FOOD/FARMED ANIMALS

Case of TB in a sheep caused by *Mycobacterium bovis* with transmission to another sheep and a steer in the same building

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SUMMARY
An adult sheep housed indoors developed chronic respiratory tract infection that was unresponsive to treatment and resulted in euthanasia. Granulomas were found in multiple organs and lymph nodes, which contained acid-fast bacilli identified in Ziehl-Neelsen stains, and *Mycobacterium bovis* was cultured from tissues, confirming tuberculosis. Tuberculin skin testing of other animals in the building subsequently identified another sheep as infected, which had been housed with the index case for 46 months, although no visible lesions were seen postmortem. A steer that shared common air space with the sheep in the same building was also identified as test reactor and *M. bovis* was cultured from the retropharyngeal lymph node. Strain typing of the isolates from the index case and the steer revealed the same genotype, suggestive of transmission from sheep to steer. This is the first documented episode of *M. bovis* transmission from sheep to cattle.

BACKGROUND
Bovine tuberculosis (bTB), caused by *Mycobacterium bovis*, is a zoonotic disease of considerable economic importance in Great Britain. In 2018, more than 40,000 cattle were slaughtered as test reactors or direct contact animals.1 By contrast, sheep are rarely affected, and usually only single cases or cases from single flocks are reported.2-10 Sheep are considered spillover hosts, which become infected when the challenge level is relatively high but do not maintain the infection in the absence of continuing acquisition from maintenance hosts.11 The risk of TB spreading from sheep to cattle has been reported in the past12 and highlighted again more recently where sheep shared farms and pastures with cattle with bTB, resulting in outbreaks in several flocks in Spain, which—unless tested—may represent a potential risk to other susceptible species.6 However, to the authors’ knowledge, there have not been any documented reports of *M. bovis* transmission from sheep back to cattle. Here we describe a clinical case of TB in a sheep that subsequently infected another sheep and a steer that was housed in the same building as part of a research project unrelated to bTB.

CASE PRESENTATION
Animal movement and housing
Female cheviot sheep N376 (index case) generated by embryo transfer was born on 28 April 2006 in a classical scrapie-free closed flock maintained under strict biosecurity and tested regularly for specific sheep diseases.13 The flock was in a region of England not known to be endemic for bTB. The sheep was moved to a farm in Warwickshire (a county in the Edge Area of England with an intermediate incidence of the disease) on 10 September 2008 as part of an environmental study and was transported to APHA Weybridge on 21 May 2012. During the 44 months in Warwickshire, it was kept on pasture with up to 81 other sheep throughout the year and only housed when the ground conditions were poor. Sheep did not have contact with cattle. In July 2010, three cattle had bTB diagnosed (three skin test reactors, two with confirmed growth of *M. bovis*) following a period of grazing on these pastures, which was only known retrospectively. At Weybridge, it was housed in a pen with another sheep from the same flock (N524) for a research project unrelated to bTB in buildings also occupied by other species (sheep, pigs and cattle) in different pens. These building companions had no history of clinical signs associated with bTB, did not originate from farms with a history of bTB, and the majority were on short-term experiments that were terminated more than 21 months before the index case was euthanased. Of particular interest is the last building that the animal occupied for 2 years before its death, which also housed cattle and sheep (see figure 1 for an overview of the building). This building was subject to specific biosecurity procedures: sheep pens were entered from side entrances with individual protective equipment (boots and overalls) for each pen, whereas the cattle pens were entered from the main entrance with boots and overalls dedicated to cattle pens. Foot dips for entering and exiting pens contained 2 per cent hypochlorite solution, which was renewed every 5 days or more frequently if too contaminated with organic matter. Each pen had its own tools for cleaning (shovels and scrapers), and manure was removed through a hatch at the rear of each pen, which was then taken to a dung heap by staff entering from a different entrance. Rodent pest control was carried out regularly.

