**ORIGINAL ARTICLE**

**Incidence of Mycobacterial Infections in Cats in Great Britain: Estimate from Feline Tissue Samples Submitted to Diagnostic Laboratories**

D. A. Gunn-Moore, C. Gaunt and D. J. Shaw

Division of Clinical Veterinary Sciences, Royal (Dick) School of Veterinary Studies and the Roslin Institute, The University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian, UK

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**Introduction**

Mycobacterial infections are recognized as a global health concern, in both humans and other animals (Glaziou et al., 2009; Lobue et al., 2010; Shiloh and DiGiuseppe Champion, 2010). One species that is known to be infected by a number of different mycobacteria is the domestic cat. Unfortunately, many aspects of mycobacteriosis in this species remain unknown. While recent studies from Great Britain (GB) have advanced our overall understanding of these infections (reviewed in Gunn-Moore, 2010; Bennett et al., 2011; Gunn-Moore et al.,

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**Keywords:**
feline mycobacterial infection; incidence; tuberculosis

**Correspondence:**
D. A. Gunn-Moore. Division of Clinical Veterinary Sciences, Royal (Dick) School of Veterinary Studies and the Roslin Institute, The University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian, Scotland EH25 9RG, UK.
Tel.: 0131 650 7650; Fax: 0131 650 7652; E-mail: danielle.gunn-moore@ed.ac.uk

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**Summary**

The aim of this study was to estimate the incidence of mycobacterial infections in cats in Great Britain (GB). This was performed using the proxy measure of feline tissue samples submitted to diagnostic laboratories in GB that were found to have histopathological changes typical of mycobacterial infection (‘MYC’). Sixteen primary diagnostic laboratories were asked for information on the number of feline samples submitted in 2009, the number with MYC, the number undergoing Ziehl–Neelsen (ZN) staining and, for comparison, the number diagnosed with lymphoma.

Eight laboratories provided full data for the whole year: 11 782 samples; lymphoma 3.2% (mean, 95% CI: 2.89, 3.5), MYC 1.16% (0.98; 1.37) and ZN-positive 0.31% (0.22; 0.43). Data on 1569 samples from seven laboratories that provided partial data on samples for the whole year revealed similar results, although all changes were more frequent: lymphoma 5.42% (4.35; 6.66), MYC 2.36% (1.66; 3.23) and ZN-positive 0.77% (0.40; 1.33). One laboratory only provided data for part of the year (4.5 months), reporting all three types of histopathology less frequently: 18 232 samples; lymphoma 0.2% (0.18; 0.32), MYC 0.07% (0.04; 0.12) and ZN-positive 0.05% (0.02; 0.09). The reasons for low reporting rates in this high-throughput laboratory are unclear.

In total, 187 samples were reported as having MYC. Five Reference laboratories were also contacted, reporting 174 feline tissue submissions in 2009, with mycobacteria being cultured from 90.

The study shows that MYC are frequently reported in tissue samples from cats in GB, being reported in ~1% of samples, with confirmation as ZN-positive in ~0.3%. Lymphoma is recognized as a common disease in cats, being seen in ~3% of samples in this study. When compared against MYC, lymphoma was reported only twice as frequently. This confirms that far from being rare, clinically significant mycobacterial infections occur commonly in cats in GB.
Incidence of Feline Mycobacteriosis in Britain

