analysis comparing laboratory-positive and laboratory-negative cases of FMD during the 2001 epidemic in the UK

| Predictor variable | Classification | #Laboratory-positive cases | #Laboratory-negative cases | Crude odds ratio (95% C.I.) | $p$-Value[a] |
|---|---|---|---|---|---|
| Type of surveillance that detected report case | Active surveillance | 196 | 181 | 0.22[b] (0.17–0.29) | <0.001 |
| | Passive surveillance | 1087 | 222 | 1 | |
| Report case within 3 km of an FMD case declared within the previous 2 weeks | Yes | 882 | 239 | 1.50 (1.18–1.90) | <0.001 |
| | No | 405 | 165 | 1 | |
| Species suspected of disease | Cattle (or cattle and sheep) | 884 | 113 | 5.65 (4.38–7.30) | <0.001 |
| | Only sheep or pigs | 403 | 291 | 1 | |
| Time to detection | Early (oldest lesion $<3$ days) | 768 | 138 | 2.85 (2.24–3.63) | <0.001 |
| | Late (oldest lesion $\geq 3$ days) | 519 | 266 | 1 | |
| Time of report case in relation to epidemic curve | First month (19 February–19 March) | 282 | 60 | 2.27 (1.67–3.10) | <0.001 |
| | Peak (20 March–5 May) | 618 | 299 | 1 | |
| | Tail (6 May–30 December) | 387 | 45 | 4.16 (2.97–5.84) | |
| Local disease control centre | 18 dummy variables | – | – | – | <0.001 |

[a] For non-dichotomous variables, refers to the significance of the predictor represented by a group of dummy variables.
[b] OR of 0.22 indicates that the odds of a clinical case being laboratory-positive were approximately one-quarter as great when the case was detected by active surveillance, compared to cases detected by passive surveillance.

Suspect cases became clinical cases more often when cattle were the species suspected of disease as compared to sheep, and there were relatively few disease reports concerning other species (Table 1). Therefore, the species suspected of disease was represented by a dichotomous variable. Reports in which the species suspected of disease included cattle formed one category, and the remaining reports constituted the other category. The time to detection was dichotomized into 'early' (oldest lesion $<3$ days) and 'late' (oldest lesion $\geq 3$ days). This variable was only used in the second regression analysis.

The method of disease detection was dichotomized into active and passive surveillance. Some investigations of suspected disease were instigated by a farmer or other member of the public. Because the disease control authorities did not initiate the visit to these premises, we referred to this method of detection as passive surveillance. Other cases of suspected disease came to the attention of the authorities during visits initiated by the local disease control centre, such as patrol visits, tracing visits, or pre-emptive culls. We considered that these cases were detected by active surveillance (Tsutsui et al., 2003).

A variable was created that represented whether or not the reporting premise was within 3 km of a case that had been declared within the previous 2 weeks. We chose this distance as 'Protection zones' were created in a 3 km radius around confirmed FMD cases. All premises with susceptible stock within these zones were subject to enhanced movement and biosecurity restrictions on an ongoing basis, and may have also received patrol visits in the days and weeks subsequent to the detection of the infected premises that caused the creation of the Protection zone. The Euclidean distance between premises was determined using the XY coordinates. This distance was calculated using SAS Version 8.2 (SAS Institute 2002, Cary, NC, USA). All other analyses were conducted using Stata (StataCorp. 2003. Stata Statistical Software: Release 8.0, College Station, TX, USA: StataCorp LP).

Methodology described by Dohoo et al. (2003, pp. 317–372) was employed to build both regression models. First, a causal web was developed for each outcome. The distribution of each variable was examined, and univariable associations with the outcome were calculated. A Chi-square test was used for dichotomous predictors, and simple logistic regression for predictors with more than two categories.