Clinical history
Loss of body condition was noticed in N376, 13 months after arrival at APHA Weybridge, which was attributed to teeth abnormalities of this sheep. However, it was treated 14 days later for suspected pneumonia (abdominal breathing, harsh lung sounds on auscultation, rectal temperature of 39.3°C and occasional coughing) with 5 mg/kg enrofloxacin (Baytril, Bayer) subcutaneously, 15 mg/kg long-acting amoxicillin (Amoxypen LA, MSD) intramuscularly

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and 0.5 mg/kg meloxicam (Metacam, Boehringer Ingelheim) subcutaneously. A 4-day course of 6.6 mg/kg gentamicin (Genta-Equine, Dechra) intramuscularly was then given instead of enrofloxacin, accompanied by a single injection of 0.06 mg/ml dexamethasone (Dexadreson, MSD) intramuscularly, because the sheep continued to display tachypnoea, and the daily rectal temperature ranged from 39.4°C to 40.1°C. Breathing and lung sounds improved eventually 15 days after the first treatment, and the sheep remained clinically unremarkable. Concerns were raised again 42 months after arrival at APHA Weybridge because of gradual loss of body condition and weight, evident tachypnoea (see online supplemental file 1) and frequent coughing. Rectal temperature was 39.5°C, and lung sounds were harsh with wheezes on auscultation. Treatment 1) and frequent coughing. Rectal temperature was 39.5°C, and lung sounds were harsh with wheezes on auscultation. Treatment

Due to deteriorating appetite a clinical examination was carried out at 46.5 months after arrival at APHA Weybridge because of gradual loss of body condition and weight, evident tachypnoea (see online supplemental file 1) and frequent coughing. Rectal temperature was 39.5°C, and lung sounds were harsh with wheezes on auscultation. Treatment

Examination of the eyes with a retinal lens revealed pale green spots in the tapetal fundus (single: left, multiple: right). Raising the hindquarters with the head held low (wheelbarrow test) did not elicit any nasal discharge. The superficial lymph nodes were normal to palpation.

INVESTIGATIONS

Results from haematology and blood biochemistry, carried out at APHA Shrewsbury, are shown in table 1. The key finding was hyperglobulinaemia, suggestive of chronic infection despite normal white blood cell count.

DIFFERENTIAL DIAGNOSIS

The clinical signs were suggestive of a chronic condition affecting the respiratory system, such as pulmonary adenomatosis, chronic suppurative pneumonia, maedi or a malignant tumour with metastases in the lungs. Caseous lymphadenitis was considered as a cause of chronic weight loss and because of past occurrence in the sheep flock, but ELISA performed by SAC Consulting Veterinary Services, Penicuik, was negative for *Corynebacterium pseudotuberculosis* antibodies. No parasitological examination was undertaken because the sheep had been housed indoors for several years.

TREATMENT

Due to the poor prognosis, the sheep was euthanased with 40 mg/kg quinalbarbitone and 2.5 mg/kg cinchocaine (Somulose, Dechra) and a postmortem examination performed.

OUTCOME AND FOLLOW-UP

Main gross abnormalities were found in cardiopulmonary, digestive, lymphoreticular and urinary systems. Inadvertently, the eyes were not collected during the postmortem examination.

The thoracic surface of the diaphragm was lined by multiple white nodules from 1 to 10 mm in diameter. There were large fibrous adhesions between the left cranial lung lobe and the parietal pleura, with mineralisation of the connective tissue. The left cranial lung lobe presented a cystic structure of approximately 10 cm in diameter containing a greenish pasty substance. Multiple white nodules similar to those described previously, with hard consistency and gritty to the cut, were identified on the pulmonary pleura (see figure 3) and throughout the pulmonary parenchyma. Areas of atelectasis and emphysema, with mild to moderate congestion and oedema, were observed microscopically. Multifocally, there were several granulomas, from areas with a few small size granulomas, capsulated, with several giant cells, epithelioid cell, lymphocytes and macrophages, to big areas of coalescent granulomas that also had necrotic centres and calcification.
 Approximately 5 mm in diameter were found on the serosa of the ileum, infiltrate was observed. Connective tissue, and, diffusely, mild lymphocytic inflammatory infiltrate. In the myocardium, there were three small granulomas, composed mainly by macrophages, giant cells and inflammatory infiltrate of neutrophils and lymphocytes, vacuolar degeneration and necrosis of hepatocytes and one non-capsulated granuloma, composed by lymphocytes, and a few neutrophils, surrounding foamy macrophages and epithelioid cells.