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Cats with mycobacterial infections can develop a number of different clinical presentations, including feline tuberculosis, feline leprosy and non-tuberculous mycobacteriosis (Gunn-Moore, 2010; Gunn-Moore et al., 2010). While the majority of cases in GB present with cutaneous lesions (Gunn-Moore et al., 2010), many veterinary surgeons do not recognize these cases as likely to be caused by mycobacterial infection (authors’ personal observations); because of this, many cases may be missed and/or misdiagnosed. This risk of misdiagnosis is exacerbated by the challenging nature of mycobacterial diagnosis. Diagnosis is usually made by finding characteristic histopathological changes in biopsies and identifying morphologically typical acid fast bacteria (AFB) on Ziehl–Neelsen (ZN) staining (Snider, 1971; Kaneene et al., 2002; Kipar et al., 2003; Ginn et al., 2007). However, finding AFB is not definitive for mycobacterial infection, and a negative ZN stain does not rule out mycobacterial infection (many cases have too few bacteria to be identified) (Gunn-Moore et al., 2011b). Confirmation is by specialist culture of fresh tissue (reviewed in Greene and Gunn-Moore, 2012) or molecular testing. Unfortunately, many samples fail to culture, even when typical AFB have been seen, and those that do can take up to 3 months to grow (Smith et al., 2009; Gunn-Moore et al., 2011a,b).

Feline mycobacterial infections are commonly believed to be rare in GB (Gunn-Moore et al., 2010). However, recent studies reported on 339 feline samples that were submitted for mycobacterial culture to the Veterinary Laboratories Agency (VLA), Weybridge, UK, over a four-year period (January 2005–December 2008) (Gunn-Moore et al., 2011a,b). The samples came from cats that had been found to have cutaneous lesions or suspicious masses at exploratory laparotomy, and when formalin-fixed samples were sent to primary diagnostic laboratories, they were found to have histopathology typical of mycobacterial infection, with granulomatous or pyogranulomatous inflammation, consisting of multifocal to coalescent infiltration with large numbers of foamy macrophages containing variable numbers of acid fast bacilli (Snider, 1971; Kaneene et al., 2002; Kipar et al., 2003; Ginn et al., 2007). The veterinary surgeons then took a further sample and submitted it without fixation to the VLA for mycobacterial culture. Given that 339 samples were submitted over four years, this suggests that these infections are not rare.

Determining the current prevalence of feline mycobacteriosis is vital to our understanding of this important group of diseases, for investigating how and why disease patterns may be changing, and in making clinicians aware of how commonly these diseases occur in cats in GB. However, it is not possible to carry out a stratified randomized survey of cats in GB where biopsy samples are taken from all cats, as this could never be performed on apparently healthy animals. Therefore, we used a proxy measure, looking at the incidence of mycobacterial infection in feline tissue samples submitted to veterinary diagnostic laboratories irrespective of the reason for submission. This assumes that in order for a cat to be sampled, it must have a clinically significant mass or lesion from which the biopsy was taken. Therefore, the aim of this study was to provide an estimate of the incidence of mycobacterial infections in cats in GB using this proxy measure.

Materials and Methods

The internet was searched for information on diagnostic laboratories within GB that perform diagnostic histopathology on feline tissue samples. Various websites were used for the search: The Vet Index, Veterinary Business Development Limited, Health Protection Agency, Veterinary Laboratories agency and the websites of the universities within the UK that teach veterinary science; London, Cambridge, Bristol, Liverpool, Edinburgh and Glasgow (Appendix A).

From these sources, the list was divided into Primary Laboratories (laboratories that perform routine histopathology for veterinary surgeons) and Reference Laboratories (specialist mycobacterial reference laboratories). Each laboratory was contacted via telephone, email or both, to establish whether they accepted feline samples and whether or not they performed any of the following diagnostic tests: histopathology, ZN staining, mycobacterial culture and/or mycobacterial PCR diagnostics. Each laboratory that replied ‘yes’ to any of the above was asked to provide information on the number of feline samples that underwent each of the diagnostic tests in the year 2009, how many had pathology typical of mycobacterial infection [as determined by their pathologists and reported as such (pathology as described by Snider, 1971; Kaneene et al., 2002; Kipar et al., 2003; Ginn et al., 2007)], how many contained AFB, and/or how many were cultured or had undergone PCR diagnostics and been positive for mycobacterial infection. The species of mycobacteria identified by culture was also requested. For comparison, each Primary Laboratory was also asked to provide the number of feline histopathology samples that were diagnosed as lymphoma. Data were collected for the year 2009.