All independent variables with evidence of association with the outcome (using a liberal $p$-value of $<0.2$) were eligible for inclusion in the regression models. Dummy variables were created to represent categorical variables with more than two levels. The authors were interested in the effects of local disease control centre, but did not report the coefficients due to confidentiality issues. A model incorporating centre as a random effect was similar to the fixed effect approach. The statistical significance of each variable was assessed either by the Wald test (dichotomous predictors) or the likelihood ratio test (non-dichotomous predictors), with the significance level for both tests set at $p \leq 0.05$. A manual backwards elimination approach was employed to build the model in which statistically insignificant variables were removed from the model one at a time, beginning with the least significant. This proceeded until all remaining variables were significant at $p \leq 0.05$.

To assess confounding, odds ratios were monitored as each predictor variable was removed from the main-effects model. If the odds ratio of a remaining predictor variable changed by more than 20%, it was considered to have a confounding relationship with the excluded variable.

All possible two-way interaction terms of the main effects (except local disease control centre) were created and subjected to the same screening tests for inclusion in the final model. Interactions with the local centres were not generated, as the resultant complexity would limit the usefulness of the model. The fit of each model was assessed using the Hosmer-Lemeshow test.

## 3. Results

The distribution of the report dates for all suspected cases over time mirrored the curve showing the report dates of only premises declared infected. Both curves peaked on 26 March (in week 6), on which there were 134 reports of suspicion that resulted in 55 premises being declared infected. The proportion of reports resulting in the declaration of disease varied over time (Fig. 1).

Samples were submitted to the Institute for Animal Health (Pirbright Laboratory) for laboratory confirmation of disease from 85% of clinical FMD cases; of these, 76% tested positive for FMD virus. The greatest proportion of samples was laboratory-negative during the peak of the epidemic, which was also when the greatest proportion of cases remained untested (Fig. 2).

Seventy-nine percent of all reports of suspected disease were generated by passive surveillance; 92% of these reports were from farmers suspicious of disease in their stock. Overall, 28% of reports that originated from passive surveillance were declared clinical cases of FMD. However, this value varied by the type of passive surveillance: only 19% of reports by private veterinary surgeons resulted in the declaration of FMD cases, compared to 29% of farmer reports. Of the FMD cases identified by passive surveillance that had samples submitted to the laboratory, 83% tested positive. The proportion of premises that

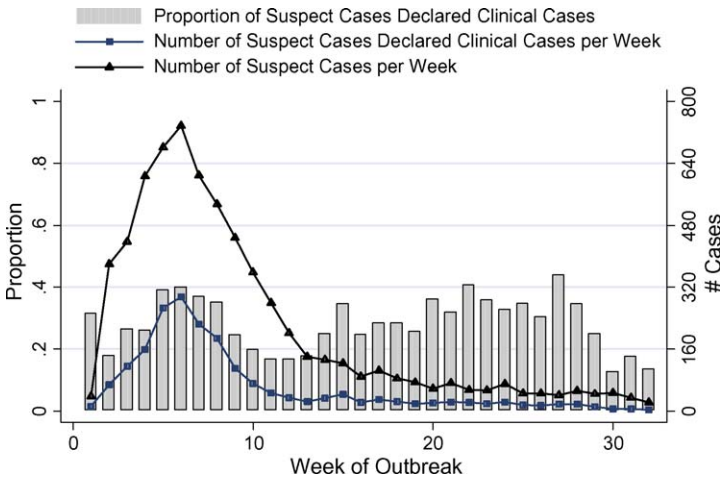


Fig. 1. Distribution of reports of suspect disease during the 2001 FMD epidemic in the UK and the percent of reports that were declared clinical cases, by week of the outbreak.

