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Review

Bovine digital dermatitis: Current concepts from laboratory to farm

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Highlights

- Bovine digital dermatitis (DD), DD treponemes, DD risk factors and DD control strategies are reviewed.
- DD lesions, hoof trimming tools and bovine GI tract are DD infection reservoirs.
- Improved hygiene and foot trimming practice could help prevent DD transmission.
- Current antibiotic treatments are not the most effective against DD treponemes.
- New antibiotics, additional transmission prevention and/or effective vaccines are needed.

Abstract

Bovine digital dermatitis (DD) is a severe infectious disease causing lameness in dairy cattle worldwide and is an important ruminant welfare problem that has considerable economic issues. Bovine DD is endemic in many regions worldwide and it is important to understand this major disease so that effective control strategies can be identified. There is substantial evidence that specific treponeme phylotypes play an important causative role in bovine DD. This review considers current research, including DD *Treponema* spp. investigations, associated DD pathobiology, and current and potential treatment and control options. Epidemiological data, alongside new microbiological data, help to delineate important transmission routes and reservoirs of infection that allow effective interventions to be identified. Better on-farm housing hygiene, pasture access, routine footbathing and claw trimming with disinfected equipment need to be implemented to significantly reduce the incidence of DD. There is a paucity of peer

reviewed research into both commonly used and novel treatments. In vitro antimicrobial susceptibility studies of DD treponemes and effective treatment of human treponematoses clearly indicate that antibiotics frequently selected for DD treatments are not the most efficacious. Whilst there are understandable concerns over milk withdrawal times in dairy cattle, more needs to be done to identify, license and implement more appropriate antibiotic treatments, since continued overuse of less efficacious antibiotics, applied incorrectly, will lead to increased disease recurrence and transmission. More research is needed into methods of preventing DD that circumvent the use of antibiotics, including vaccination and transmission blocking studies, in order to reduce or hopefully eradicate DD in the future.

Keywords: Bovine digital dermatitis; Papillomatous digital dermatitis; Treponemes; Spirochaetes

Introduction

Bovine digital dermatitis (DD) was first reported in the 1970s (Cheli and Mortellaro, 1974) and is also called Mortellaro's disease in Europe, whereas papillomatous DD (PDD) or hairy foot/heel-warts (Read and Walker, 1998) is frequently used in North and South America and Australasia. The contagious nature of this severe disease and poor treatment response has resulted in a major worldwide problem in nearly all countries with dairy cattle. Substantial focal lesions on one or both rear feet of cattle are the typical presentation of DD, which is often extremely painful. The ensuing lameness is an important animal health and welfare concern, resulting in reduced milk yield and reproductive performance, with substantial costs of treatment and control. An effective prevention or treatment capable of eliminating bovine DD has yet to be identified. Spirochaetes and, more specifically, treponemes have been implicated as important in the aetiology of DD. This review discusses worldwide research that advances our understanding of current concepts in DD and the role of associated treponemes, with implications for best practices.

Presentation, epidemiology and impact of the disease

The main clinical feature of bovine DD is lameness resulting from an ulcerative lesion consisting of an extensive or localised superficial dermatitis immediately on or above the coronary band between the heel bulbs (Weaver et al., 1981; Blowey and Sharp, 1988). The majority of lesions (~80-90%) are typically found on hind feet, with far fewer occurring on the front feet (~10-20%) (Murray et al., 2002). Animals with DD are frequently severely lame and, as a result, may walk on their toes or shift their weight from foot to foot (Cheli and Mortellaro, 1974; Read and Walker, 1998). Lesions adjacent to the interdigital space often extend locally to involve interdigital skin (Read and Walker 1994) and long standing lesions frequently (42%)

develop wart-like papillary keratotic proliferations (Read and Walker, 1998). A relevant scoring system for DD based on macroscopic lesion characteristics has been described (Dopfer et al., 1997) and recently adapted, now including six stages (Berry et al., 2012) (Table 1).

In the 20 years following the initial report from Italy (Cheli and Mortellaro, 1974), bovine DD subsequently appeared across the world, being reported in the USA (Rebhun et al., 1980), UK (Blowey and Sharp, 1988) and Japan (Kimura et al., 1993). Bovine DD is now endemic in dairy cattle populations across several European countries, including Germany, the Netherlands, Denmark, France and the UK (Laven, 2001; Koenig et al., 2005; Holzhauer et al., 2006; Capion et al., 2008; Relun et al., 2013), and the USA, including California, Georgia, Iowa and Wisconsin (Read and Walker, 1998; Brown et al., 2000; Faust et al., 2001). Globally, the problem is now common and there have also been case reports of DD from Egypt, South Africa, Turkey, Chile, Brazil, Canada and New Zealand (van Amstel et al., 1995; Rodriguez-Lainz et al., 1998; Cruz et al., 2001; el-Ghoul and Shaheed, 2001; Demirkan and Güzel, 2004; Vermunt and Hill, 2004; Cramer et al., 2009).

The impact of bovine DD is considerable. Bovine DD can cause severe pain, making it an important animal welfare issue (Bruijnis et al., 2012), especially considering the number of animals worldwide with this disease. Furthermore, bovine DD is an important worldwide economic issue, since it results in reduced milk yields and reproductive performance (Argaez-Rodriguez et al., 1997). The economic impact resulting from milk production losses in the USA has been calculated at US$190 million[1] per year (Losinger, 2006). In the UK, the cost of bovine

[1] US$1.00 = UK£0.61 = €0.78 at 25 September 2014.

DD has been estimated at UK£99.00 per case (GB Cattle Health and Welfare Group, 2014), whilst in The Netherlands, the cost per dairy holding of 65 cows was estimated at US$1,517.00/year including milk loss and treatment costs (Bruijnis et al., 2010). Another study reported the cost as US$132.96 per case of DD consisting of US$35.41 for milk loss, US$41.37 for decreased fertility and US$56.18 for treatment costs (Cha et al., 2010). Therefore bovine DD has substantial economic implications.

Aetiology

Epidemiological evidence, such as geographic spread and healing after antibiotic treatment, has implicated bovine DD as an infectious disease caused by bacteria (Read and Walker, 1998). Initially, the aetiology of DD was unclear, mainly due to the plethora of microorganisms present on the lesion surface as a result of the slurry environment that many dairy cows stand in. Various types of bacteria have been identified within bovine DD manifestations, including spirochaetes, *Bacterioides* spp., *Guggenheimella bovis*, *Campylobacter* spp., *Fusobacterium* spp. and *Peptococccus* spp. (Blowey and Sharp, 1988; Sabo et al., 1988; Read et al., 1992; Koniarova et al., 1993; Blowey et al., 1994; Dopfer et al., 1997; Schlafer et al., 2008). A recent systematic microbiological study of DD anaerobes and aerobes additionally reported *Porphyromonas levii, Mycoplasma* spp., *Prevotella* spp. and spirochaetes as lesion associated (Berry et al., 2010). However, when considering all studies in entirety, the spirochaetes and specifically treponemes are the only microorganisms where there is substantial evidence of an aetiological association.

An initial study involving cloning and sequencing of bacterial 16S rRNA genes from bovine DD lesions in Germany identified five phylotypes of treponemes within lesions (Choi et

al., 1997). Subsequent immunohistochemistry with molecular detection methods demonstrated both large numbers of treponemes within bovine DD lesions (Dopfer et al., 1997; Demirkan et al., 1998; Moter et al., 1998). Eight spirochaetes were isolated from bovine DD lesions in the USA, with seven forming a distinct phenotypic group (Walker et al., 1995); subsequently, a German BDD spirochaete (*Treponema brennaborense*) was reported to be quite different (Schrank et al., 1999). A genetic typing study of six isolates from the USA identified three phylotypes (Walker et al., 1995; Stamm et al., 2002).

In a further study, four USA bovine DD spirochaetes were identified as similar to *Treponema phagedenis* (Trott et al., 2003). A spirochaete isolated from a UK BDD lesion was identified as similar to USA bovine DD isolates (Demirkan et al., 2006). Most recently, a larger number (n = 23) of treponemes from bovine DD lesions were isolated in the UK and were characterised both genotypically and phenotypically, demonstrating three distinct taxonomic groups analogous to USA DD phylotypes (Evans et al., 2008). In line with previous studies, these were designated as *Treponema medium*/*Treponema vincentii*-like, *Treponema phagedenis*-like and *Treponema putidum*/*Treponema denticola*-like spirochaetes. These phylogroups were very similar to human treponemes and therefore described as '-like' (pending further taxonomic propositions) and by 16S rRNA gene phylogenetics were identical to 3/5 phylotypes identified in bovine DD lesions in the initial German study (Choi et al., 1997). Following additional characterisation, one isolated bovine DD treponeme phylogroup, the *T. putidum*/*T. denticola*-like, was designated as a new species, *Treponema pedis* (Evans et al., 2009b); the other two isolated phylogroups still require further taxonomic appraisal.

Immunohistochemistry and PCR assays targeting the three isolated phylotypes in the UK, along with German and Danish fluorescent in situ hybridisation (FISH) studies of bovine DD lesions, have identified multiple unique treponeme phylotypes together in bovine DD lesions, suggesting that the disease is polytreponemal rather than more broadly polymicrobial (Klitgaard et al., 2008; Nordhoff et al., 2008; Evans et al., 2009c). Subsequently, this hypothesis of multiple treponemal infection has being substantiated by further molecular metagenomic studies from Europe, Japan and the USA (Yano et al., 2010b; Santos et al., 2012; Klitgaard et al., 2013). Whilst similar DD treponemes have been isolated in the UK and USA; there have been some differences identified in the treponeme phylotypes highly associated with DD lesions between European countries such as Denmark and the UK suggesting regional differences in DD aetiology (Klitgaard et al., 2008; Evans et al., 2009).

In hand with the considerable molecular evidence supporting specific treponeme phylotypes as playing an important causative role in DD, some workers have partially fulfilled Koch's postulates towards definitively demonstrating a treponemal aetiology for bovine DD. Transmission has been previously demonstrated using foot inoculation of 4-month-old naive calves with lesional material (Read and Walker, 1996) and this was repeated recently using the same protocol on yearling cattle. In the latter experiment, lesional material achieved a lesion success rate of 4/6 animals, whereas a single treponeme isolate produced an incipient DD lesion in 1/4 animals (Gomez et al., 2012), suggesting that, if the experimental conditions were more optimal, a full-blown DD lesion may have developed. When experimental lesions were studied pathologically treponemes were the primary, predominant and the deepest invaders (Read et al. 1998) suggesting they play an important pathogenic role in DD. In the above described experiments, cows' feet were wrapped to reproduce conditions of prolonged moisture

(maceration) and reduced access to air before and after application of infectious material. Such conditions were required for transmission and could be considered to mimic the cows' feet environment in a typical dairy farm unit.

Similar disease manifestations in cattle

New forms of bovine foot lesions have been described that previously were considered to be non-infectious, including toe necrosis, sole ulcers and white line disease. The new forms are chronic lesions that appear refractory to conventional treatment, are patently infected with bacteria, have a raised, red stippled appearance (granulation tissue) and the same pungent smell as bovine DD lesions. These non-healing foot lesions have a high association with DD treponemes (Blowey, 2008; Evans et al., 2011a), are particularly destructive and may have an even greater economic and animal welfare cost than DD itself. Ulcerative mammary dermatitis (UMD) also has an association with DD treponemes (Read et al., 2003; Stamm et al., 2009; Evans et al., 2010) although the association does not appear to be strong, suggesting that the disease may be more polymicrobial (Evans et al., 2010).

'Digital dermatitis in non-bovine species'

DD has now also emerged in sheep, causing contagious ovine DD (CODD), which was first reported in the UK as severe virulent ovine footrot (Harwood et al., 1997) and, after confirmation of treponeme involvement, reclassified as CODD (Davies et al., 1999). Treponemes have been implicated in CODD through serological and molecular studies (Dhawi et al., 2005; Moore et al., 2005; Sayers et al., 2009) although *Dichelobacter nodosus* may also have a role in this disease (Moore et al., 2005; Duncan et al., 2012). Furthermore a CODD-like infection has now been reported in dairy goats in the UK (Sullivan et al., 2015) and a similar manifestation has

been reported in Wild Elk in Washington State, USA (Clegg et al., 2015) suggesting an even greater economic, animal welfare and global cost of this disease.

Treponeme phylotypes involved in DD have recently been implicated in porcine ear necrosis and shoulder ulcers in Sweden (Pringle et al., 2009; Karlsson et al., 2013). It appears that DD treponemes are continually emerging into new hosts and disease presentations, suggesting these bacteria pose a much greater threat than first conceived.

Host genetics, immune and inflammatory responses

There has been growing interest in host genetics of bovine DD in recent years. Heritability of bovine DD has been reported to be as low as 0.039 in one study (Onyiro et al., 2008) and as high as 0.4 in another (Oberbauer et al., 2013), lending support for further heritability studies as well as genetic studies to identify loci contributing to DD susceptibility. Another study linked eight single nucleotide polymorphisms (SNPs), on three chromosomes, with dairy cattle DD susceptibility (Scholey et al., 2012). Larger studies are needed to further identify important loci and there is a need to develop diagnostic screening and targeted breeding to reduce the prevalence of DD.

Pathological and immunohistochemical investigations of bovine DD lesions are described in Table 1. Lesions consistently have large numbers of spirochaetes invading the superficial skin layers, along with necrosis (Bassett et al., 1990; Read and Walker, 1994, 1998; Dopfer et al., 1997). Infection with DD treponemes generates a strong but ineffective immune response for a relatively short duration (Demirkan et al., 1999; Trott et al., 2003), which neither resolves disease nor offers future protection.

In terms of inflammatory host responses, after in vitro exposure of bovine macrophages to bovine DD treponeme constituents, there is decreased expression of many genes associated with wound repair and immunity (Zuerner et al., 2007). Subsequent tissue culture studies have demonstrated that skin fibroblasts, but not keratinocytes, are responsive to BDD treponemes, producing macrophage elastase and RANTES, potentially important inflammatory mediators, which are also upregulated in human psoriasis (Evans et al., 2014). A host transcriptomics study of whole host lesion tissues reiterated an absence of innate immune responses in lesions. There was also increased expression of α2-macroglobulin-like 1, a protein potentially involved in bacterial immune evasion and bacterial survival, as well as increases in keratin 6A and interleukin 1β (Scholey et al., 2013).

Molecular pathogenesis of digital dermatitis

Recent work has isolated and compared commensal bovine gastrointestinal tract treponemes with bovine DD treponemes and identified these microorganisms as belonging to two large separate phylogenetic clusters (Evans et al., 2011b). Bovine DD treponemes belong to a proteolytic, serum-dependent cluster whose members have a gene encoding tissue attachment machinery and demonstrated haemolytic ability, whilst the bovine gastrointestinal treponemes belonged to a saccharolytic cluster which do not require or were inhibited by serum, do not have a gene encoding tissue attachment machinery and do not exhibit haemolysis. A previous review has detailed likely pathogenic mechanisms through comparison with human oral treponemes (Edwards et al., 2003a). These include a large number of shared cell surface proteins important for binding the host extracellular matrix (ECM). In a study of two DD treponeme strains, the

bacteria bound to a panel of mostly skin ECM proteins, including fibronectin, laminin, collagen type I, gelatin and keratin (Edwards et al., 2003b).

Inflammatory dysregulation is also considered to make a key contribution to treponemal pathogenesis (Radolf et al., 2006). As aforementioned, the treponemes appear to allow immune evasion by downregulating key inflammatory markers in macrophages (Zuerner et al., 2007) whilst causing increased expression of substantial inflammatory markers in fibroblasts (Evans et al., 2014). Interestingly the treponeme-mediated increase in macrophage elastase production by fibroblasts should enable degradation of elastin, a key ECM protein responsible for skin integrity (Evans et al., 2014).

Infection reservoirs and risk factors

In a comprehensive PCR study of the presence of bovine DD treponemes in the dairy farm environment, in bovine tissues and gastrointestinal tract content, DD treponemes were occasionally present in two non-pedal bovine regions, the oral cavity (14.3% of cattle tested) and the rectum (14.8% of cattle tested) (Evans et al., 2012b). Interestingly, single phylotypes were detected in the oral cavity, whilst two rectal tissues yielded DNA from multiple DD treponeme phylotypes. In contrast, all farm environmental samples, including faeces, together with insects and gastrointestinal tract content samples, were negative using bovine DD treponeme PCR assays. Since DD treponemes were present in non-pedal tissues in only a small number of samples and animals, they do not appear to be part of the typical treponeme microbiota of the bovine gastrointestinal tract. Interestingly, there was a significant association between rectal presence of *T. phagedenis*-like DD treponemes and the housing period. Given the housing association for both carriage at the rectoanal junction and the occurrence of DD (Murray et al.,

1996; Somers et al., 2005), similarities could be drawn with *Brachyspira* spp., pathogenic spirochaetes responsible for pig dysentery which are spread by the faecal oral route, with increased infection prevalence resulting from group housing (Haggman et al., 2013; Weber et al., 2013). Further studies are required to characterise the contribution of oral and rectal carriage of DD treponemes to BDD transmission.

Given parallels with the non-venereal human skin treponematosis, yaws, where touch is implicated in transmission (Antal et al., 2002), direct skin-to-skin contact may be a major route of transmission of DD treponemes. Recently, foot trimming equipment has been implicated as an important transmission route for DD treponemes, which were identified on the knife blade both before and after disinfection in some cases (Sullivan et al., 2014). Since hoof trimming provides both a direct method of contact, as well as exposure to potentially infected cattle foot tissues, this may well be an important mechanism by which the DD treponemes gain easy access to host tissues and are able to initiate disease. The recently identified chronic necrotic horn lesions might be considered to be a direct cause of such transmission (Sullivan et al., 2014).

Another newly described transmission route may be M4.1, a chronic stage of the DD lesion with an active painful M1 focus. It has been suggested that healed M4 lesions can revert to this state because the lesion was not treated effectively in the first instance and then the infectious agents can be passed from animal to animal again (Berry et al., 2010, 2012).

These newly identified infection reservoirs give a biological basis for many of the well-established risk factors identified from epidemiology based studies (Table 2). Importantly, these infection reservoirs validate previously identified important risk factors and allow a more

thorough argument for better preventative farm management strategies. Indeed, these identified transmission routes can be readily targeted through farm management practices such as better hygiene and thus the results need to be heeded and utilised.

Treatment and control

Given the plethora of data now supporting treponemes as causal of DD, it would be reasonable to propose that treponeme targeted antibiotics, vaccines or transmission blocking may allow for reduction or even eradication of this disease.

Towards effective antibiotic treatment

In an excellent review of DD treatment strategies that explained both relevant research and implementation difficulties, Laven and Logue (2006) identified a lack of peer reviewed published articles describing controlled clinical trials of DD treatment and that relevant research was urgently needed (Laven and Logue, 2006). To assist decisions regarding antibiotic choice on farms, in vitro antimicrobial susceptibility data can be most useful and there have now been several such studies on DD treponemes (Evans et al., 2009a, 2012a; