The Veterinary Journal 271 (2021) 105647

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Invited review

Ovine footrot: A review of current knowledge

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ARTICLE INFO

Keywords:
Aetiology
Diagnostics
Disease control
Epidemiology
Footrot

ABSTRACT

Footrot is a contagious foot disease mainly affecting sheep. It is caused by the Gram-negative anaerobic bacterium *Dichelobacter nodosus*. Warm, wet environmental conditions favour development of footrot, and under perfect conditions, it takes just 2–3 weeks from infection to manifestation of clinical signs. Affected sheep show lameness of various degrees and often graze while resting on their carpi. Local clinical signs vary in severity and extent from interdigital inflammation (benign footrot) to underrunning of the complete horn shoe in advanced stages of virulent footrot. Laboratory diagnosis ideally involves collection of four-foot interdigital swab samples followed by competitive real time PCR, allowing for detection of the presence of *D. nodosus* and differentiation between benign and virulent strains. Laboratory-based diagnostics at the flock level based on risk-based sampling and pooling of interdigital swab samples are recommended. The list of treatment options of individual sheep includes careful removal of the loose undermined horn, local or systemic administration of antimicrobials, systemic administration of non-steroidal anti-inflammatories (NSAIDs) and disinfectant footbathing. Strategies for control at the flock level are manifold and depend on the environmental conditions and the procedures traditionally implemented by the respective country. Generally, measures consist of treatment/culling of infected sheep, vaccination and prevention of reinfection of disease-free flocks. Gaining deeper insight into the beneficial effects of NSAIDs, screening for eco-friendly footbath solutions, developing better vaccines, including the development of a robust, reproducible infection model and elucidation of protective immune responses, as well as the elaboration of effective awareness training programs for sheep farmers, are relevant research gaps.

Introduction

Ovine footrot is a clinically well-defined contagious foot disease of sheep caused by the Gram-negative anaerobic bacterium *Dichelobacter nodosus* (Dewhirst et al., 1990). Besides sheep, other domesticated animals such as cattle, goats and South American camelids, as well as wild ruminants, may harbor *D. nodosus*, but expression of clinical signs is rather rare in these animals. Footrot has been described to occur in sheep-producing countries worldwide (Bennett et al., 2009a). The economic and welfare impact of the disease on sheep farming and affected animals respectively is considerable. The identification of the molecular mechanisms underlying disease pathogenesis, in particular the paramount role of AprV2 in bacterial virulence, was a stepping stone in understanding factors that influence disease outcomes (Kennan et al., 2014). Moreover, it contributed to the diagnosis of virulent strains using real time PCR, which in turn enabled progressive disease control in recent years in different parts of the world (Stauble et al., 2014b). Despite the progress and diverse control strategies that have been developed and implemented in the past, ovine footrot prevalence is still high.

This review describes the current state of knowledge relating to aetiology/bacteriology, virulence/pathogenesis, clinical signs and diagnostics, laboratory diagnostics, epidemiology, economics, treatment and control of ovine footrot.

Aetiology and bacteriology

D. nodosus is the primary aetiological agent of ovine footrot and was first described as *Fusiformis* (*Bacteroides*) *nodosus* (Beveridge, 1941). The species is the only member of the genus *Dichelobacter* which together with *Cardiobacterium* and *Suttonella* belongs to the family *Cardiobacteriaceae* (Dewhirst et al., 1990). *D. nodosus* is a Gram-negative bacterium that forms straight or slightly curved rods which are 1–1.7 μm wide and 3–6 μm long with rounded

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http://dx.doi.org/10.1016/j.tvjl.2021.105647

ends (Dewhirst et al., 1990). Cells exhibit limited motility leading to spreading of colonies on solid media (revealing a 'fuzzy' appearance). The species is anaerobic but aerotolerant and therefore resists a certain level of oxygen exposure.

It is assumed that *D. nodosus* can only successfully infect interdigital skin in combination with physical injury, poor claw hygiene, moist environmental conditions or infection with other microorganisms (Thomas, 1962[2]). Typical lesions of footrot contain bacterial members of various other genera such as *Fusobacterium necrophorum* and different *Treponema* species besides *D. nodosus* (Frosth et al., 2015; Maboni et al., 2017; Gelasakis et al., 2019). Currently, only *F. necrophorum* has been convincingly shown to contribute to the clinical outcome, however it acts as a secondary invader and not as driver of the infection, even though its role as an initiator of infection with *D. nodosus*, or a synergistic action of both, has been suggested (Winter, 2008; Bennett et al., 2009a; Clifton and Green, 2016; Witcomb et al., 2014).

Microbiome studies indicate that the amount and composition of the bacterial population undergoes some dynamic changes depending on the clinical state (Calvo-Bado et al., 2011b; Maboni et al., 2017; McPherson et al., 2019). Numbers of virulent *D. nodosus* are highest in feet with interdigital dermatitis at a very early stage of clinical disease and decrease afterwards, probably as a result of subsequent mixed infections (Stauble et al., 2014a; Witcomb et al., 2014, 2015; Maboni et al., 2016).

The genome of *D. nodosus* is relatively small with 1.4 MB and has a GC content of 44.4% (Myers et al., 2007). Genome sequences derived from 103 globally distributed isolates revealed that they were highly conserved with >95% sequence identity (Kennan et al., 2014). This study further indicated that the species forms two distinct clades, showing a bimodal population structure which is globally conserved and correlates with benign and virulent phenotypes and genotypes. Despite a rather conserved genome, *D. nodosus* is naturally transformable allowing horizontal gene transfer (HGT; Kennan et al., 1998, 2001). Phage-like structures have also been detected phenotypically as well as genetically in *D. nodosus* and these are likely to mediate transduction (Gradin et al., 1991; Myers et al., 2007; Cheetham et al., 2008). Moreover, genomic islands known as mobile genetic elements are part of the *D. nodosus* genome (Rood, 2002).

Virulence and pathogenesis

Severity of the disease depends on the virulence of the strain, environmental conditions (temperature, moisture) and host factors (Graham and Egerton, 1968; Bishop, 2015; Mucha et al., 2015). Since the genome of *D. nodosus* is rather stable and conserved, genes including those encoding virulence traits do not appear to be transferred between strains. Moreover, many scientific efforts to find and define virulence traits in *D. nodosus* have been rather cumbersome and inconclusive mainly due to the absence of appropriate genetic tools for *D. nodosus* (Billington et al., 1996; Kennan et al., 2011). The 'virulence-related locus' (*vrl*) was suggested to contain genes encoding virulence traits, since it was initially assumed to be correlated with virulence, but later shown to just represent remnants of a prophage (Katz et al., 1991; Haring et al., 1995; Billington et al., 1999). Similarly, genomic islands harbouring the virulence associated protein (*vap*) regions did not reveal coding sequences of any pathogenicity-related function (Katz et al., 1991; Kennan et al., 2014). One of the integrase genes flanking the *vap* regions, the *intA* gene, was found to be correlated with virulence in some studies, but not confirmed in others (Cheetham et al., 2006; Dhungyel et al., 2013b; Kennan et al., 2014).

According to the current state of knowledge, virulence of *D. nodosus* is only determined by extracellular proteases and type IV fimbriae. Type IV fimbriae encoded by *fimA* confer adhesion to host cells and also produce a flagella-independent motility referred to as twitching motility (Han et al., 2008). Furthermore, proteases are secreted by a type II-related secretion process that directly involves components of the type IV fimbriae secretion machinery (Han et al., 2007). Finally, these fimbriae are the basis for serotyping and the classification of isolates into 10 serogroups named A to I and M (Claxton et al., 1983; Chetwin et al., 1991; Dhungyel et al., 2015, 2002). While it is not difficult to imagine that motility and adhesion are essential for virulence and pathogenesis, however there are no specific serotypes associated with strain virulence even though outbreak-specific serotypes can be found (Kennan et al., 2001; McPherson et al., 2018; Wani et al., 2019).

D. nodosus produces at least three extracellular serine proteases. Virulent strains express two acidic proteases, the heat-stable AprV2 and AprV5, and the basic protease BprV. Benign strains produce corresponding proteases AprB2, AprB5 and BprB. However, a role in virulence has only be shown for AprV2 in the seminal work of Kennan et al. (2010). Further studies showed that presence of the gene for AprV2, but not those for the other two proteases AprV5 and BprV, were associated with flocks having virulent footrot (Stauble et al., 2014b).

Infection dynamics indicate that virulent strains outcompete benign strains at the start of an infection (Stauble et al., 2014a; Kuhnert et al., 2019). This could indicate different strategies of the two virulotypes of *D. nodosus* with the benign strain representing a member of the physiological microbiome of the hoof, while the virulent strains are more aggressive. After progressive control of ovine footrot via elimination of virulent strains through diagnosis of infected animals/flocks and treatment or removal of infected animals, benign strains persist and might replace the niche of the virulent strains (Allworth and Egerton, 2018b; Locher et al., 2018).

Clinical signs and clinical diagnostics

The clinical signs of footrot may vary from mild interdigital dermatitis (benign footrot), underrunning of the heel, to separation of the sole and abaxial wall, resulting in underrunning of the toe including complete separation of the hoof capsule (virulent footrot; Table 1; Figs. 1–6; Egerton et al., 1969; Egerton and Parsonson, 1969; Depiazzi et al., 1998; Abbott and Egerton, 2003). The degree of clinical signs depends, besides the presence/absence of the protease AprV2, on environmental conditions, and on differences in host susceptibility (Graham and Egerton, 1968; Billington et al., 1996; Depiazzi et al., 1998; Zhou and Hickford, 2000). Sheep of all ages and sexes are susceptible to footrot. It usually takes 2–3 weeks from the beginning of infection to the manifestation of the disease (Kuhnert et al., 2019). Virulent footrot is very painful and represents a relevant animal welfare problem (Ley et al., 1994). Affected sheep often stand on three legs and exhibit lameness on ambulation, and sometimes eat while resting on their carpi (Fig. 7).

Individual lame sheep can best be identified by observing or recording the animals walking in a single line, for example in yards or when entering a race, barn or milking parlor. This can be done by observing the sheep's gait and using an appropriate locomotion scoring system. Alternatively, novel digital technologies like sensors, computer-assisted vision techniques, infrared thermography and reaction-force measuring platforms may be used (Gelasakis et al., 2019). In order to classify the severity and extent of the lesions in a standardised procedure, a scoring system for the subjective assessment of footrot was developed (Egerton and

[2] See: Buller N and Eamens G (2014). https://www.agriculture.gov.au/sites/default/files/sitecollectiondocuments/animal/ahl/ANZSDP-Ovine-footrot.pdf (Accessed 18 February 2021).

Table 1
Swiss scoring system for footrot adapted from Stewart and Claxton (1993). The definitions are given in the table and the corresponding clinical findings are shown in the figures. The duration is an approximate indication and depends strongly on the infection pressure and predisposing factors (Strobel et al., 2014).

Score	Clinical findings	Disease duration	Figure
0	Healthy, dry foot		1
1	Moist and inflamed interdigital space with some hair loss		2
2	Extensive skin inflammation, damaged horn in the interdigital space	3–4 days	3
3	Detachment of the axial horn wall, underrunning of the horn towards the sole		4
4	Underrunning (including separation) expands to the outer horn wall (abaxial), pododerma heavily affected	7–14 days	5
5	Removal of the hoof capsule (complete separation), extended pododerma lacerations	>21 days	6

Fig. 1. Healthy, dry foot.