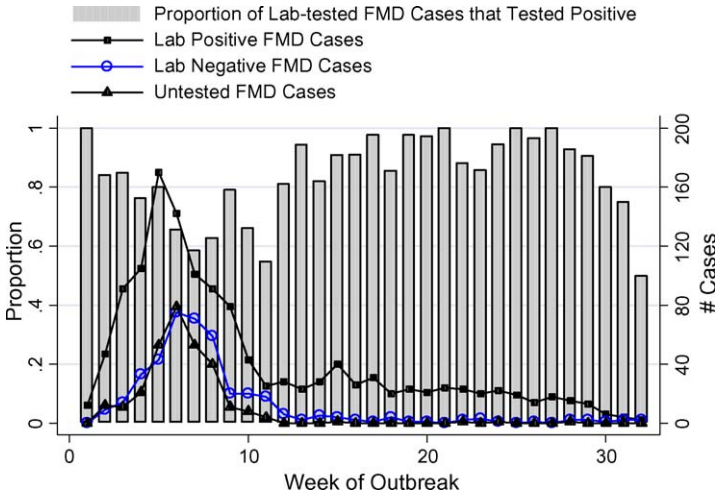


Fig. 2. Distribution of FMD cases categorised by results of laboratory testing, and the proportion that were laboratory positive, by week, during the 2001 FMD epidemic in the UK.

tested laboratory-positive was very similar for all categories of passive surveillance (Table 4).

Sixteen percent of reports of suspected disease were generated by active surveillance: 46% of these were from patrols, 28% from pre-emptive culls, and 26% from tracings.

Table 4
Description of the origin of report cases during the 2001 UK foot and mouth disease epidemic

| Source of report | | All reports | | | Declared FMD cases | | | |
|---|---|---|---|---|---|---|---|---|
| Surveillance | Origin | Frequency | | Declared FMD cases[a] (%) | Frequency | | Lab-tested (%) | Lab-positive[b] (%) |
| | | # | % | | # | % | | |
| Passive | Owner | 4969 | 73 | 28.6 | 1423 | 70.2 | 87.3 | 83.1 |
| | Private vet | 297 | 4.4 | 18.9 | 56 | 2.8 | 96.4 | 85.2 |
| | Abattoir vet | 92 | 1.4 | 14.1 | 13 | 0.7 | 84.6 | 81.8 |
| | Police | 13 | 0.2 | 0 | 0 | 0 | N/A | N/A |
| | Local authority | 7 | 0.1 | 28.6 | 2 | 0.1 | 100.0 | 0.0 |
| | Total (passive) | 5378 | 79 | 27.8 | 1494 | 73.7 | 87.6 | 83.1 |
| Active | Patrol | 508 | 7.4 | 40.3 | 205 | 10.5 | 91.2 | 52.4 |
| | Pre-emptive cull | 309 | 4.5 | 63.4 | 196 | 9.7 | 64.3 | 48.4 |
| | Tracing | 280 | 4.1 | 31.1 | 87 | 4.3 | 73.6 | 57.8 |
| | Total (active) | 1097 | 16 | 44.5 | 488 | 24.1 | 77.3 | 52.0 |
| Sero-surveillance | | 39 | 5.7 | 100 | 39 | 1.9 | 100.0 | 100.0 |
| Unknown | | 287 | 4.2 | 1.7 | 5 | 0.2 | 100.0 | 80.0 |
| | Total | 6801 | | 29.8 | 2026 | | 85.4 | 76.7 |

[a] Declared to be FMD cases at the national disease control centre.
[b] Of premises that were laboratory tested, percent that were laboratory-positive.

Overall, 45% of reports that originated from active surveillance were declared clinical FMD cases. Suspect reports that originated from any category of active surveillance were more likely to result in the declaration of a clinical case than reports that were generated from any type of passive surveillance. Reports from pre-emptive culls were the most likely to be declared infected: 63% of these reports resulted in the declaration of clinical cases. Of laboratory-tested FMD cases identified by active surveillance, 52% were positive for FMD. The proportion of FMD cases that tested positive was similar for all categories of active surveillance (Table 4).

Passive surveillance was more likely to result in the report of suspected disease in cattle than active surveillance. For passive surveillance, approximately 37% of suspect cases that were not declared to be FMD (i.e. negative report cases) involved cattle, compared to 25% of negative report cases detected by active surveillance ($\chi^2 = 6.20$, $p = 0.013$). Of FMD cases, only 34% of those detected by active surveillance resulted from suspected disease in cattle, compared to 64% of cases found by passive surveillance ($\chi^2 = 130.48$, $p < 0.001$).

The location (XY coordinates) of all FMD cases and 4662 of 4775 of the negative reports was recorded. Overall, 60% of premises that reported suspected disease were within 3 km of an FMD case that had been declared within the previous 2 weeks.

Veterinarians working at 24 different local disease control centres filed reports of suspected disease to the national disease control centre. The number of reports from each centre varied from 7 to 1725. At 18 of the 24 centres, some of the suspect cases became clinical cases; the number of clinical cases associated with each centre ranged from 2 to 878. Whereas overall 29% of reports of suspect disease were declared clinical cases, the percentage from each centre ranged from 0% to 53%. Ten local disease control centres submitted samples to the laboratory from more than 50 clinical cases. Of these, the proportion of laboratory-positive samples varied from 30% to 93%.

Multivariable logistic regression was used to compare the features of suspect cases that became clinical cases of FMD to those that did not. All of the predictor variables were statistically associated with the outcome in the univariable analysis (Table 2). The final model is presented in Table 5. Due to missing values, particularly in the 'species suspected' variable, the final model used data from 2635 of 6801 reports. The Hosmer-Lemeshow test indicated that model fit the data (Chi-square with eight degrees of freedom = 5.04, $p = 0.7533$). There was evidence of confounding between local disease control centre and the variable that indicated whether a suspect case was within 3 km of a recently confirmed FMD case. Both of these variables were also statistically significant, and thus did not need to be forced into the model. Four significant two-way interactions were identified, these are interpreted in Table 6.

Suspect cases were more likely to become clinical cases if they were identified by active surveillance rather than passive surveillance. The relationship between type of surveillance and declaration was stronger when sheep were the species suspected of disease as opposed to cattle, and also when there was no other FMD case within 3 km compared to when there was another FMD case nearby (Table 6).

Suspect cases were also more likely to be declared clinical cases if cattle versus sheep were the species suspected of disease, or if the suspect case was located within 3 km of a

Table 5
Results of the logistic regression analysis comparing report cases that resulted in the declaration of FMD to those that did not, during the 2001 epidemic in the UK ($n = 2635$ report cases)

| Variable | OR | 95% CI | |
|---|---|---|---|
| Type of surveillance that detected report case | | | |
| Passive surveillance | 1 | – | – |
| Active surveillance | 4.19[a] | 2.74 | 6.40 |
| Species suspected of disease | | | |
| Cattle | 1.44 | 1.03 | 2.02 |
| No cattle (primarily sheep) | 1 | – | – |
| Within 3 km of infected premises confirmed within previous 2 weeks | | | |
| Yes (local) | 2.72 | 1.95 | 3.80 |
| No (not local) | 1 | – | – |
| Time of report in relation to epidemic curve | | | |
| First month | 0.69 | 0.46 | 1.04 |
| Peak | 1 | – | – |
| End of peak | 0.35 | 0.21 | 0.57 |
| Tail | 0.08 | 0.04 | 0.15 |
| Active surveillance × cattle suspected | 0.53 | 0.30 | 0.94 |
| Active surveillance × local | 0.39 | 0.23 | 0.66 |
| Time × species suspected interactions | | | |
| First month × cattle suspected | 1.22 | 0.72 | 2.05 |
| End of peak × cattle suspected | 2.60 | 1.38 | 4.91 |
| Tail × cattle suspected | 9.47 | 4.48 | 20.00 |
| Time × local interactions | | | |
| First month × local | 0.93 | 0.55 | 1.59 |
| End of peak × local | 0.89 | 0.47 | 1.70 |
| Tail × local | 7.55 | 3.46 | 16.47 |

All estimates are adjusted for local disease control centre. The overall model deviance was 2233.47 and the likelihood ratio Chi-square was 717.34 with 31 d.f., $p < 0.0001$.

[a] OR = 4.19 indicates that the odds of a report case being declared an FMD case at the national disease control centre were 4.19 times higher if the case was detected by active surveillance as compared to passive surveillance. Because of interactions, this value depends on species suspected, and whether the closest prior case was within 3 km (i.e. "local") as shown in Table 6.

recently identified FMD case, compared to if it was not. Both of these associations were much stronger in the tail of the epidemic, but were not statistically significant if the report of suspicion originated with active surveillance (Table 6).

Generally, premises on which suspect disease was reported during the peak of the epidemic were more likely to be declared clinical cases than those on which suspicion was reported at any other time. However, the differences between the times of the epidemic were not statistically significant if cattle were suspected of disease (Table 6).

This logistic model was reconstructed with the variable representing species suspected omitted from the analysis (results not shown) using data from 6261 of 6801 reports. All of the predictors remained significant in both models, and the direction of association was consistent for the main predictors (three local disease control centres changed direction of

Table 6
Details of significant interaction terms in the logistic regression model comparing, with odds ratios, report cases that resulted in the declaration of FMD to those that did not, during the 2001 epidemic in the UK

| Predictor | Comparison | Interacting term | OR | 95% CI | |
|---|---|---|---|---|---|
| Type of surveillance that detected report case | Active surveillance vs. passive surveillance | Cattle suspected | 2.24[a] | 1.27 | 3.94 |
| | | Sheep suspected | 4.19 | 2.75 | 6.40 |
| | | Local[b] | 1.63 | 1.06 | 2.50 |
| | | Not local | 4.19 | 2.75 | 6.40 |
| Species suspected | Cattle vs. sheep | Found by active surveillance | 0.77 | 0.44 | 1.37 |
| | | Found by passive surveillance | 1.45 | 1.03 | 2.02 |
| | | In first month | 1.76 | 1.15 | 2.68 |
| | | In peak | 1.45 | 1.03 | 2.02 |
| | | At end of peak | 3.76 | 2.13 | 6.62 |
| | | In tail | 13.68 | 6.86 | 27.29 |
| Report was within 3 km of an FMD case declared within previous 2 weeks | Yes vs. no | Found by active surveillance | 1.06 | 0.62 | 1.82 |
| | | Found by passive surveillance | 2.72 | 1.95 | 3.80 |
| | | In first month | 2.54 | 1.64 | 3.95 |
| | | In peak | 2.72 | 1.95 | 3.80 |
| | | At end of peak | 2.44 | 1.36 | 4.37 |
| | | In tail | 20.56 | 9.79 | 43.18 |
| | First month vs. peak | Cattle suspected | 0.85 | 0.53 | 1.35 |
| | | Sheep suspected | 0.70 | 0.46 | 1.04 |
| | | Local[b] | 0.65 | 0.41 | 1.02 |
| | | Not local | 0.70 | 0.46 | 1.04 |
| Time in outbreak | End of peak vs. peak | Cattle suspected | 0.91 | 0.51 | 1.60 |
| | | Sheep suspected | 0.35 | 0.21 | 0.57 |
| | | Local[b] | 0.31 | 0.17 | 0.56 |
| | | Not local | 0.35 | 0.21 | 0.57 |
| | Tail vs. peak | Cattle suspected | 0.71 | 0.41 | 1.22 |
| | | Sheep suspected | 0.08 | 0.04 | 0.15 |
| | | Local[b] | 0.57 | 0.30 | 1.09 |
| | | Not local | 0.08 | 0.04 | 0.15 |

[a] An OR of 2.24 indicates that, when cattle were the species suspected, the odds of a report case being declared an FMD case at the national disease control were approximately twice as great when the case was detected by active surveillance, compared to cases detected by passive surveillance.

[b] 'Local' means that report was within 3 km of an FMD case declared within previous 2 weeks.

association in relation to the referent centre). However, the magnitude of the odds ratios differed between the two models. The odds ratio for the variable representing the type of surveillance changed the most; it increased by 68% in the sample model compared to the model excluding species. The odds ratio for the variable representing the proximity of the report to previous FMD cases decreased by 21% in the sample model.

The multivariable analysis that compared laboratory-positive and laboratory-negative FMD cases was conducted using 1685 of the 1730 cases that had laboratory samples submitted; the 39 cases detected by serological testing, 5 cases with missing values, and 1 observation that represented a covariate pattern with no variability (i.e. predicted the outcome perfectly) were not included in the analysis.

Table 7
Results of the logistic regression analysis comparing laboratory-positive and laboratory-negative FMD clinical cases during the 2001 FMD epidemic in the UK ($n = 1685$ premises)

| Variable | OR | 95% CI | |
|---|---|---|---|
| Type of surveillance that detected report case | | | |
| Passive surveillance | 1 | – | – |
| Active surveillance | 0.22[a] | 0.13 | 0.37 |
| Species suspected of disease | | | |
| Cattle | 4.62 | 3.23 | 6.61 |
| No cattle (primarily sheep) | 1 | – | – |
| Time to detection | | | |
| Early (oldest lesion $<$ 3 days) | 1.62 | 1.21 | 2.18 |
| Late (oldest lesion $\geq$ 3 days) | 1 | – | – |
| Time in outbreak | | | |
| First month | 3.26 | 2.09 | 5.08 |
| Peak | 1 | – | – |
| Tail | 2.98 | 1.51 | 5.86 |
| Active surveillance $\times$ cattle suspected | 0.41 | 0.22 | 0.77 |
| Time $\times$ type of surveillance interactions | | | |
| First month $\times$ active surveillance | 2.60 | 1.14 | 5.93 |
| Tail $\times$ active surveillance | 1.84 | 0.77 | 4.41 |

All estimates are adjusted for local disease control centre. The final model had a deviance of 1271.88 and the likelihood ratio Chi-square was highly significant (582.03 with 24 d.f., $p < 0.0001$).

[a] OR = 0.22 indicates that the odds of an FMD case being laboratory-positive were 0.22 times as high when the case was detected by active surveillance compared to passive surveillance. Because of interactions, this value depends on time in the outbreak and species suspected of disease (Table 8).

All univariable associations between the risk factors and the laboratory results were significant (Table 3). The variable that represented whether there was another recently declared FMD case within 3 km did not remain significant in the multivariable model and was dropped (Table 7). The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data (Hosmer-Lemeshow Chi-square = 12.17 with 7 d.f., $p = 0.095$). There was evidence of confounding between: (1) time in the epidemic and surveillance (active versus passive), (2) time in the epidemic and local disease control centre, (3) local disease control centre and surveillance, and (4) time to detection and species suspected. All of these variables were also statistically significant. Two interactions were significant (Table 8).

Clinical cases found by passive surveillance were more likely to be laboratory positive than those detected by active surveillance. This relationship was stronger when cattle were suspected of disease, compared to sheep or pigs. The relationship also was stronger in the peak of the epidemic than in the first month or in the tail.

Laboratory results were also more likely to be positive when cattle were suspected of disease than when they were not; this association was stronger for premises detected by passive surveillance than active surveillance. FMD cases where the oldest lesions were less than 3 days old were more likely to be laboratory-positive than cases that involved animals with older lesions. Finally, FMD cases reported in the first month or in the tail of the epidemic were more likely to be laboratory-positive than cases reported during the peak of

Table 8
Details of interaction terms significant in the logistic regression model comparing, using odds ratios, laboratory-positive and laboratory-negative FMD clinical cases during the 2001 FMD epidemic in the UK

| Predictor | Comparison | Interacting term | OR | 95% CI | |
|---|---|---|---|---|---|
| Type of surveillance that detected report case | Active surveillance vs. passive surveillance | Cattle suspected | 0.09[b] | 0.05 | 0.16 |
| | | Sheep suspected | 0.22 | 0.13 | 0.37 |
| | | In first month | 0.57 | 0.28 | 1.17 |
| | | In peak | 0.22 | 0.13 | 0.37 |
| | | In tail of epidemic | 0.41 | 0.18 | 0.92 |
| Species suspected | Cattle vs. sheep | Found by active surveillance | 1.88 | 1.10 | 3.19 |
| | | Found by passive surveillance | 4.62 | 3.22 | 6.62 |
| Time to detection | Early vs. late[a] | | 1.62 | 1.21 | 2.18 |
| Time in outbreak | First month vs. peak | Found by active surveillance | 8.47 | 4.12 | 17.39 |
| | | Found by passive surveillance | 3.26 | 2.09 | 5.08 |
| | Tail vs. peak | Found by active surveillance | 5.49 | 3.01 | 10.00 |
| | | Found by passive surveillance | 2.98 | 1.51 | 5.86 |

[a] See Table 7 for definition of early and late.
[b] An OR of 0.09 indicates that, when cattle were the species suspected of disease, the odds of an FMD case being laboratory-positive were 0.09 times as high when cases were detected by active surveillance, as compared to cases detected by passive surveillance.

the epidemic. This relationship was stronger for cases detected by active surveillance than passive surveillance.

## 4. Discussion

To identify factors associated with whether or not a report of suspected disease resulted in the declaration of FMD, we performed a logistic regression analysis. Given the importance of the variable representing species suspected in this analysis, we included it in the final model despite the fact that we could only use 2635 out of 6801 observations. However, as the interpretation of the results did not change significantly when this variable was omitted, we believe that the information gained from this model may be applied to the population of report cases during the 2001 outbreak in the UK.

Suspect premises were more likely to be declared clinical cases if they were in close proximity to other declared FMD cases. This may be because they were more likely to receive patrol visits, during which farmers were educated about typical FMD clinical signs. Additionally, stock on these premises were more likely to be exposed to FMD, as the nearby infected premises had been shedding virus. Thus, suspect cases near other recently identified infected premises were more likely to be truly diseased than suspect cases remote from any other FMD cases.

Suspect cases involving cattle were more likely to be declared cases of FMD than suspect cases involving sheep because the clinical diagnosis of FMD is easier in cattle than sheep. For this reason, clinical cases involving cattle were also more likely to be truly infected (i.e. laboratory-positive) than those involving sheep. The severity of the clinical

symptoms of FMD varies between species. During an epidemic, the clinical signs in cattle and pigs are usually sufficiently pathognomonic to allow clinical diagnosis of disease (Kitching, 2002; Davies, 2002a). However, the clinical expression of disease is often much milder in sheep and goats, and diagnosis based solely on clinical signs may be difficult (Barnett and Cox, 1999; Kitching and Hughes, 2002; Davies, 2002b).

It is more difficult to clinically distinguish FMD from other disease conditions when the suspect case is chronic or involves sheep, as the clinical signs are less consistent and characteristic. Compared to passive surveillance, active surveillance was more likely to detect older disease (McLaws et al., in press), and also disease in sheep. Thus, it appears that passive surveillance usually detected the more obvious cases of disease, whereas active surveillance 'mopped-up' the more difficult cases.

Premises on which suspect disease was reported by active surveillance were more likely to be declared FMD cases than premises on which the suspicion originated from passive surveillance. This may have been because the diagnostic process differed slightly depending on how the disease control authorities became aware of the suspect case. For passive surveillance, the veterinarian from the local centre was obliged to file a telephone report with the national disease control centre, regardless of his level of suspicion. For active surveillance however, a telephone report was only filed if a veterinarian from the local centre, specifically trained to recognize FMD, was suspicious of disease.

Although suspect cases detected by active surveillance were more likely to be declared clinical cases than suspect cases found by passive surveillance, they were less likely to be subsequently verified as infected by the laboratory. This may be because the cases detected by active surveillance were more difficult to diagnose clinically. Alternatively, there may have been a bias at the national disease emergency control centre to declare as FMD reports that originated from government veterinarians, compared to reports generated from other sources.

Like those detected by active surveillance, suspect cases reported during the peak of the epidemic were more likely to be declared clinical cases compared to reports filed at other times, but less likely to be laboratory-positive. During the peak of the epidemic, reports of suspect disease may have been more likely to be declared clinical cases due to heightened pressure to control the disease. Our findings suggest that additional caution should be applied when considering reports of suspect disease generated by active surveillance, and/or during times of enhanced pressure to control disease.

Both the odds of a suspect case becoming a clinical case, and the odds of a clinical case being laboratory-positive, varied significantly between the local disease control centres. Some of these differences probably resulted from particular characteristics of the local areas; there was regional variation in livestock demographics, husbandry systems, and the burden of disease. Additionally, a bias towards or against certain centres may have existed in the clinical diagnostic process at the national disease control centre. Our findings may also reflect the variable management practices and availability of resources at different centres. The organisational structure of each centre was determined locally. Therefore, some centres may have functioned more effectively, and established better communication with the national disease control centre and/or with the public. This is worthy of further investigation, as the efficiency and accuracy of the diagnostic process may be improved by the identification of the most effective management practices at the local control centre level.

Hugh-Jones (1976) described the reporting of suspect disease during the 1967–1968 FMD epidemic in the UK. While this epidemic was similar in size (2364 infected premises) to the 2001 epidemic, a much greater proportion (95%) of the outbreaks involved cattle and/or pigs. The 1967–1968 outbreak was also more localised, affecting a much smaller geographical area (Anderson, 2002).

In both 1967–1968 and 2001, private veterinarians detected outbreaks more frequently at the beginning of the epidemic. In 1967–1968, they also reported more often as the epidemic waned, which did not occur in 2001. Overall, private veterinary surgeons played a much larger role in the 1967–1968 outbreak, in which they detected 21% of cases in cattle and pigs (Hugh-Jones, 1976). The diminished role of the private veterinarians in 2001 might be a reflection of their generally reduced presence on farms compared to 1967–1968 (Anderson, 2002; Royal Society of London, 2002). Active surveillance played a larger role in the 2001 epidemic than in 1967–1968, when only 4% of outbreaks were reported by patrols (Hugh-Jones, 1976). Perhaps this was due to the importance of subtle disease in sheep during the 2001 epidemic; alternatively, patrols and other government veterinarians might have partially filled the role played by the private veterinarian in 1967–1968.

In 1967–1968, the number of negative reports received by each local disease control centre rose to a plateau by approximately 7 days from the first report and remained at this level until the epidemic died in that area (Hugh-Jones, 1976). We plotted the number of negative report cases per day and the epidemic curve by centre for this epidemic and found that negative reports mirrored the epidemic curve for most centres (not shown), as it did overall. The plateau of negative report cases described by Hugh-Jones was not observed in any of the centres in 2001. The reasons for this difference are not apparent, but might be related to the greater role played by sheep in the 2001 epidemic and the ambiguity of clinical signs in that species.

Although we recognise that each FMD epidemic has unique characteristics and inherent problems, we hope that these results may be used to improve the detection of cases in future outbreaks. If resources are limited, guidelines may be developed to prioritise the response to reports of suspect disease. Our findings suggest that reports that describe suspected early disease in cattle should be prioritised, as they are more likely to be truly FMD than other reports, whereas suspect cases involving sheep may be given a lower priority. Such a recommendation is also prudent as cattle shed more virus than sheep, and thus cattle are more likely to contribute to environmental contamination resulting in the infection of new premises (Kitching and Hughes, 2002). The results of our analysis may also be used to guide the clinical diagnosis of disease from a remote location such as a national disease control centre. For example, suspect cases during the peak of the epidemic, or that originate from active surveillance should be approached with caution, as they are likely more difficult cases to diagnose.

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