Most of the lymph nodes examined, including those of the head and the thoracic and abdominal cavity, were enlarged and firm, with cartilage-like or bone-like texture. The cut surface showed the presence of gritty sandy material and, in a few cases in the thoracic cavity, a creamy yellow to green material. A single hard white nodule of around 1–2 mm in diameter was found in one kidney. These changes were identified as granulomas similar to the ones found in the lungs. The findings of granulomatous inflammation in most of the organs (granulomatous pleuropneumonia, lymphadenitis, focal myocarditis and mild hepatitis with leucocytosis) were suspicious of tuberculosis (TB). Acid-fast bacilli were identified by Ziehl-Neelsen stains of sections of the lung, kidney, parietal pleura, medial retropharyngeal and mesenteric lymph nodes with and without formic acid treatment (figure 4). A mix of liver, kidney and mesenteric lymph node was prepared for culture and molecular typing. Approximately 20 g of tissue was ground in a stomacher, decontaminated with oxalic acid, centrifuged and the pellet resuspended in sterile phosphate-buffered saline (PBS) and molecular typing. Approximately 20 g of tissue was ground in a stomacher, decontaminated with oxalic acid, centrifuged and the pellet resuspended in sterile phosphate-buffered saline (PBS) and molecular typing. Approximately 20 g of tissue was ground in a stomacher, decontaminated with oxalic acid, centrifuged and the pellet resuspended in sterile phosphate-buffered saline (PBS) and molecular typing. Approximately 20 g of tissue was ground in a stomacher, decontaminated with oxalic acid, centrifuged and the pellet resuspended in sterile phosphate-buffered saline (PBS) and molecular typing.

Molecular typing of the positive, heat-killed strain 15 identified (VNTR) typing to characterise the M. bovis strain. 15, 16 identified the isolate as genotype 17:a (spoligotype 17 (SB0263), VNTR type 7-5-5-5*−3–3.1)).

Movement restrictions were imposed and single intradermal comparative cervical tuberculin (SICCT) testing 17 was carried out in all animals housed in the same building 5 months after euthanasia of the index case. The TB incident occurred in pen 6, which housed the other sheep N524 and another sheep introduced as companion replacement for TB case N376. Pen 7, adjacent to pen

Some areas in the left ventricle wall of the heart were discoloured and the thickness of the ventricular wall was 1:0:1:5. The surface of the heart valves was slightly rough. Histopathologically, there was mild pericardial oedema with mild lymphocytic inflammatory infiltrate. In the myocardium, there were three small granulomas, composed mainly by macrophages, giant cells and lymphocytes, with a few neutrophils, surrounded by a capsule of connective tissue, and, diffusely, mild lymphocytic inflammatory infiltrate was observed.

Multiple round to oval, white, nodular structures of approximately 5 mm in diameter were found on the serosa of the ileum, which were well demarcated and of hard consistency and gritty to the section, containing mineralised/calcified material. The liver was enlarged, with round edges, rough surface and a slightly yellow appearance, surrounded by fibrotic tissue. At the cut surface, they were yellow with gritty consistency.

There were numerous nodular structures similar to the ones described earlier, with a multifocal distribution throughout the organs, and in sizes ranging from 2 mm in diameter to several centimeters and with the presence of coalescent lesions. On histopathology, there were distension of the hepatic sinusoids by a mild inflammatory infiltrate of neutrophils and lymphocytes, vacuolar degeneration and necrosis of hepatocytes and one non-capsulated granuloma, composed by lymphocytes, and a few neutrophils, surrounding foamy macrophages and epithelioid cells.