Fig. 2. Humid and inflamed interdigital space with some hair loss.

Fig. 3. Extensive skin inflammation, damaged horn in the interdigital space.

Roberts, 1971). All four feet must be examined. In order to distinguish more clearly between the different stages of the disease progression, alternative scoring systems have later been developed, representing modifications of the original scoring system (Table 1; Stewart and Claxton, 1993; Welsh et al., 1993; Woolaston, 1993; Whittington, 1995; Conington et al., 2008; Kaler et al., 2009; Foddai et al., 2012).

On the basis of the characteristic changes of the hoof horn, the associated behaviour and the typical, distinctive strong foul odour, virulent footrot can be diagnosed with adequate accuracy by trained farm personnel (Kaler and Green, 2008a,b; Phythian et al., 2016).

In advanced stages, the hoof horn in the interdigital and heel area is undermined and loose. In severe cases, the whole hoof horn detaches (Kennan et al., 2011; Winter, 2004a). In rare cases, slow spontaneous healing may eventually occur, which is unacceptable from an animal welfare viewpoint. The hooves may remain deformed or show localized anomalies, such as cracks and discoloration of the horn. Such animals can remain carriers and pose a great risk to the flock, as they can maintain the infection cycle (Winter, 2008).

Likewise, chronically infected carrier animals often do not have modified interdigital skin, because the pathogens are located in horn pockets which are difficult to detect (Bennett et al., 2009a). For this reason, it is difficult or even impossible to diagnose such carrier animals by clinical examination alone, and diagnostic procedures must be extended to include laboratory analysis.

Laboratory diagnostics

Culture and phenotypic identification

D. nodosus is a fastidious, difficult to grow bacterium. Besides anaerobic conditions, specific nutrients have to be provided in

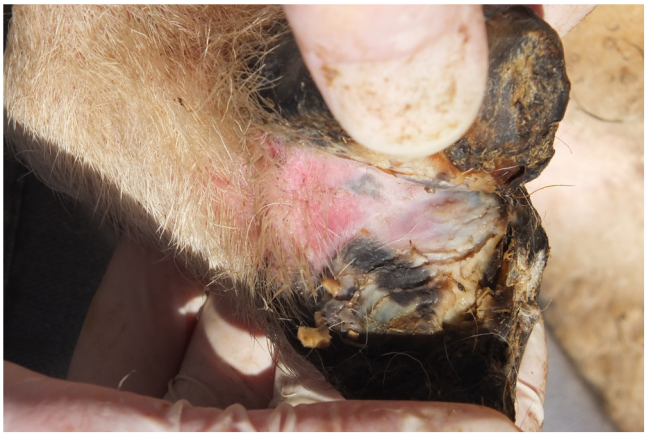

Fig. 4. Detachment of the axial horn wall, underrunning of the horn towards the sole.

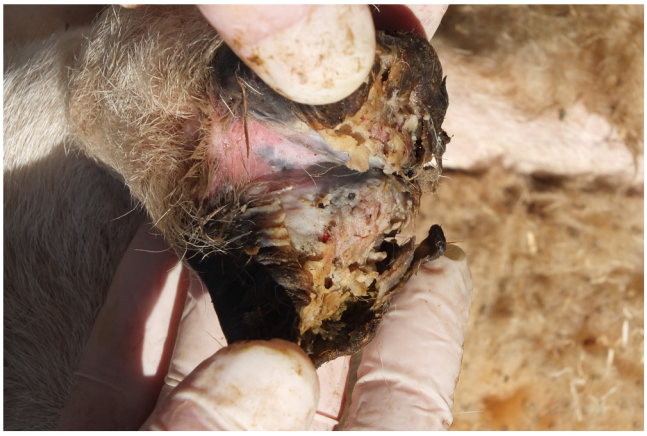

Fig. 5. Underrunning (including separation) expands to the outer horn wall (abaxial), pododerma heavily affected.

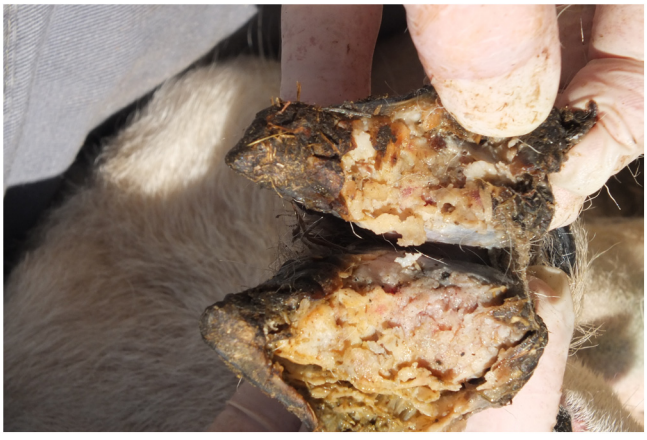

Fig. 6. Removal of the hoof capsule (complete separation), extended pododerma damages.

order to grow the organism. Primary isolation is especially challenging. Agar plates containing hoof powder have proven beneficial for this purpose (Thomas, 1958; Stewart and Claxton, 1993; Locher et al., 2018). The sample is streaked on part of the agar plate and a grid pattern is then made into the agar using a sterile toothpick (Fig. 8, Panel A). Typical colonies grow slightly beyond the grid allowing the operator to pick them for further purification

Fig. 7. A ewe and lamb with typical clinical signs of severe foorot: the ewe is standing on three legs and the lamb is grazing while resting on both carpi.

steps on agar plates using the same procedure as used for primary isolation (Fig. 8, Panel B). Once in pure culture, the organism can be propagated on less complex and commercially available media, such as Brucella agar with 5% sheep blood, hemin and vitamin K1. These cultures can be rapidly identified/confirmed as *D. nodosus* by MALDI-TOF MS (Locher et al., 2018).

Virulent strains can be phenotypically discriminated from benign ones using the gelatine gel thermostability test which differentiates heat-stable and heat-labile extracellular proteases corresponding to AprV2 and AprB2, respectively (Palmer, 1993).

Sampling

The simplest way to sample the interdigital space is by using a cotton swab, either dry or moistened with sterile water. The swabs can then be used directly for template preparation in appropriate lysis buffer (Stauble et al., 2014b), or directly be used for culturing of the pathogen. For culture, a moistened swab and immediate plating on hoof-agar plates at the site of sampling is recommended, which are then placed into anaerobic jars and transported to the laboratory to minimize the time of oxygen exposure (Locher et al., 2018). Alternatively, transport media like Transwab Amies Charcoal (Medical Wire and Equipment) can be used which allow transport to the laboratory where culture and lysate preparation can then be performed. We isolated *D. nodosus* from foot swabs kept in charcoal transport medium for more than a week (unpublished data).

Pooling has been shown to be an easy, efficient and cost-effective way to probe individual sheep and entire flocks (Greber et al., 2018). For this purpose, samples are collected using a single swab, including all four feet. Pools consisting of up to 10 swabs (representing 10 animals) can be used in a single PCR. Three such pools collected on a risk-based manner are recommended for confidently testing at flock level (Greber et al., 2018).

Molecular identification

PCR is the method of choice for rapid and specific molecular diagnosis especially of infections with fastidious bacteria like *D. nodosus*. Several PCRs have been described based on the 16S rRNA gene, *fimA* or *intA* (La Fontaine et al., 1993; Liu and Webber, 1995; Dhungyel et al., 2002; Cheetham et al., 2006; Belloy et al., 2007; Frosth et al., 2012). However, none were able to discriminate between virulent and benign *D. nodosus*. The subsequent

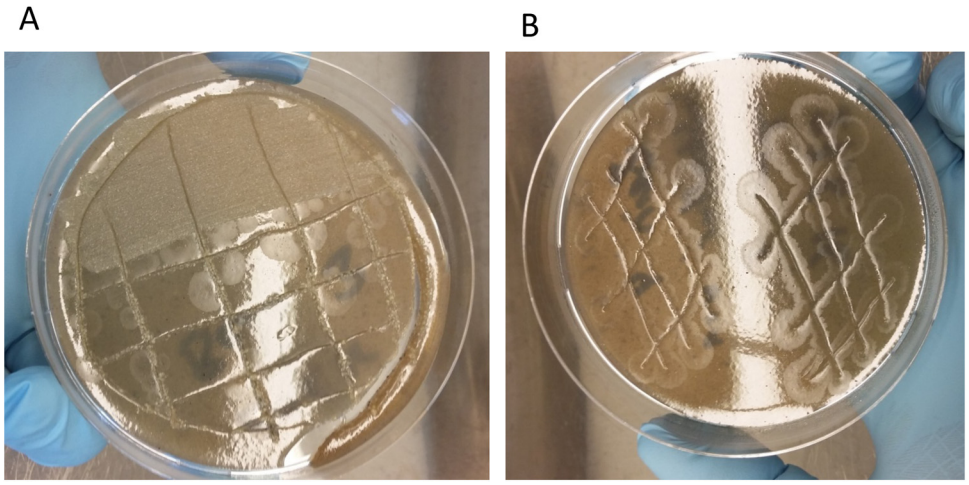

Fig. 8. Primary culture (Panel A) and pure cultures (Panel B) of *Dichelobacter nodosus* on hoof agar plates.

introduction of a competitive real-time PCR enabled discrimination of virulent from benign strains based on the presence of *aprV2* and *aprB2*, respectively (Stauble et al., 2014a). This discrimination of benign and virulent strains is based on a dinucleotide difference at positions 661/662 (TA/GC) resulting in a single amino acid difference (Tyr92Arg) in the mature AprV2 and AprB2 proteins, respectively (Riffkin et al., 1995; Kennan et al., 2010, 2014; Stauble et al., 2014a,b). The same target site was further explored in the development and optimization of LAMP-based assays for isothermal in-field testing (Best et al., 2018b, 2019a,b). Recently, a real-time PCR was developed, allowing differentiation of live and dead virulent *D. nodosus*, to assist the assessment of different disinfection protocols and to monitor sanitation programs (Hidber et al., 2020).

Typing

For epidemiological studies, typing of *D. nodosus* is paramount. Virulotypes can be identified based on the presence of the AprV2 and AprB2 proteins and their genes *aprV2* and *aprB2* in phenotypic and genetic assays, respectively, as described above (Palmer, 1993; Stauble et al., 2014a). Molecular serotyping based on 'surface antigens' now known as type IV pili encoded by *fimA* can be achieved by a multiplex PCR from cultured bacteria (Dhungyel et al., 2002) or directly from foot swabs (Best et al., 2018a), replacing the laborious slide agglutination test (Claxton et al., 1983).

Several molecular typing methods have been described for *D. nodosus* in the past. Restriction fragment length polymorphism (RFLP) based on PCR amplicons of the gene for the major outer membrane protein Omp1 was developed to study field cases of footrot in Nepal (Ghimire and Egerton, 1999). This was followed by classical pulsed-field gel-electrophoresis (PFGE) applied to a large collection of Australian isolates (Buller et al., 2010). These methods were succeeded by typing based on DNA sequence data, which provides globally comparable data that can be readily exchanged. Amplification and sequencing of the Pgr protein encoding genes *pgrA* and *pgrB*, which contain repeat regions, proved useful to discriminate *D. nodosus* strains from different countries (Calvo-Bado et al., 2011a). Multiple locus variable number tandem repeat (VNTR) analysis (MLVA) based on four loci was developed to study the diversity of a global collection of isolates (Russell et al., 2014) and further used to analyze the within flock dynamics of *D. nodosus* (Smith et al., 2017). Finally, a classical multi-locus sequence typing scheme (MLST) based on 7 loci was established and is publicly available at pubMLST.org (Blanchard et al., 2018). All these techniques have certain advantages and disadvantages; however sequence data are generally superior as they can be fully exchanged and compared between laboratories. It is expected that whole genome data will replace the methods above and become the gold standard, and a basis for population analyses and other epidemiological studies (Kennan et al., 2014).

In summary, classical diagnosis by culture and phenotypic virulence assessment including serotyping is time and cost intensive, is not routinely done and is limited to a number of specialized laboratories. Real-time PCR of pooled samples is a cost and time efficient approach for routine diagnosis. Furthermore, it allows analysis of high sample numbers and may detect positive animals/flocks even before manifestation of clinical signs. This strategy, focusing on detection of virulent *D. nodosus*, is currently applied in the Swiss national footrot control program with expected costs of approximately 100 Euro per flock tested. For more research-oriented epidemiological studies, a series of genotyping methods are available with whole genome sequence analysis providing the most compelling information.

Epidemiology and economics

The first reports of ovine footrot date from the end of the eighteenth century (Delafond, 1838) and today the disease is prevalent worldwide. However, investment in footrot research mainly occurs in countries with intensive sheep production and climate conditions that favour footrot. As such, studies on prevalence estimates have been mainly reported from Australia (Dhungyel et al., 2013a; Raadsma and Egerton, 2013), Bhutan (Gurung et al., 2006a), Great Britain (Green and George, 2008; Winter et al., 2015; Winter and Green, 2017), Greece (Gelasakis et al., 2013b, 2015), India (Sreenivasulu et al., 2013; Wani et al., 2015, 2019), Iran (Azizi et al., 2011), New Zealand (Wild et al., 2019), Norway (Gilhuus et al., 2014; Groneng et al., 2015), Sweden (König et al., 2011) and Switzerland (Friedrich et al., 2012; Greber and Steiner, 2013; Locher et al., 2018; Zingg et al., 2017; Ardüser et al., 2019). Although prevalence estimates are manifold, comparisons between countries and studies are difficult, because of different case definitions (clinical footrot vs. presence of *D. nodosus*), designs (e.g. surveys vs. laboratory diagnostics) and study populations (e.g. farms vs. market) used.

Footrot impacts animal health and welfare, and consequently leads to substantial economic losses for the sheep industry. Direct costs are caused by reduced reproduction in ewes (Wassink et al.,

2010b), increased fattening time of lambs (Nieuwhof et al., 2008a; Härdi-Landerer et al., 2017), and reduction in milk yield (Gelasakis et al., 2013b, 2015) and wool quality (Marshall et al., 1991). In addition, treatment, prevention and control represent indirect costs as high as the direct costs (e.g. in UK, where indirect costs accounts for >£10 million of the £24 million annual costs; Nieuwhof and Bishop, 2005) or higher amounts, as for example in Switzerland (Zingg et al., 2017). Intangible costs related to reduced welfare for footrot affected sheep also occur, but are challenging to estimate. In an expert elicitation undertaken in Switzerland, intangible annual costs were estimated at CHF33 million for the Swiss sheep population (Zingg et al., 2017). However, as these costs are caused by consumers perceptions of animal welfare, they are difficult to accurately estimate and are highly dependent on the respective society.

Sheep are the main host affected by footrot with all ages and both sexes being susceptible. There is evidence that some breeds, such as Merinos (a popular breed in Australia and New Zealand for wool production), or brown-headed meat sheep (a Swiss multi-purpose breed), are more susceptible than others; however such findings could not be confirmed by other studies (Emery et al., 1984; Greber and Steiner, 2013; Ardüser et al., 2019; McPherson et al., 2019). For some breeds (such as Swiss White Alpine, Texel or Scottish Blackface) studies successfully identified genetic markers indicating varying resistance towards footrot, yet there is no conclusive quantification of the role of genetics leading to resistance (Skerman and Moorhouse, 1987; Escayg et al., 1997; Nieuwhof et al., 2008b; Ennen et al., 2009; Gelasakis et al., 2013a; Mucha et al., 2015; Niggeler et al., 2017). It is argued that other factors, notably the environment and management, are more important than the genetics of the host that accounts for 15–25% of the resistance (Raadsma and Egerton, 2013; Gelasakis et al., 2019).

The epidemiological relevance of ungulates other than sheep was explored in several countries. Cattle co-grazing with footrot affected sheep in Norway were identified as carriers for the virulent strain of *D. nodosus* for a period of up to 10 months (Knappe-Poindecker et al., 2014). However, in two countrywide studies in Switzerland, where co-grazing of cattle and sheep is rare, only the benign strains were diagnosed in cattle (Alsaaod et al., 2019; Ardüser et al., 2019). *Dichelobacter nodusus* was also detected in cattle in New Zealand, however at a low prevalence and at that time, a distinction between the virulent and benign strain was not performed (Bennett et al., 2009b). Goats can be experimentally infected by *D. nodosus* (Ghimire et al., 1999), and presence of the agent could be detected in flocks with lame goats (Bennett et al., 2009c; Groenevelt et al., 2015). In another study, only the benign strains of *D. nodosus* were found in goats (Ardüser et al., 2019). The role of goats in footrot epidemiology therefore needs some more investigation. Only one study investigated the presence of *D. nodosus* in domesticated South American camelids, identifying a low to moderate prevalence of 1.5% and 7.4% for virulent and benign strains, respectively (Ardüser et al., 2019). Virulent and benign types of *D. nodosus* have also been detected in free-ranging wild ungulates, and virulent types were also associated with severe clinical signs (Belloy et al., 2007; Volmer et al., 2008; Wimmershoff et al., 2015; Moore-Jones et al., 2020). However, in comparative studies on the prevalence of *D. nodosus* in various species, it has been concluded that footrot in wildlife should be irrelevant epidemiologically for ovine footrot (Ardüser et al., 2019; Moore-Jones et al., 2020).

Footrot is a multifactorial disease transmitted to susceptible sheep via an environment that is contaminated by infected sheep (Abbott and Lewis, 2005). *D. nodosus* can persist in wet soil up to 24 days (Cederlöf et al., 2013), whereas low tenacity is found in dry environments (Clifton et al., 2019). Under ideal conditions (i.e. warm and wet), both pastures and stables may stay contaminated for 7–10 days (Whittington, 1995; Green and George, 2008; Azizi et al., 2011), leading to high within-flock prevalences (Friedrich et al., 2012; Greber et al., 2016; Ardüser et al., 2019; Kuhnert et al., 2019). Seasonal dependency of the prevalence was demonstrated in several studies, with lower prevalences during dry seasons (Friedrich et al., 2012; Angell et al., 2018; Ardüser et al., 2019). However, it was pointed out that the seasonality of footrot is not only caused by the climate, but also the production cycle of the ewes (Gelasakis et al., 2019). Iatrogenic transmission of *D. nodosus*, e.g. through trimming knives (Locher et al., 2018), may also play a role in disease spread within flocks. Transmission of footrot between flocks occurs particularly through migration of infected sheep or through contamination of the environment during markets or exhibitions (Green and George, 2008; Grøneng et al., 2014; Locher et al., 2018). Genetic typing of *D. nodosus* revealed the important role of animal migration between countries, for example from Denmark to previously footrot free Norway (Gilhuus et al., 2014; Russell et al., 2014). In Bhutan, farms with a migratory background were found to have an increased odds to be infected (Gurung et al., 2006a).

Long-term immunity within sheep after disease does not exist (Egerton and Roberts, 1971). Healthy sheep carrying virulent *D. nodosus* could be detected in several studies (Stauble et al., 2014a; Locher et al., 2015; Kraft et al., 2020), however in most cases, sheep developed clinical signs at a later stage unless treated. Although the role of healthy carriers in footrot epidemiology is unclear, detection of virulent *D. nodosus* through laboratory diagnostics may detect carrier animals before clinical signs occur, which is important in disease surveillance and control.

Treatment of ovine footrot

Strategies for treatment of footrot in sheep vary between and within different production systems. Depending on the flock size, type of husbandry, management resources or climatic factors, a multifaceted approach to treatment may be required. In general, prompt treatment within 3 days of onset of lameness is highly effective at reducing the prevalence of footrot related lameness (Green et al., 2012; Winter et al., 2015; Green and Clifton, 2018; Prosser et al., 2019).

Foot trimming

Functional foot trimming restores the ideal shape of the hoof and improves the gait of the animal (Gelasakis et al., 2019). If lameness due to footrot is present, careful and minimal foot trimming may be helpful for diagnostic confirmation (Winter, 2008, 2011). A significantly higher prevalence of footrot was observed in flocks when routine foot trimming was performed more than once a year (Wassink et al., 2004; Kaler and Green, 2009). This observation might be the result of increased transmission of *D. nodosus* due to congregation of diseased and sound sheep, or poor foot trimming techniques that increase disease susceptibility or increase disease duration. A positive association between footrot prevalence and foot trimming frequency was found in a longitudinal study (Green et al., 2007). Excessive trimming provoked a delay in healing and recovery because of physical damage to the sensitive dermis of the foot, causing pain and granulomatous proliferations (Kaler et al., 2010b). Grouping sheep for routine claw trimming can enhance the transmission of *D. nodosus* via direct contact of infected feet (Green and George, 2008). It is essential to avoid the transmission of *D. nodosus* at claw trimming by decontaminating trimming equipment after each animal by wiping the blade at least once with a disposable disinfecting towel containing 60% ethanol. When combined with an additional bath in a 4% formaldehyde solution

and a second (mechanical) cleaning with a disinfectant towel a higher reduction of *D. nodosus* was achieved (Locher et al., 2018). It was further recommended that personnel should change disposable gloves after each animal handled, and all horn trimmings must be collected and disposed with household waste (Locher et al., 2018).

Footbathing

The use of footbaths is one of the popular control measures for footrot, although acceptance by sheep farmers is variable (Härdi-Landerer et al., 2019; Wassink et al., 2010a). Footbaths should be constructed in a race, with gates available at both ends, to facilitate keeping animals in the footbath solution for the required time period (Figs. 9 and 10; Gelasakis et al., 2019). However, there is no consistent information available defining minimal or maximal duration and frequency of footbathing (Skerman et al., 1983a,b; Bulgin et al., 1986; Malecki and Coffey, 1987; Parajuli and Goddard, 1989). The duration recommended in the literature is very variable and ranges from merely walking through with only a few seconds of contact with the solution to 1 h of contact time. The footbathing procedure in general consists of removal of mud and manure from the hooves by walking first through a clean water bath. This enables the subsequent bath solution, containing the disinfectant, to penetrate the hoof horn. The solution level in the bath should be at least 6 cm deep, and sheep should stand in the bath for at least 10 min. After bathing, sheep must remain on a firm and clean floor until the hooves are dry (Reed and Alley, 1996; Skerman et al., 1983a). The most commonly used disinfectants for footbaths are solutions of zinc sulphate, formaldehyde or copper sulphate (Winter, 2011; Härdi-Landerer et al., 2019).

Fig. 9. Sheep waiting in a race, with gates at both sides.

Fig. 10. Sheep in a stand-in footbath, filled with 4% formaldehyde.

Repeated daily footbathing in a 15–18% zinc sulphate solution with surfactant combined with prolonged exposure to dry environment eradicated footrot in sheep (Jelinek et al., 2001). In a follow-up study, however, the eradication associated with *D. nodosus* strain A198, which produced deep, covert lesions that facilitated the survival of *D. nodosus*, failed (Jelinek and Depiazzi, 2003). Instead, Greber et al. successfully eliminated virulent strains of *D. nodosus* from 28 sheep flocks using a 10% zinc sulphate disinfectant solution within 6–19 weeks of weekly footbathing, without the use of antibiotics and with minimal culling of animals (Greber et al., 2016). In several other studies, a walk-through footbath filled with zinc sulphate resulted in a reduction in prevalence of clinical footrot but not in complete eradication (Cross and Parker, 1981; Skerman et al., 1983a,b; Bulgin et al., 1986; Parajuli and Goddard, 1989; Allworth and Egerton, 2018a). An alternative method for footrot control is repeated walk-through footbathing in formaldehyde (Winter, 2008). It should ideally be used as a 2–5% solution, but not exceed 5%, as this may cause hoof cracks by hardening the horn when used repeatedly (Härdi-Landerer et al., 2019; Winter, 2004b, 2011). The effect of formaldehyde is reduced by organic material such as mud or faeces and therefore the footbath needs to be changed more often as compared to copper- and zinc sulphate solutions (Winter, 2004b).

Copper sulphate solution as footbath is effective and cheap; its solubility is satisfactory and remains active even in the presence of organic matter (Gelasakis et al., 2019). Reed and Alley (1996) determined the efficacy of a copper based footbath preparation and used it for the progressive eradication of ovine footrot. Copper sulphate should not be disposed in water drains, as it is highly toxic both to sheep and wildlife. In a clinical report, sheep were separated and kept without water for at least 17 h before

undergoing a footrot treatment in a 5% copper sulfate footbath solution. The deprivation of drinking water was the decisive management failure that contributed to the intake of the copper solution resulting in acute poisoning (Ortolani et al., 2004). Formaldehyde is carcinogenic and copper- and zinc sulphate are environmental pollutants. A recent study by Hidber et al. (2020) tested in vitro and ex vivo alternative disinfectants, which are non-carcinogenic, environmentally acceptable and suitable for licensing for future use as footbath solution in a footrot control program. They found one registered commercial biocide (Desintec) containing organic acids and glutaraldehyde was suitable for that purpose.

Antimicrobials

For many years, antimicrobials have been used for effective treatment of footrot. Wassink et al. (2010b) concluded that prompt systemic and topical antibacterial treatment of sheep with footrot reduced prevalence and incidence, and improved health, welfare and productivity. Antibiotics of different classes of active substances have been used in numerous studies that demonstrated clinical cure rates with oxytetracycline (Grogono-Thomas et al., 1994; Rendell and Callinan, 1997; Piriz et al., 2001; Sagliyan et al., 2008; Kaler et al., 2010a; Wassink et al., 2010b; Kaler et al., 2012; Strobel et al., 2014), florfenicol (Strobel and Stauch, 2014), amoxicillin (Duncan et al., 2012), penicillin-streptomycin (Sagliyan et al., 2008), lincomycin and spectinomycin (Venning et al., 1990), enrofloxacin (Kaler et al., 2012), gamithromycin (Forbes et al., 2014; Strobel et al., 2014; Kraft et al., 2020) and erythromycin (Piriz et al., 2001). Tilmicosin has not been recommended for the elimination of footrot in flocks (Angell et al., 2016). Although the use of most of the above-mentioned antibiotics has contributed to successful treatment of footrot, we should not overlook the important point that The World Health Organization has classified certain antimicrobial classes as 'Highest Priority Critically Important Antimicrobials' to ensure that these critically important antimicrobials are used prudently both in human and veterinary medicine.[3] Due to increased political and societal pressure, antibiotic usage should be reduced, especially the use of macrolides (erythromycin, gamithromycin, tilmicosin) and quinolones (enrofloxacin), which should only be applied in justified cases (Green and Clifton, 2018).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are underutilized in sheep. They should immediately be administered if signs of pain are recognised (Lizarraga and Chambers, 2012). However, treatment with the NSAID flunixin meglumine did not change the time to recovery from lameness of sheep with footrot (Kaler et al., 2010a). Nevertheless, one should not be discouraged by the result of this study. With animal welfare aspects in mind, further research on the analgesic effect of NSAIDs in sheep are warranted.

Disease prevention and control

Control interventions against footrot at the farm level include regular footbathing and trimming, antibiotic usage (systemic or topical), culling of chronically infected animals, vaccination, and genetic selection for resistance (Abbott and Lewis, 2005; Bennett and Hickford, 2011). There is no clear distinction between treatment and control of the disease in a flock; therefore, some aspects concerning the use of footbaths have been presented in the section 'treatment of ovine footrot'. To prevent footrot-free farms from acquiring the disease, quarantine and testing of newly purchased animals are essential. This should be accompanied with avoidance of co-mingling with other flocks on pasture or during exhibitions.

The overall aim of control programs is either to limit the incidence and severity of the disease, or the eradication of the disease from the flock. While the former often is the first step for the latter, in regions with ideal climatic conditions for footrot transmission, eradication is challenging (Abbott and Lewis, 2005). In these regions, it needs thorough, well communicated and often labor intensive management programs that focus on different measures, such as on the antibiotic usage in the UK (Grant et al., 2018; Wassink et al., 2010b) or footbathing in Norway or Switzerland (Greber et al., 2016; Vatn et al., 2012). In all programs, culling of chronically infected sheep is considered as essential measure for success (Winter, 2011; Witt and Green, 2018), up to total destocking of infected flocks that was a strategy that was well received by farmers with flocks of less than 500 sheep during the New South Wales footrot eradication program in Australia (Mills et al., 2012).

Another control strategy is genetic selection for resistant individuals within breeds, either based on genotypes (Dukkipati et al., 2006; Bishop and Morris, 2007; Niggeler et al., 2017), or phenotypes by the selection of good hoof quality or indirectly by culling of chronically infected animals (Bennett and Hickford, 2011).

Vaccination to control and eliminate footrot on flock level has a long and successful tradition in Australia (Dhungyel et al., 2014). An essential step was the finding that parallel vaccination against several serogroups of *D. nodosus* lacked the development of cross-immunity between serogroups, and produced immunological competition, and thus unsatisfactory results (Hunt et al., 1994; Raadsma et al., 1994; Schwartzkoff et al., 1993). Therefore, identification of circulating serogroups is key for successful eradication of footrot using vaccination (Abbott and Lewis, 2005; Dhungyel et al., 2015; Lacasta et al., 2015; McPherson et al., 2018; Wani et al., 2019). It has been shown in several countries, such as Australia (Dhungyel et al., 2008, 2013a), Bhutan (Gurung et al., 2006b) and Nepal (Egerton et al., 2002), that elimination of the disease using mono- or bivalent vaccines (i.e. against one or two serogroups, respectively) could be reached within four years. The immunity developed through such vaccines lasts for 12–16 weeks, which is long enough to protect the flock during the season of footrot transmission in the Australian context (Thorley and Egerton, 1981; Stewart et al., 1986). To avoid immunological competition between vaccines, a serial approach of bi- or monovalent vaccines at three-month intervals was shown to be effective in eradication of footrot from flocks with multiple serogroups (Dhungyel et al., 2013a; Dhungyel and Whittington, 2009). Multivalent vaccines are also available (Gelasakis et al., 2019). However, the duration of immunity produced by them is reduced to 10 weeks and vaccination rarely leads to complete elimination of the disease (Abbott and Lewis, 2005). Yet, multivalent vaccines can be used as a supportive control strategy (Ennen et al., 2009; Härdi-Landerer et al., 2012). Side effects are swelling at the vaccination site, particularly with oil type adjuvants and after use of improper injection techniques (Walduck and Opdebeeck, 1996; Härdi-Landerer et al., 2012). Overall, vaccination is highly effective in flocks with few identified serogroups and regions with periods of footrot non-transmission. Attempts to develop a vaccine producing immunity across serogroups have so far been unsuccessful (Myers et al., 2007; Dhungyel et al., 2014), but should be pursued in the future.

[3] See: World Health Organization, Food Safety, Highest Priority Critically Important Antimicrobials https://www.who.int/foodsafety/cia/en/ (Accessed 18 February, 2021).

In summary, it has been shown that several approaches can lead to disease elimination of footrot within flocks (Kraft et al., 2020). In addition to epidemiological success, decisions for or against certain strategies, also depend on other considerations such as avoiding the use of critically important antibiotics (Kraft et al., 2020), the best means of communicating control strategies to farmers and increasing their disease awareness (Wassink et al., 2010a; Best et al., 2020), and cost-effectiveness (Friedrich et al., 2012; Winter and Green, 2017; Zingg et al., 2017).

Conclusions

The fact that footrot was first described more than 180 years ago, and yet it is still endemic in many countries, explains the complexity of the disease and the considerable number of scientific studies on it. Although remarkable progress has been made in the past decade in many areas of footrot research such as laboratory diagnostics or whole flock antimicrobial treatment, there are still ample topics for further study. These include investigations on the beneficial effect of NSAIDs; the screening for effective but still eco-friendly footbath solutions as a preventive as well as a treatment tool; the development of robust and reproducible infection/challenge models for footrot (an ex vivo model would be most desirable); increased in-depth knowledge of the immunological mechanisms involved, to assist the development of more effective multivalent vaccines, and the elaboration of effective awareness training programs for sheep farmers.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Acknowledgements

We would like to thank the Swiss Consulting and Health Service for Small Ruminants (BGK/SSPR) allowing us to use Figs. 1–6, 9 and 10 for this review.

References

Abbott, K.A., Egerton, J.R., 2003. Effect of climatic region on the clinical expression of footrot of lesser clinical severity (intermediate footrot) in sheep. Australian Veterinary Journal 81, 756–762.

Abbott, K.A., Lewis, C.J., 2005. Current approaches to the management of ovine footrot. The Veterinary Journal 169, 28–41.

Allworth, M.B., Egerton, J.R., 2018a. Comparison of footbathing and vaccination to control ovine footrot in an experimentally infected flock. Australian Veterinary Journal 96, 395–399.

Allworth, M.B., Egerton, J.R., 2018b. Relationship between the likelihood of footrot elimination from a flock and the virulence of the strain of *Dichelobacter nodosus* present. Australian Veterinary Journal 96, 400–407.

Alsaaod, M., Locher, I., Jores, J., Grimm, P., Brodard, I., Steiner, A., Kuhnert, P., 2019. Detection of specific *Treponema* species and *Dichelobacter nodosus* from digital dermatitis (Mortellaro's disease) lesions in Swiss cattle. Schweizer Archiv für Tierheilkunde 161, 207–215.

Angell, J.W., Grove-White, D.H., Williams, H.J., Duncan, J.S., 2016. Whole-flock, metaphylactic tilmicosin failed to eliminate contagious ovine digital dermatitis and footrot in sheep: a cluster randomised trial. Veterinary Record 179 308–308.

Angell, J.W., Grove-White, D.H., Duncan, J.S., 2018. Sheep and farm level factors associated with footrot: a longitudinal repeated cross-sectional study of sheep on six farms in the UK. Veterinary Record 182 293–293.

Ardüser, F., Moore-Jones, G., Gobeli Brawand, S., Dürr, S., Steiner, A., Ryser-Degiorgis, M.-P., Zanolari, P., 2019. *Dichelobacter nodosus* in sheep, cattle, goats and South American camelids in Switzerland—assessing prevalence in potential hosts in order to design targeted disease control measures. Preventive Veterinary Medicine 104688.

Azizi, S., Tehrani, A.A., Dalir-Naghadeh, B., Hemmati, M., 2011. The effects of farming system and season on the prevalence of lameness in sheep in northwest Iran. New Zealand Veterinary Journal 59, 311–316.

Belloy, L., Giacometti, M., Boujon, P., Waldvogel, A., 2007. Detection of *Dichelobacter nodosus* in wild ungulates (*Capra ibex ibex* and *Ovis aries musimon*) and domestic sheep suffering from foot rot using a two-step polymerase chain reaction. Journal of Wildlife Diseases 43, 82–88.

Bennett, G.N., Hickford, J.G., 2011. Ovine footrot: new approaches to an old disease. Veterinary Microbiology 148, 1–7.

Bennett, G., Hickford, J., Sedcole, R., Zhou, H., 2009a. *Dichelobacter nodosus*, *Fusobacterium necrophorum* and the epidemiology of footrot. Anaerobe 15, 173–176.

Bennett, G., Hickford, J., Zhou, H., Laporte, J., Gibbs, J., 2009b. Detection of *Fusobacterium necrophorum* and *Dichelobacter nodosus* in lame cattle on dairy farms in New Zealand. Research in Veterinary Science 87, 413–415.

Bennett, G., van Loenen, A., Zhou, H., Sedcole, R., Hickford, J., 2009c. The detection of *Dichelobacter nodosus* and *Fusobacterium necrophorum* from footrot lesions in New Zealand goats. Anaerobe 15 177–177.

Best, N., Gwozdz, J., Suter, R., Rawlin, G., Beddoe, T., 2018a. Direct serogrouping of *Dichelobacter nodosus* from Victorian farms using conventional multiplex polymerase chain reaction. BMC Research Notes 11, 108.

Best, N., Rodoni, B., Rawlin, G., Beddoe, T., 2018b. The development and deployment of a field-based loop mediated isothermal amplification assay for virulent *Dichelobacter nodosus* detection on Australian sheep. PLoS One 13, e0204310.

Best, N., Rawlin, G., Suter, R., Rodoni, B., Beddoe, T., 2019a. Optimization of a loop mediated isothermal amplification (LAMP) assay for in-field detection of *Dichelobacter nodosus* with *aprV2* (VDN LAMP) in Victorian sheep flocks. Frontiers in Veterinary Science 6, 67.

Best, N., Rodoni, B., Rawlin, G., Beddoe, T., 2019b. Evaluation of loop-mediated isothermal amplification (LAMP) assay for detection of *aprV2* positive *Dichelobacter nodosus* in-field by secondary users. BMC Research Notes 12, 534.

Best, N., Menendez, R., Rawlin, G., Suter, R., Rodoni, B., Beddoe, T., 2020. The consequences of stigma for knowledge production: sheep producers' attitudes to footrot diagnostics and control in Australia. Frontiers in Veterinary Science 7, 354.

Beveridge, W.I.B., 1941. Foot-Rot in Sheep: A Transmissible Disease Due to Infection with *Fusiformis nodosus* (n. sp.); Studies on its Cause, Epidemiology, and Control. Council for Scientific and Industrial Research (Australia) Bulletin no. 140.

Billington, S.J., Johnston, J.L., Rood, J.I., 1996. Virulence regions and virulence factors of the ovine footrot pathogen, *Dichelobacter nodosus*. FEMS Microbiology Letters 145, 147–156.

Billington, S.J., Huggins, A.S., Johanesen, P.A., Crellin, P.K., Cheung, J.K., Katz, M.E., Wright, C.L., Haring, V., Rood, J.I., 1999. Complete nucleotide sequence of the 27-kilobase virulence related locus (vrl) of *Dichelobacter nodosus*: evidence for extrachromosomal origin. Infection and Immunity 67, 1277–1286.

Bishop, S.C., 2015. Genetic resistance to infections in sheep. Veterinary Microbiology 181, 2–7.

Bishop, S.C., Morris, C.A., 2007. Genetics of disease resistance in sheep and goats. Small Ruminant Research 70, 48–59.

Blanchard, A.M., Jolley, K.A., Maiden, M.C.J., Coffey, T.J., Maboni, G., Staley, C.E., Bollard, N.J., Warry, A., Emes, R.D., Davies, P.L., et al., 2018. The applied development of a tiered multilocus sequence typing (MLST) scheme for *Dichelobacter nodosus*. Frontiers in Microbiology 9, 551.

Bulgin, M.S., Lincoln, S.D., Lane, V.M., Matlock, M., 1986. Comparison of treatment methods for the control of contagious ovine foot rot. Journal of the American Veterinary Medical Association 189, 194–196.

Buller, N.B., Ashley, P., Palmer, M., Pitman, D., Richards, R.B., Hampson, D.J., 2010. Understanding the molecular epidemiology of the footrot pathogen *Dichelobacter nodosus* to support control and eradication programs. Journal of Clinical Microbiology 48, 877–882.

Calvo-Bado, L.A., Green, L.E., Medley, G.F., Ul-Hassan, A., Grogono-Thomas, R., Buller, N., Kaler, J., Russell, C.L., Kennan, R.M., Rood, J.I., et al., 2011a. Detection and diversity of a putative novel heterogeneous polymorphic proline-glycine repeat (Pgr) protein in the footrot pathogen *Dichelobacter nodosus*. Veterinary Microbiology 147, 358–366.

Calvo-Bado, L.A., Oakley, B.B., Dowd, S.E., Green, L.E., Medley, G.F., Ul-Hassan, A., Bateman, V., Gaze, W., Witcomb, L., Grogono-Thomas, R., et al., 2011b. Ovine pedomics: the first study of the ovine foot 16S rRNA-based microbiome. International Society of Microbial Ecology Journal 5, 1426–1437.

Cederlöf, S.E., Hansen, T., Klaas, I.C., Angen, Ø., 2013. An evaluation of the ability of *Dichelobacter nodosus* to survive in soil. Acta Veterinaria Scandinavica 55 4–4.

Cheetham, B.F., Tanjung, L.R., Sutherland, M., Druitt, J., Green, G., McFarlane, J., Bailey, G.D., Seaman, J.T., Katz, M.E., 2006. Improved diagnosis of virulent ovine footrot using the *intA* gene. Veterinary Microbiology 116, 166–174.

Cheetham, B.F., Parker, D., Bloomfield, G.A., Shaw, B.E., Sutherland, M., Hyman, J.A., Druitt, J., Kennan, R.M., Rood, J.I., Katz, M.E., 2008. Isolation of the bacteriophage DinoHI from *Dichelobacter nodosus* and its interactions with other integrated genetic elements. Open Microbiology Journal 2, 1–9.

Chetwin, D.H., Whitehead, L.C., Thorley, S.E., 1991. The recognition and prevalence of *Bacteroides nodosus* serotype M in Australia and New Zealand. Australian Veterinary Journal 68, 154–155.

Claxton, P.D., Ribeiro, L.A., Egerton, J.R., 1983. Classification of *Bacteroides nodosus* by agglutination tests. Australian Veterinary Journal 60, 331–334.

Clifton, R., Green, L., 2016. Pathogenesis of ovine footrot disease: a complex picture. Veterinary Record 179, 225–227.

Clifton, R., Giebel, K., Liu, N.L.B.H., Purdy, K.J., Green, L.E., 2019. Sites of persistence of *Fusobacterium necrophorum* and *Dichelobacter nodosus*: a paradigm shift in understanding the epidemiology of footrot in sheep. Scientific Reports 9 14429–14429.

Conington, J., Hosie, B., Nieuwhof, G., Bishop, S., Bünger, L., 2008. Breeding for resistance to footrot—the use of hoof lesion scoring to quantify footrot in sheep. Veterinary Research Communications 32, 583–589.
Cross, R.F., Parker, C.F., 1981. Oral administration of zinc sulfate for control of ovine foot rot. Journal of the American Vetereinary Medical Association 178, 704–705.
Delafond, O., 1838. Traité sur la police sanitaire des animaux domestiques. Béchet Jeune.
Depiazzi, L.J., Roberts, W.D., Hawkins, C.D., Palmer, M.A., Pitman, D.R., McQuade, N. C., Jelinek, P.D., Devereaux, D.J., Rippon, R.J., 1998. Severity and persistence of footrot in Merino sheep experimentally infected with a protease thermostable strain of *Dichelobacter nodosus* at five sites. Australian Veterinary Journal 76, 32–38.
Dewhirst, F.E., Paster, B.J., La Fontaine, S., Rood, J.I., 1990. Transfer of *Kingella indologenes* (Snell and Lapage 1976) to the genus *Suttonella* gen. nov. as *Suttonella indologenes* comb. nov.; transfer of *Bacteroides nodosus* (Beveridge 1941) to the genus *Dichelobacter* gen. nov. as *Dichelobacter nodosus* comb. nov.; and assignment of the genera *Cardiobacterium*, *Dichelobacter*, and *Suttonella* to *Cardiobacteriaceae* fam. nov. in the gamma division of *Proteobacteria* on the basis of 16S rRNA sequence comparisons. International Journal of Systematic Bacteriology 40, 426–433.
Dhungyel, O.P., Whittington, R.J., 2009. Modulation of inter-vaccination interval to avoid antigenic competition in multivalent footrot (*Dichelobacter nodosus*) vaccines in sheep. Vaccine 28, 470–473.
Dhungyel, O.P., Whittington, R.J., Egerton, J.R., 2002. Serogroup specific single and multiplex PCR with pre-enrichment culture and immuno-magnetic bead capture for identifying strains of *D. nodosus* in sheep with footrot prior to vaccination. Molecular and Cellular Probes Journal 16, 285–296.
Dhungyel, O.P., Lehmann, D.R., Whittington, R.J., 2008. Pilot trials in Australia on eradication of footrot by flock specific vaccination. Veterinary Microbiology 132, 364–371.
Dhungyel, O., Schiller, N., Eppleston, J., Lehmann, D., Nilon, P., Ewers, A., Whittington, R., 2013a. Outbreak-specific monovalent/bivalent vaccination to control and eradicate virulent ovine footrot. Vaccine 31, 1701–1706.
Dhungyel, O.P., Hill, A.E., Dhand, N.K., Whittington, R.J., 2013b. Comparative study of the commonly used virulence tests for laboratory diagnosis of ovine footrot caused by *Dichelobacter nodosus* in Australia. Veterinary Microbiology 162, 756–760.
Dhungyel, O., Hunter, J., Whittington, R., 2014. Footrot vaccines and vaccination. Vaccine 32, 3139–3146.
Dhungyel, O., Schiller, N., Whittington, R., 2015. Identification and characterization of serogroup M *Dichelobacter nodosus* from sheep with virulent footrot. Veterinary Microbiology 176, 378–381.
Dukkipati, V.S.R., Blair, H.T., Garrick, D.J., Murray, A., 2006. 'Ovar-MHC'—ovine major histocompatibility complex: role in genetic resistance to diseases. New Zealand Veterinary Journal 54, 153–160.
Duncan, J.S., Grove-White, D., Moks, E., Carroll, D., Oultram, J.W., Phythian, C.J., Williams, H.W., 2012. Impact of footrot vaccination and antibiotic therapy on footrot and contagious ovine digital dermatitis. Veterinary Record 170, 462.
Egerton, J.R., Parsonson, I.M., 1969. Benign foot-rot—a specific interdigital dermatitis of sheep associated with infection by less proteolytic strains of *Fusiformis nodosus*. Australian Veterinary Journal 45, 345–349.
Egerton, J.R., Roberts, D.S., 1971. Vaccination against ovine foot-rot. Journal of Comparative Pathology 81, 179–185.
Egerton, J.R., Roberts, D.S., Parsonson, I.M., 1969. The aetiology and pathogenesis of ovine foot-rot. I. A histological study of the bacterial invasion. Journal of Comparative Pathology 79, 207–215.
Egerton, J.R., Dhungyel, O.P., Abbott, K.A., Kristo, C., Ghimire, S.C., Shrestha, H.K., Joshi, H.D., Joshi, B.R., 2002. Eradication of virulent footrot from sheep and goats in an endemic area of Nepal and an evaluation of specific vaccination. Veterinary Record 151, 290–295.
Emery, D.L., Stewart, D.J., Clark, B.L., 1984. The comparative susceptibility of five breeds of sheep to foot-rot. Australian Veterinary Journal 61, 85–88.
Ennen, S., Hamann, H., Distl, O., Hickford, J., Zhou, H., Ganter, M., 2009. A field trial to control ovine footrot via vaccination and genetic markers. Small Ruminant Research 86, 22–25.
Escayg, A.P., Hickford, J.G.H., Bullock, D.W., 1997. Association between alleles of the ovine major histocompatibility complex and resistance to footrot. Research in Veterinary Science 63, 283–287.
Foddai, A., Green, L.E., Mason, S.A., Kaler, J., 2012. Evaluating observer agreement of scoring systems for foot integrity and footrot lesions in sheep. BMC Veterinary Research 8 65–65.
Forbes, A.B., Strobel, H., Stamphoj, I., 2014. Field studies on the elimination of footrot in sheep through whole flock treatments with gamithromycin. Veterinary Record 174, 146.
Friedrich, C., Moors, E., Gauly, M., 2012. Die bedeutung der moderhinke - Eine Umfrage in Deutschland, Österreich und der Schweiz. Züchtungskunde 84, 250–259.
Frosth, S., Slettemeas, J.S., Jorgensen, H.J., Angen, O., Aspan, A., 2012. Development and comparison of a real-time PCR assay for detection of *Dichelobacter nodosus* with culturing and conventional PCR: harmonisation between three laboratories. Acta Veterinaria Scandinavica 54, 6.
Frosth, S., Konig, U., Nyman, A.K., Pringle, M., Aspan, A., 2015. Characterisation of *Dichelobacter nodosus* and detection of *Fusobacterium necrophorum* and *Treponema* spp. in sheep with different clinical manifestations of footrot. Veterinary Microbiology 179, 82–90.
Gelasakis, A.I., Arsenos, G., Hickford, J., Zhou, H., Psifidi, A., Valergakis, G.E., Banos, G., 2013a. Polymorphism of the MHC-DQA2 gene in the Chios dairy sheep population and its association with footrot. Livestock Science 153, 56–59.
Gelasakis, A.I., Oikonomou, G., Bicalho, R.C., Valergakis, G.E., Fthenakis, G.C., Arsenos, G., 2013b. Effect of lameness on milk production in a flock of dairy sheep. Journal of the Hellenic Veterinary Medical Society 64, 123–130.
Gelasakis, A.I., Arsenos, G., Valergakis, G.E., Banos, G., 2015. Association of lameness with milk yield and lactation curves in Chios dairy ewes. Journal of Dairy Research 82, 193–199.
Gelasakis, A.I., Kalogianni, A.I., Bossis, I., 2019. Aetiology, risk factors, diagnosis and control of foot-related lameness in dairy sheep. Animals (Basel) 9.
Ghimire, S.C., Egerton, J.R., 1999. PCR-RFLP of outer membrane proteins gene of *Dichelobacter nodosus*: a new tool in the epidemiology of footrot. Epidemiology and Infection 122, 521–528.
Ghimire, S.C., Egerton, J.R., Dhungyel, O.P., 1999. Transmission of virulent footrot between sheep and goats. Australian Veterinary Journal 77, 450–453.
Gilhuus, M., Kvitle, B., L'Abée-Lund, T.M., Vatn, S., Jørgensen, H.J., 2014. A recently introduced *Dichelobacter nodosus* strain caused an outbreak of footrot in Norway. Acta Veterinaria Scandinavica 56 29–29.
Gradin, J.L., Sonn, A.E., Bearwood, D.E., Schmitz, J.A., Smith, A.W., 1991. Electron microscopic study of *Bacteroides nodosus* pili and associated structures. American Journal of Veterinary Research 52, 206–211.
Graham, N.P., Egerton, J.R., 1968. Pathogenesis of ovine foot-rot: the role of some environmental factors. Australien Veterinary Journal 44, 235–240.
Grant, C., Kaler, J., Ferguson, E., O'Kane, H., Green, L.E., 2018. A comparison of the efficacy of three intervention trial types: postal, group, and one-to-one facilitation, prior management and the impact of message framing and repeat messages on the flock prevalence of lameness in sheep. Preventive Veterinary Medicine 149, 82–91.
Greber, D., Steiner, A., 2013. Die aktuelle Situation der Moderhinke in Schweizer Schafzuchtbetrieben. Forum Kleinwiederkäuer, pp. 6–11.
Greber, D., Bearth, G., Lüchinger, R., Schuepbach-Regula, G., Steiner, A., 2016. Elimination of virulent strains (aprV2) of *Dichelobacter nodosus* from feet of 28 Swiss sheep flocks: a proof of concept study. The Veterinary Journal 216, 25–32.
Greber, D., Locher, I., Kuhnert, P., Butty, M.A., Holdener, K., Frey, J., Schupbach-Regula, G., Steiner, A., 2018. Pooling of interdigital swab samples for PCR detection of virulent *Dichelobacter nodosus*. Journal of Veterinary Diagnostic Investigation 30, 205–210.
Green, L., Clifton, R., 2018. Diagnosing and managing footrot in sheep: an update. In Practice 40, 17–26.
Green, L.E., George, T.R.N., 2008. Assessment of current knowledge of footrot in sheep with particular reference to *Dichelobacter nodosus* and implications for elimination or control strategies for sheep in Great Britain. The Veterinary Journal 175, 173–180.
Green, L.E., Wassink, G.J., Grogono-Thomas, R., Moore, L.J., Medley, G.F., 2007. Looking after the individual to reduce disease in the flock: a binomial mixed effects model investigating the impact of individual sheep management of footrot and interdigital dermatitis in a prospective longitudinal study on one farm. Preventive Veterinary Medicine 78, 172–178.
Green, L., Kaler, J., Wassink, G., King, E., Grogono Thomas, R., 2012. Impact of rapid treatment of sheep lame with footrot on welfare and economics and farmer attitudes to lameness in sheep. Animal Welfare 21, 65–71.
Grøneng, G.M., Green, L.E., Kaler, J., Vatn, S., Hopp, P., 2014. A longitudinal study of the risks for introduction of severe footrot into sheep flocks in the south west of Norway. Preventive Veterinary Medicine 113, 241–248.
Groenevelt, M., Anzuino, K., Langton, D.A., Grogono-Thomas, R., 2015. Association of treponeme species with atypical foot lesions in goats. Veterinary Record 176 626–626.
Grogono-Thomas, R., Wilsmore, A., Simon, A., Izzard, K., 1994. The use of long-acting oxytetracycline for the treatment of ovine footrot. British Veterinary Journal 150, 561–568.
Groneng, G.M., Vatn, S., Kristoffersen, A.B., Nafstad, O., Hopp, P., 2015. The potential spread of severe footrot in Norway if no elimination programme had been initiated: a simulation model. Veterinary Research 46, 10.
Gurung, R., Tshering, P., Dhungyel, O., Egerton, J., 2006a. Distribution and prevalence of footrot in Bhutan. The Veterinary Journal 171, 346–351.
Gurung, R.B., Dhungyel, O.P., Tshering, P., Egerton, J.R., 2006b. The use of an autogenous *Dichelobacter nodosus* vaccine to eliminate clinical signs of virulent footrot in a sheep flock in Bhutan. The Veterinary Journal 172, 356–363.
Han, X., Kennan, R.M., Parker, D., Davies, J.K., Rood, J.I., 2007. Type IV fimbrial biogenesis is required for protease secretion and natural transformation in *Dichelobacter nodosus*. Journal of Bacteriology 189, 5022–5033.
Han, X., Kennan, R.M., Davies, J.K., Reddacliff, L.A., Dhungyel, O.P., Whittington, R.J., Turnbull, L., Whitchurch, C.B., Rood, J.I., 2008. Twitching motility is essential for virulence in *Dichelobacter nodosus*. Journal of Bacteriology 190, 3323–3335.
Härdi-Landerer, M.C., Leu, M., Steiner, A., 2012. Evaluation of an polyvalent footrot vaccine in a field trial. Tierärztliche Praxis Ausgabe G: Grosstiere - Nutztiere 40, 294–300.
Härdi-Landerer, M.C., Grieder, S., Mengelt, R., Hillmann, E., 2017. Performance loss and changes in behaviour caused by footrot. Schweizer Archiv für Tierheilkunde 159, 293–300.
Härdi-Landerer, M.C., Stoffel, A., Dürr, S., Steiner, A., 2019. Footbath as treatment of footrot in sheep. Current-situation on Swiss sheep farms. Schweizer Archiv für Tierheilkunde 161, 377–386.

Haring, V., Billington, S.J., Wright, C.L., Huggins, A.S., Katz, M.E., Rood, J.I., 1995. Delineation of the virulence-related locus (*vrl*) of *Dichelobacter nodosus*. Microbiology 141 (Pt 9), 2081–2089.
Hidber, T., Pauli, U., Steiner, A., Kuhnert, P., 2020. In vitro and ex vivo testing of alternative disinfectants to currently used more harmful substances in footbaths against *Dichelobacter nodosus*. PLoS One 15, e0229066.
Hunt, J.D., Jackson, D.C., Brown, L.E., Wood, P.R., Stewart, D.J., 1994. Antigenic competition in a multivalent foot rot vaccine. Vaccine 12, 457–464.
Jelinek, P., Depiazzi, L., 2003. Failure to eradicate ovine footrot associated with *Dichelobacter nodosus* strain A198 by repeated daily footbathing in zinc sulphate with surfactant. Australian Veterinary Journal 81, 58–62.
Jelinek, P., Depiazzi, L., Galvin, D., Spicer, I., Palmer, M., Pitman, D., 2001. Eradication of ovine footrot by repeated daily footbathing in a solution of zinc sulphate with surfactant. Australian Veterinary Journal 79, 431–434.
Kaler, J., Green, L.E., 2008a. Naming and recognition of six foot lesions of sheep using written and pictorial information: a study of 809 English sheep farmers. Preventive Veterinary Medicine 83, 52–64.
Kaler, J., Green, L.E., 2008b. Recognition of lameness and decisions to catch for inspection among sheep farmers and specialists in GB. BMC Veterinary Research 4 41–41.
Kaler, J., Green, L.E., 2009. Farmers' practices and factors associated with the prevalence of all lameness and lameness attributed to interdigital dermatitis and footrot in sheep flocks in England in 2004. Preventive Veterinary Medicine 92, 52–59.
Kaler, J., Wassink, G.J., Green, L.E., 2009. The inter- and intra-observer reliability of a locomotion scoring scale for sheep. The Veterinary Journal 180, 189–194.
Kaler, J., Daniels, S.L., Wright, J.L., Green, L.E., 2010a. Randomized clinical trial of long-acting oxytetracycline, foot trimming, and flunixine meglumine on time to recovery in sheep with footrot. Journal of Veterinary Internal Medicine 24, 420–425.
Kaler, J., Medley, G.F., Grogono-Thomas, R., Wellington, E.M.H., Calvo-Bado, L.A., Wassink, G.J., King, E.M., Moore, L.J., Russell, C., Green, L.E., 2010b. Factors associated with changes of state of foot conformation and lameness in a flock of sheep. Preventive Veterinary Medicine 97, 237–244.
Kaler, J., Wani, S.A., Hussain, I., Beg, S.A., Makhdoomi, M., Kabli, Z.A., Green, L.E., 2012. A clinical trial comparing parenteral oxytetracyline and enrofloxacin on time to recovery in sheep lame with acute or chronic footrot in Kashmir, India. BMC Veterinary Research 8 12–12.
Katz, M.E., Howarth, P.M., Yong, W.K., Riffkin, G.G., Depiazzi, L.J., Rood, J.I., 1991. Identification of three gene regions associated with virulence in *Dichelobacter nodosus*, the causative agent of ovine footrot. Journal of General and Applied Microbiology 137, 2117–2124.
Kennan, R.M., Billington, S.J., Rood, J.I., 1998. Electroporation-mediated transformation of the ovine footrot pathogen *Dichelobacter nodosus*. FEMS Microbiology Letters 169, 383–389.
Kennan, R.M., Dhungyel, O.P., Whittington, R.J., Egerton, J.R., Rood, J.I., 2001. The type IV fimbrial subunit gene (*fimA*) of *Dichelobacter nodosus* is essential for virulence, protease secretion, and natural competence. Journal of Bacteriology 183, 4451–4458.
Kennan, R.M., Wong, W., Dhungyel, O.P., Han, X., Wong, D., Parker, D., Rosado, C.J., Law, R.H., McGowan, S., Reeve, S.B., et al., 2010. The subtilisin-like protease AprV2 is required for virulence and uses a novel disulphide-tethered exosite to bind substrates. PLoS Pathology 6, e1001210.
Kennan, R.M., Han, X., Porter, C.J., Rood, J.I., 2011. The pathogenesis of ovine footrot. Veterinary Microbiology 153, 59–66.
Kennan, R.M., Gilhuus, M., Frosth, S., Seemann, T., Dhungyel, O.P., Whittington, R.J., Boyce, J.D., Powell, D.R., Aspan, A., Jorgensen, H.J., et al., 2014. Genomic evidence for a globally distributed, bimodal population in the ovine footrot pathogen *Dichelobacter nodosus*. MBio 5, e01821–01814.
Knappe-Poindecker, M., Gilhuus, M., Jensen, T.K., Vatn, S., Jørgensen, H.J., Fjeldaas, T., 2014. Cross-infection of virulent *Dichelobacter nodosus* between sheep and co-grazing cattle. Veterinary Microbiology 170, 375–382.
König, U., Nyman, A.-K.J., de Verdier, K., 2011. Prevalence of footrot in Swedish slaughter lambs. Acta Veterinaria Scandinavica 53 27–27.
Kraft, A.F., Strobel, H., Hilke, J., Steiner, A., Kuhnert, P., 2020. The prevalence of *Dichelobacter nodosus* in clinically footrot-free sheep flocks: a comparative field study on elimination strategies. BMC Veterinary Research 16, 21.
Kuhnert, P., Cippa, V., Hardi-Landerer, M.C., Schmicke, M., Ulbrich, S., Locher, I., Steiner, A., Jores, J., 2019. Early infection dynamics of *Dichelobacter nodosus* during an ovine experimental footrot in contact infection. Schweizer Archiv für Tierheilkunde 161, 465–472.
La Fontaine, S., Egerton, J.R., Rood, J.I., 1993. Detection of *Dichelobacter nodosus* using species-specific oligonucleotides as PCR primers. Veterinary Microbiology 35, 101–117.
Lacasta, D., Ferrer, L.M., Ramos, J.J., González, J.M., Ortín, A., Fthenakis, G.C., 2015. Vaccination schedules in small ruminant farms. Veterinary Microbiology 181, 34–46.
Ley, S.J., Waterman, A.E., Livingston, A., Parkinson, T.J., 1994. Effect of chronic pain associated with lameness on plasma cortisol concentrations in sheep: a field study. Research in Veterinary Science 57, 332–335.
Liu, D., Webber, J., 1995. A polymerase chain reaction assay for improved determination of virulence of *Dichelobacter nodosus*, the specific causative pathogen for ovine footrot. Veterinary Microbiology 43, 197–207.
Lizarraga, I., Chambers, J.P., 2012. Use of analgesic drugs for pain management in sheep. New Zealand Veterinary Journal 60, 87–94.
Locher, I., Greber, D., Holdener, K., Lüchinger, R., Haerdi-Landerer, C., Schüpbach-Regula, G., Frey, J., Steiner, A., 2015. Longitudinal *Dichelobacter nodosus* status in 9 sheep flocks free from clinical footrot. Small Ruminant Research 132, 128–132.
Locher, I., Giger, L., Frosth, S., Kuhnert, P., Steiner, A., 2018. Potential transmission routes of *Dichelobacter nodosus*. Veterinary Microbiology 218, 20–24.
Maboni, G., Frosth, S., Aspan, A., Totemeyer, S., 2016. Ovine footrot: new insights into bacterial colonisation. Veterinary Record 179, 228.
Maboni, G., Blanchard, A., Frosth, S., Stewart, C., Emes, R., Totemeyer, S., 2017. A distinct bacterial dysbiosis associated skin inflammation in ovine footrot. Scientific Reports 7, 45220.
Malecki, J.C., Coffey, L., 1987. Treatment of ovine virulent footrot with zinc sulphate/sodium lauryl sulphate footbathing. Australian Veterinary Journal 64, 301–304.
Marshall, D.J., Walker, R.I., Cullis, B.R., Luff, M.F., 1991. The effect of footrot on body weight and wool growth of sheep. Australian Veterinary Journal 68, 45–49.
McPherson, A.S., Dhungyel, O.P., Whittington, R.J., 2018. Detection and serogrouping of *Dichelobacter nodosus* infection by use of direct PCR from lesion swabs to support outbreak-specific vaccination for virulent footrot in sheep. Journal of Clinical Microbiology 56.
McPherson, A.S., Dhungyel, O.P., Whittington, R.J., 2019. The microbiome of the footrot lesion in Merino sheep is characterized by a persistent bacterial dysbiosis. Veterinary Microbiology 236, 108378.
Mills, K., McClenaughan, P., Morton, A., Alley, D., Lievaart, J., Windsor, P.A., Egerton, J. R., 2012. Effect on time in quarantine of the choice of program for eradication of footrot from 196 sheep flocks in southern New South Wales. Australian Veterinary Journal 90, 14–19.
Moore-Jones, G., Ardüser, F., Dürr, S., Gobeli Brawand, S., Steiner, A., Zanolari, P., Ryser-Degiorgis, M.-P.P., 2020. Identifying maintenance hosts for infection with *Dichelobacter nodosus* in free-ranging wild ruminants in Switzerland: a prevalence study. PLoS One 15, e0219805.
Mucha, S., Bunger, L., Conington, J., 2015. Genome-wide association study of footrot in Texel sheep. Genetics Selection Evolution 47, 35.
Myers, G.S., Parker, D., Al-Hasani, K., Kennan, R.M., Seemann, T., Ren, Q., Badger, J.H., Selengut, J.D., Deboy, R.T., Tettelin, H., et al., 2007. Genome sequence and identification of candidate vaccine antigens from the animal pathogen *Dichelobacter nodosus*. Nature Biotechnology 25, 569–575.
Nieuwhof, G.J., Bishop, S.C., 2005. Costs of the major endemic diseases of sheep in Great Britain and the potential benefits of reduction in disease impact. Animal Science 81, 23–29.
Nieuwhof, G.J., Bishop, S.C., Hill, W.G., Raadsma, H.W., 2008a. The effect of footrot on weight gain in sheep. Animal 2, 1427–1436.
Nieuwhof, G.J., Conington, J., Bunger, L., Haresign, W., Bishop, S.C., 2008b. Genetic and phenotypic aspects of foot lesion scores in sheep of different breeds and ages. Animal 2, 1289–1296.
Niggeler, A., Tetens, J., Stäuble, A., Steiner, A., Drögemüller, C., 2017. A genome-wide significant association on chromosome 2 for footrot resistance/susceptibility in Swiss White Alpine sheep. Animal Genetics 48, 712–715.
Ortolani, E.L., Antonelli, A.C., De Souza Sarkis, J.E., 2004. Acute sheep poisoning from a copper sulfate footbath. Veterinary and Human Toxicology 46, 315–318.
Palmer, M.A., 1993. A gelatin test to detect activity and stability of proteases produced by *Dichelobacter* (*Bacteroides*) *nodosus*. Veterinary Microbiology 36, 113–122.
Parajuli, B., Goddard, P.J., 1989. A comparison of the efficacy of footbaths containing formalin or zinc sulphate in treating ovine foot-rot under field conditions. British Veterinary Journal 145, 467–472.
Phythian, C.J., Cripps, P.J., Grove-White, D., Michalopoulou, E., Duncan, J.S., 2016. Inter-observer agreement for clinical examinations of foot lesions of sheep. The Veterinary Journal 216, 189–195.
Piriz, S., Pobel, T., Jimenez, R., Mateos, E.M., Martin-Palomino, P., Vila, P., Vadillo, S., 2001. Comparison of erythromycin and oxytetracycline for the treatment of ovine footrot. Acta Veterinaria Hungarica 49, 131–139.
Prosser, N.S., Purdy, K.J., Green, L.E., 2019. Increase in the flock prevalence of lameness in ewes is associated with a reduction in farmers using evidence-based management of prompt treatment: a longitudinal observational study of 154 English sheep flocks 2013–2015. Preventive Veterinary Medicine 173, 104801.
Raadsma, H.W., Egerton, J.R., 2013. A review of footrot in sheep: aetiology, risk factors and control methods. Livestock Science 156, 106–114.
Raadsma, H.W., O'Meara, T.J., Egerton, J.R., Lehrbach, P.R., Schwartzkoff, C.L., 1994. Protective antibody titres and antigenic competition in multivalent *Dichelobacter nodosus* fimbrial vaccines using characterised rDNA antigens. Veterinary Immunology and Immunopathology 40, 253–274.
Reed, G.A., Alley, D.U., 1996. Efficacy of a novel copper-based footbath preparation for the treatment of ovine footrot during the spread period. Australian Veterinary Journal 74, 375–382.
Rendell, D.K., Callinan, A.P., 1997. Comparison of erythromycin and oxytetracycline for the treatment of virulent footrot in grazing sheep. Australien Veterinary Journal 75, 354.
Riffkin, M.C., Wang, L.F., Kortt, A.A., Stewart, D.J., 1995. A single amino-acid change between the antigenically different extracellular serine proteases V2 and B2 from *Dichelobacter nodosus*. Gene 167, 279–283.
Rood, J.I., 2002. Genomic islands of *Dichelobacter nodosus*. Current Topics in Microbiology and Immunology 264, 47–60.
Russell, C.L., Smith, E.M., Calvo-Bado, L.A., Green, L.E., Wellington, E.M., Medley, G.F., Moore, L.J., Grogono-Thomas, R., 2014. Multiple locus VNTR analysis highlights that geographical clustering and distribution of *Dichelobacter nodosus*, the

causal agent of footrot in sheep, correlates with inter-country movements. Infection Genetics and Evolution 22, 273–279.
Sagliyan, A., Gunay, C., Han, M.C., 2008. Comparison of the effects of oxytetracycline and penicillin-streptomycin in the treatment of footrot in sheep. Journal of Animal and Veterinary Advances 7, 986–990.
Schwartzkoff, C.L., Egerton, J.R., Stewart, D.J., Lehrbach, P.R., Elleman, T.C., Hoyne, P. A., 1993. The effects of antigenic competition on the efficacy of multivalent footrot vaccines. Australian Veterinary Journal 70, 123–126.
Skerman, T.M., Moorhouse, S.R., 1987. Broomfield corriedales: a strain of sheep selectively bred for resistance to footrot. New Zealand Veterinary Journal 35, 101–106.
Skerman, T.M., Green, R.S., Hughes, J.M., Herceg, M., 1983a. Comparison of footbathing treatments for ovine footrot using formalin or zinc sulphate. New Zealand Veterinary Journal 31, 91–95.
Skerman, T.M., Moorhouse, S.R., Green, R.S., 1983b. Further investigations of zinc sulphate footbathing for the prevention and treatment of ovine footrot. New Zealand Veterinary Journal 31, 100–102.
Smith, E.M., Gilbert, A., Russell, C.L., Purdy, K.J., Medley, G.F., Muzafar, M., Grogono-Thomas, R., Green, L.E., 2017. Within-flock population dynamics of *Dichelobacter nodosus*. Frontiers in Veterinary Science 4, 58.
Sreenivasulu, D., Vijayalakshmi, S., Raniprameela, D., Karthik, A., Wani, S.A., Hussain, I., 2013. Prevalence of ovine footrot in the tropical climate of southern India and isolation and characterisation of *Dichelobacter nodosus*. Revue Scientifique et Technique de l'OIE 32, 869–877.
Stauble, A., Steiner, A., Frey, J., Kuhnert, P., 2014a. Simultaneous detection and discrimination of virulent and benign *Dichelobacter nodosus* in sheep of flocks affected by foot rot and in clinically healthy flocks by competitive real-time PCR. Journal of Clinical Microbiology 52, 1228–1231.
Stauble, A., Steiner, A., Normand, L., Kuhnert, P., Frey, J., 2014b. Molecular genetic analysis of *Dichelobacter nodosus* proteases AprV2/B2, AprV5/B5 and BprV/B in clinical material from European sheep flocks. Veterinary Microbiology 168, 177–184.
Stewart, D.J., Claxton, P.D., 1993. Ovine foot rot: Clinical diagnosis and bacteriology. Australian Standard Diagnostic Techniques for Animal Diseases. CSIRO Publications, Victoria, Australia, pp. 1–27.
Stewart, D.J., Clark, B.L., Emery, D.L., Peterson, J.E., Jarrett, R.G., O'Donnell, I.J., 1986. Cross-protection from *Bacteroides nodosus* vaccines and the interaction of pili and adjuvants. Australian Veterinary Journal 63, 101–106.
Strobel, H., Stauch, S., 2014. Metaphylactic antibiotic treatment of footrot in sheep using Florfenicol. Berliner und Münchner Tierärztliche Wochenschrift 127, 211–215.
Strobel, H., Lauseker, M., Forbes, A.B., 2014. Targeted antibiotic treatment of lame sheep with footrot using either oxytetracycline or gamithromycin. Veterinary Record 174, 46.
Thomas, J.H., 1958. A simple medium for the isolation and cultivation of *Fusiformis nodosus*. Australian Veterinary Journal 34, 1.
Thomas, J.H., 1962. The bacteriology and histopathology of footrot in sheep. Australian Journal of Agricultural Research 13, 8.
Thorley, C.M., Egerton, J.R., 1981. Comparison of alum-absorbed or non-alum-absorbed oil emulsion vaccines containing either pilate or non-pilate *Bacteroides nodosus* cells in inducing and maintaining resistance of sheep to experimental foot rot. Research in Veterinary Science 30, 32–37.
Vatn, S., Hektoen, L., Høyland, B., Reiersen, A., Kampen, A.H., Jørgensen, H.J., 2012. Elimination of severe footrot from the Norwegian sheep population—a progress report. Small Ruminant Research 106, 11–13.
Venning, C.M., Curtis, M.A., Egerton, J.R., 1990. Treatment of virulent footrot with lincomycin and spectinomycin. Australian Veterinary Journal 67, 258–260.
Volmer, K., Hecht, W., Weiß, R., Grauheding, D., 2008. Treatment of foot rot in free-ranging mouflon (*Ovis gmelini* musimon) populations—does it make sense? European Journal of Wildlife Research 54, 657–665.
Walduck, A.K., Opdebeeck, J.P., 1996. Effect of adjuvants on antibody responses of sheep immunised with recombinant pili from *Dichelobacter nodosus*. Australian Veterinary Journal 74, 451–455.
Wani, A.H., Verma, S., Sharma, M., Wani, S.A., 2015. Infectious lameness among migratory sheep and goats in north-west India, with particular focus on anaerobes. Revue Scientifique et Technique de l'OIE 34, 855–867.
Wani, S.A., Farooq, S., Kashoo, Z.A., Hussain, I., Bhat, M.A., Rather, M.A., Aalamgeer, S., 2019. Determination of prevalence, serological diversity, and virulence of *Dichelobacter nodosus* in ovine footrot with identification of its predominant serotype as a potential vaccine candidate in J and K, India. Tropical Animal Health and Production 51, 1089–1095.
Wassink, G.J., Green, L.E., Grogono-Thomas, R., Moore, L.J., 2004. Risk factors associated with the prevalence of interdigital dermatitis in sheep from 1999 to 2000. Veterinary Record 154, 551–555.
Wassink, G.J., George, T.R.N., Kaler, J., Green, L.E., 2010a. Footrot and interdigital dermatitis in sheep: farmer satisfaction with current management, their ideal management and sources used to adopt new strategies. Preventive Veterinary Medicine 96, 65–73.
Wassink, G.J., King, E.M., Grogono-Thomas, R., Brown, J.C., Moore, L.J., Green, L.E., 2010b. A within farm clinical trial to compare two treatments (parenteral antibacterials and hoof trimming) for sheep lame with footrot. Preventive Veterinary Medicine 96, 93–103.
Welsh, E.M., Gettinby, G., Nolan, A.M., 1993. Comparison of a visual analog scale and a numerical rating-scale for assessment of lameness, using sheep as a model. American Journal of Veterinary Research 54, 976–983.
Whittington, R.J., 1995. Observations on the indirect transmission of virulent ovine footrot in sheep yards and its spread in sheep on unimproved pasture. Australian Veterinary Journal 72, 132–134.
Wild, R., McFadden, A.M.J., O'Connor, C., O'Grady, K., Wada, M., 2019. Prevalence of lameness in sheep transported to meat processing plants in New Zealand and associated risk factors. New Zealand Veterinary Journal 67, 188–193.
Wimmershoff, J., Ryser-Degiorgis, M., Marreros, N., Frey, J., Romanens, P., Gendron, K., Origgi, F.C., 2015. Outbreak of severe foot rot associated with benign *Dichelobacter nodosus* in an Alpine ibex colony in the Swiss Prealps. Schweizer Archiv für Tierheilkunde 157, 277–284.
Winter, A., 2004a. Lameness in sheep 1. Diagnosis. In Practice 26, 58–63.
Winter, A., 2004b. Lameness in sheep 2. Treatment and control. In Practice 26, 130–139.
Winter, A.C., 2008. Lameness of sheep. Small Ruminant Research 76, 5.
Winter, A.C., 2011. Treatment and control of hoof disorders in sheep and goats. Veterinary Clinics of North America: Food Animal Practice 27, 187–192.
Winter, J.R., Green, L.E., 2017. Cost-benefit analysis of management practices for ewes lame with footrot. The Veterinary Journal 220, 1–6.
Winter, J.R., Kaler, J., Ferguson, E., KilBride, A.L., Green, L.E., 2015. Changes in prevalence of, and risk factors for, lameness in random samples of English sheep flocks: 2004–2013. Preventive Veterinary Medicine 122, 121–128.
Witcomb, L.A., Green, L.E., Kaler, J., Ul-Hassan, A., Calvo-Bado, L.A., Medley, G.F., Grogono-Thomas, R., Wellington, E.M., 2014. A longitudinal study of the role of *Dichelobacter nodosus* and *Fusobacterium necrophorum* load in initiation and severity of footrot in sheep. Preventive Veterinary Medicine 115, 48–55.
Witcomb, L.A., Green, L.E., Calvo-Bado, L.A., Russell, C.L., Smith, E.M., Grogono-Thomas, R., Wellington, E.M., 2015. First study of pathogen load and localisation of ovine footrot using fluorescence in situ hybridisation (FISH). Veterinary Microbiology 176, 321–327.
Witt, J., Green, L., 2018. Development and assessment of management practices in a flock-specific lameness control plan: a stepped-wedge trial on 44 English sheep flocks. Preventive Veterinary Medicine 157, 125–133.
Woolaston, R.R., 1993. Factors affecting the prevalence and severity of footrot in a Merino flock selected for resistance to *Haemonchus contortus*. Australian Veterinary Journal 70, 365–369.
Zhou, H., Hickford, J.G., 2000. Extensive diversity in New Zealand *Dichelobacter nodosus* strains from infected sheep and goats. Veterinary Microbiology 71, 113–123.
Zingg, D., Steinbach, S., Kuhlgatz, C., Rediger, M., Schüpbach-Regula, G., Aepli, M., Grøneng, G.M., Dürr, S., 2017. Epidemiological and economic evaluation of alternative on-farm management scenarios for ovine footrot in Switzerland. Frontiers in Veterinary Science 4, 70.