Minitab 15 (Minitab Ltd, Coventry, UK) was used to calculate the 95% confidence intervals (CI).
Results

The internet search identified 49 diagnostic laboratories in GB that could potentially accept tissue samples from cats. They were all contacted by telephone and/or email to determine whether this was the case. The calls and emails were made in the autumn/winter of 2010 and spring 2011. The laboratories were asked to supply data for the year of 2009. Twenty-six of the laboratories said that they accepted feline tissue, 21 said that they did not, and no response could be gained from two of the laboratories. Of the 26 that accepted feline samples, 21 (16 Primary and five Reference Laboratories) were able to provide information about the feline samples they received in the year 2009.

Primary laboratories

Sixteen laboratories were able to supply data; of these, eight supplied full data for the entire year, seven supplied partial data on samples for the entire year (see below), and one (Laboratory 16) supplied full data for only part of the year (4.5 months).

The data from the eight laboratories able to provide a full data set for the whole year are shown in Table 1. Of the 11 782 feline samples submitted and assessed, lymphoma was reported in 3.2% of the samples (mean, 95% CI: 2.89, 3.5), changes typical of mycobacterial infection were reported in 1.16% (mean, 95% CI: 0.98, 1.37), and ZN-positive AFB reported in 0.31% (mean, 95% CI: 0.22, 0.43).

Of the seven laboratories that provided partial data on samples for the whole of 2009, two provided the total number of feline histology samples they received, three provided the number of feline histopathology samples for the year (see below), and one (Laboratory 16) supplied full data for only part of the year (4.5 months).

The data from the eight laboratories able to provide a full data set for the whole year are shown in Table 1. Of the 11 782 feline samples submitted and assessed, lymphoma was reported in 3.2% of the samples (mean, 95% CI: 2.89, 3.5), changes typical of mycobacterial infection were reported in 1.16% (mean, 95% CI: 0.98, 1.37), and ZN-positive AFB reported in 0.31% (mean, 95% CI: 0.22, 0.43).

Of the seven laboratories that provided partial data on samples for the whole of 2009, two provided the total number of feline histology samples they received, three provided the number of feline histopathology samples they had seen with changes typical of mycobacterial infection, three provided the number of samples that underwent ZN staining, seven provided the number of samples with ZN-positive AFB, and two provided the number of feline histopathology samples that they had diagnosed as lymphoma. Summary data from these laboratories are also shown in Table 1. The results of these 1569 samples were similar to those for above, but all of the changes were reported more frequently: lymphoma in 5.42% (mean, 95% CI: 4.35, 6.65), changes typical of mycobacterial infection in 2.36% (mean, 95% CI: 1.67, 3.24) and ZN-positive AFB in 0.76% (mean, 95% CI: 0.40, 1.33).

Laboratory 16 could only provide data from January to the middle of May in 2009 (because of time constraints and the volume of data). This laboratory reported all three types of histopathology considerably less frequently than the other Primary Laboratories (Table 1). In these 18 232 samples, lymphoma was recorded in only 0.2% (mean, 95% CI: 0.18, 0.32), changes typical of mycobacterial infection in 0.07% (mean, 95% CI: 0.04, 0.12) and ZN-positive AFB in 0.05% (mean, 95% CI: 0.02, 0.09).

Between the 16 Primary Laboratories, they reported 187 samples with histopathology changes typical of mycobacteriosis. Of these samples, 137 were reported by the laboratories that provided full data for the year, 37 by the laboratories that provided partial data on the samples for the whole year, and 13 were reported by Laboratory 16, which only supplied data for 4.5 months of the year.

Reference laboratories

Of the five laboratories that provided data, two had received no feline samples in 2009. Three provided data on the number of feline samples cultured, the number of these that cultured positively for mycobacterial infection and the species of mycobacteria that was identified (Table 2). Of the 174 samples that were assessed by culture, mycobacteria were grown from 90 (52%). One laboratory provided information relating to PCR diagnostics; however, of the four samples that underwent this test, none were positive for mycobacteria.

Discussion

This is the first study that has tried to estimate the incidence of clinically significant feline mycobacteria infection within a country. As it is not possible to assess all pet cats for signs of infection, we used the proxy measure of the incidence of mycobacterial infection in feline tissue samples submitted to and evaluated by veterinary diagnostic laboratories. The study assessed a large number of samples (31 583) by accessing data from diagnostic histopathology laboratories in GB. In the eight laboratories able to provide a full data set for the whole year, histopathology typical of mycobacterial infection was reported in ~1% of samples, with confirmation of ZN-positive AFB in ~0.3%. The Primary Laboratories reported 187 cases with changes typical of mycobacterial infection, and within the same period, 174 cases were submitted to Reference Laboratories for mycobacterial culture; culture was successful in 90 cases. Given the accepted difficulties in culturing mycobacteria (Smith et al., 2009; Gunn-Moore et al., 2011b), our findings suggest that feline mycobacterial infections are more prevalent in GB than previously thought.

To put the incidence of feline mycobacteriosis into perspective, we compared it against the incidence of lymphoma. Lymphoma is a commonly reported disease in cats and the most common feline malignancy (Gabor et al., 1998; Malik et al., 2003). In 1968, lymphoma had an estimated incidence of 200 cases per 100 000 cats (0.2%) (Dorn, 1967; Dorn et al., 1968; Hardy, 1981). A
<table>
<thead>
<tr>
<th>Laboratories</th>
<th>No. histo samples received</th>
<th>No. histo diagnosed as lymphoma</th>
<th>No. histo typical of mycobacterial infection</th>
<th>No. ZN stained</th>
<th>No. ZN +ve</th>
<th>% LSA</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratories providing full data for the entire year</td>
<td>11,782</td>
<td>377</td>
<td>137</td>
<td>134</td>
<td>37</td>
<td>3.20</td>
<td>2.89, 3.53</td>
<td>1.16</td>
<td>0.98, 1.37</td>
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<tr>
<td>Median</td>
<td>266</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>3.51</td>
<td>2.15–5.32</td>
<td>0–4.35</td>
<td>0–0.58</td>
</tr>
<tr>
<td>Range</td>
<td>23–8480</td>
<td>1–269</td>
<td>0–111</td>
<td>0–93</td>
<td>0–29</td>
<td>2.15–5.32</td>
<td>0–4.35</td>
<td>0–0.58</td>
<td></td>
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<tr>
<td>Laboratories 9–15 providing partial data on samples for the entire year</td>
<td>Total 1569</td>
<td>85</td>
<td>37</td>
<td>29</td>
<td>12</td>
<td>5.42</td>
<td>4.35, 6.66</td>
<td>2.36</td>
<td>1.67, 3.24</td>
</tr>
<tr>
<td>Laboratory 16 – providing data for only part of the year</td>
<td>Total 18,232</td>
<td>44</td>
<td>13</td>
<td>13</td>
<td>9</td>
<td>0.24</td>
<td>0.18, 0.32</td>
<td>0.07</td>
<td>0.04, 0.12</td>
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</table>

*Upper bound.

No., number; histo, histopathology; ZN, Ziehl–Neelsen stain; ZN +ve, positive result, that is, acid fast bacteria (AFB) were identified; LSA, lymphoma; CI, confidence interval.
more recent study from the University of California, Davis, USA, has shown that the incidence of lymphoma appears to be increasing: they reported that feline leukaemia virus (FeLV)-negative lymphoma increased from an average of 18 cats per year in patients from 1984 to 1994 (patient load of 1881 cats in 1993; lymphoma in ~1%) to an average of ~32 cases from 1994 to 2003 (patient load of 2324 in 2003; lymphoma in ~1.5%) (Louwerens et al., 2005). Another study has shown that the incidence of specific types of lymphoma is also increasing, for example, intestinal lymphoma, where 85 cases were entered into the Veterinary Medical Database of the University of Missouri, Columbia between 1964 and 1984, rising to 534 cases between 1985 and 2004 (Rissetto et al., 2011). In the current study, lymphoma was reported in ~3% of the biopsy samples, and this is only twice as frequent as the reported mycobacteriosis. This shows that feline mycobacteriosis is not a rare cause disease in GB.

Of the samples sent for mycobacterial culture in this study, culture was successful in 52%, with Mycobacterium microti (19.5% of the samples) and Mycobacterium bovis (17%) being reported most frequently, followed by Mycobacterium avium (7.5%). The number of samples submitted, the percentage successfully cultured and frequency with which the individual infections were reported were similar to those reported in our previous study in which the VLA received 339 feline tissue samples with histopathology typical of mycobacterial infection over the 4-year period to December 2008. Of those samples, 47% could be cultured, with M. microti being cultured from 19%, M. bovis 15%, M. avium 7% and non-M. avium non-tuberculous mycobacteria 6% (Gunn-Moore et al., 2011a,b).

There are number of significant caveats to this study which mean that the findings must be considered as only an estimate of incidence, not a true finding:

1. Diagnosis of mycobacterial infection is challenging, and while histopathology is useful at establishing the initial diagnosis of a mycobacterial infection and differentiating lesions from other conditions such as other infections or neoplasia, this is not a definitive diagnosis and different pathologist may interpret changes differently (Gunn-Moore et al., 2011b). While finding typical AFB provides additional information, ZN staining is notoriously unreliable for detecting mycobacterial infections, especially when the number of bacteria in the lesions is small, which is often the case with M. microti and M. bovis infections (Mishra et al., 2005; Smith et al., 2009).

2. Samples will not have been received from all potential cases of feline mycobacterial infection that occurred in GB in 2009. This was because a large number of steps have to be taken before a sample was submitted to the primary diagnostic laboratory, and even more before a sample is submitted for specialist culture. These included the following: the lesions have to be large enough for the owner to notice and/or the cat to be sufficiently ill; the owner has to be able to afford to take their cat to a veterinary surgeon; the veterinary surgeon has to send the sample off to a diagnostic laboratory for histopathology; the laboratory has to recommend that the primary clinician collects a second sample and sends it for specialist culture; the cat has to have another lesion suitable for biopsy; and the owner has to be willing to pay for the repeat procedure. Unfortunately, few veterinary surgeons have mycobacterial infections on their differential diagnosis list when they collect the primary sample, so it is only when the Primary Laboratory reports their findings that the veterinary surgeon knows they need a fresh sample for culture. Ideally, when a veterinary surgeon takes a biopsy from a suspicious lesion or an enlarged lymph node, they would section it and send one sample for histopathology and store the second sample in the freezer pending the histopathology result.

3. The data can at best be considered a subset of the total data for the laboratories in GB as there were difficulties in retrieving data from some of the laboratories in this study. Only 21 of the 26 laboratories that accepted feline samples supplied data. Owing to lack of manpower, time, funds or to the limited search capability of their

### Table 2. Data from the five mycobacterial reference laboratories for 2009

<table>
<thead>
<tr>
<th>No. samples</th>
<th>No. PCR +ve</th>
<th>No. samples cultured</th>
<th>No. culture +ve and species</th>
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<tbody>
<tr>
<td>underwent PCR</td>
<td>PCR</td>
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<tr>
<td>Total</td>
<td>4</td>
<td>0</td>
<td>174</td>
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No., number; PCR, polymerase chain reaction; +ve, positive result.
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Acknowledgements

We would like to thank all of the participating diagnostic laboratories for sharing their data, particularly Dr. Alex Schock of the VLA. We would also like to thank Chris Palgrave and Aileen Brown for their advice on identifying the diagnostic laboratories.

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**Appendix A: Laboratory contact details**


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