### Table 1 Haematology and blood biochemistry values for the index case 2 weeks before cull

| Test                           | N376  | Reference range | Units |
|-------------------------------|-------|-----------------|-------|
| Haemoglobin                   | 10.0  | 9–15            | g/dl  |
| MCH                           | 8–12  | 13.4            | pg    |
| MCHC                          | 28.7  | 31–34           | g/dl  |
| MCV                           | 28–40 | 46.7            | fl    |
| PCV                           | 0.35  | 0.25–0.45       | U/l   |
| RBC                           | 7.5   | 9–15            | x 10^11/l |
| WBC                           | 11.7  | 4–12            | x 10^11/l |
| Neutrophils                   | 6.4 (55%) | 0.7–6.0 | x 10^9/l |
| Band neutrophils              | Rare  | 0               | x 10^9/l |
| Lymphocytes                   | 4.9 (42%) | 2–9      | x 10^9/l |
| Eosinophils                   | 0.2 (2%) | 0–1      | x 10^9/l |
| Monocytes                     | 0.1 (1%) | 0–0.8    | x 10^9/l |
| Basophils                     | 0 (0%) | 0–0.3         | x 10^9/l |
| Glutathione peroxidase        | 301.1 | >50            | U/ml RBCs |
| Albumin                       | 17.7  | 24–34           | g/l   |
| Alkaline phosphatase          | 150   | 70–390          | U/l   |
| Aspartate aminotransferase    | 566   | 100–280         | U/l   |
| Beta-hydroxybutyrate          | 0.38  | 0–1.2           | mmol/l |
| Calcium                       | 2.25  | 2–3             | mmol/l |
| Creatine Kinase               | 438   | 0–200           | U/l   |
| Cobalt (Vitamin B12)          | >2000 | >188           | µmol/l |
| Copper (Plasma)               | 27.8  | 9–19            | µmol/l |
| Creatinine                    | 85    | 44–150          | µmol/l |
| Gamma-glutamyl transpeptidase | 75    | 0–30            | U/l   |
| Glutamate dehydrogenase       | 26    | 0–25            | U/l   |
| Globulin                      | 70.7  | 32–45           | g/l   |
| Glucose                       | 2.27  | 2.7–4.4         | mmol/l |
| Haptoglobin                   | 0.08  | 0–0.4           | g/l   |
| Inorganic phosphate           | 1.89  | 1.0–2.5         | mmol/l |
| Magnesium                     | 0.74  | 0.7–1.3         | mmol/l |
| Total protein                 | 88.4  | 60–79           | g/l   |
| Total bilirubin               | 6.6   | 0–7             | µmol/l |
| Urea                          | 4.22  | 2.6–6.6         | mmol/l |
| Vitamin E (alpha-tocopherol)  | 1.9   | >2.3            | µmol/l |
| Zinc (serum)                  | 6.8   | Marginal <9     | µmol/l |
|                                 |       | deficient <3–6 | µmol/l |
| Manganese (blood)             | 318   | 100–550         | nmol/l |

MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; PCV, packed cell volume; RBC, red blood cell; WBC, white blood cell.
6, housed two sheep and pens 3, 2 and 1 on the other side housed four, four and three steers, respectively (see figure 1). Sheep N524, which had been housed with the index case for 46 months, was identified as test reactor based on the skin test technique described previously,7 with a skin thickness difference of 8.5 cm between the reactions to avian and bovine tuberculin measured 72 hours after injection. The sheep was euthanased (40 mg/kg quinalbarbitone, 2.5 mg/kg cinchocaine, Somulose), together with the companion sheep, which was test-negative. No lesions suggestive of TB were detected on gross examination. One steer (7201) in pen 2 had a skin thickness difference of 2 mm between the avian and bovine tuberculin injection site, which was classified as an inconclusive skin test result. It was subsequently quarantined in another building that was otherwise empty, with a steer (7197) of the same pen as companion. A SICCT retest 77 days later identified this steer as reactor with a skin thickness difference of 6 mm, and it was euthanased with 140 mg/kg pentobarbital (Pentobarbital, Ayrton Saunders). Visible lesions of TB were observed in the left medial retropharyngeal (see figure 5) and left bronchial lymph nodes, from which \( M. bovis \) of a genotype identical to the sheep (genotype 17:a) was cultured. There was no record of TB on the source farm of this steer around the time when this animal was moved to Weybridge.

While the companion steer was culled due to an unrelated disease before further TB tests could be carried out (no visible lesions observed, negative culture on medial retropharyngeal lymph node), all sheep and cattle sharing the accommodation were subjected to a further SICCT test with negative results. In addition, blood samples from the remaining nine cattle in the building tested negative by the Gamma Interferon test (BOVIGAM TB Kit, Thermo Fisher Scientific according to the manufacturer’s instructions)18 so that the restrictions were eventually lifted. All cattle in the pen had been subject to weekly passive behavioural observations19 for 15 minutes late morning as part of a research project where any incidence of coughing was recorded. Retrospective analysis of the coughing frequency in all cattle (7195, 7197 and 7203), which were in contact with the bTB reactor 7191 in this pen during a period of 31 months when the sheep index case moved in the building and the bTB reactor was culled, revealed that coughing was observed quite regularly from 8 months before cull in this steer but not in the companions (see table 2). A timeline of events is displayed in figure 6.

**DISCUSSION**

bTB caused by \( M. bovis \) is an endemic disease of cattle in England and Wales, which continues to spread despite extensive efforts to control or eradicate it. Although all terrestrial mammals, including humans, are susceptible to infection, cattle and other bovine species are considered the primary reservoirs for maintaining the infection (maintenance hosts), whereas other species are considered spill-over hosts, where the infection occurs within the species only as long as there is input from a maintenance host. Sheep were long considered dead-end hosts that did not play any significant role in the transmission to the same or other species. Indeed, sheep had been considered fairly resistant to infection, although there have been various reports of outbreaks in sheep caused by \( M. bovis \).\(^{5-7,10,20,21}\) A study in Spain,\(^6\) which demonstrated bTB in the
The current report describes an unexpected clinical case of TB in a sheep that was permanently housed after arrival at APHA before cull of the TB reactor. Months without recorded coughing were left out except for the last 2 months before cull of the TB reactor.

The disease in this sheep was chronic and slowly progressive, and the main clinical signs were dyspnoea with coughing and weight loss, identical to those described for clinical cases of ovine TB in Spain, although ill-thrift was the only sign reported in an outbreak of bTB in Lleyn sheep in England. Clinical pathological findings were unspecific despite the widespread pathological changes in multiple organs. Marianelli and others reported a generalised infection in sheep, where no clinical signs were observed, but a systemic infection with dissemination in other organs seems to be rarer in sheep than a respiratory infection affecting lungs and associated lymph nodes. Hyperglobulinaemia was suggestive of a chronic infectious disease, such as pulmonary adenomatosis, which was considered the most likely diagnosis, even though the wheelbarrow test used as clinical marker for this disease was negative. Serum haptoglobin, described as a useful marker for acute bacterial infections in sheep, although its usefulness in chronic infections was not known, was not increased. More advanced diagnostic techniques, such as radiography or ultrasonography, were not available to make a more definite clinical diagnosis.

M. bovis infection was subsequently transmitted to the companion sheep of the index case based on its positive SICCT result. The absence of any gross pathological lesions of bTB in this sheep was relatively surprising, given that both were housed together for over 46 months (since the arrival of the second sheep). This supports the view that sheep are naturally less susceptible than cattle to M. bovis infection, as mentioned before. However, a steer housed in the same building but not in a pen adjacent to the index case became infected and lesions suggestive of bTB were found in the medial retropharyngeal lymph node, which revealed M. bovis in culture and the same genotype as the index case. As different protective clothing was worn for the sheep and cattle pens, different equipment was used and pens were accessed via different entrances, infection was likely acquired air-borne because both animals shared the

### Learning points

- Tuberculosis (TB) should be considered in sheep reared in areas of endemic bovine TB with chronic weight loss and respiratory signs that are unresponsive to treatment.
- Knowledge of previous locations and movement records of this sheep would have helped to include TB in the list of differential diagnoses.
- Transmission of TB between sheep and between sheep and a steer sharing the same air space was demonstrated.
same air space. The infected steer had a habit of standing with his head reaching over the door into the main corridor that connected all pen entrances, which may have increased the probability of infection. Indeed, a study in cattle to investigate cattle-to-cattle transmission of BTB in a building demonstrated that transmission can occur between cattle kept in different pens and without having nose-to-nose contact, either through transfer of contaminated material, which is unlikely in the current case, or through the shared air space.

This report confirmed for the first time that sheep can act as a source of TB in cattle, which has previously only been hypothesised.\textsuperscript{6,8}\textsuperscript{28} The housing of cattle and sheep for a prolonged period in the same building is unlikely to be representative of normal farming practice, but this case nevertheless demonstrates that excretion of viable bacilli and potential contamination of the environment by infected sheep is possible.

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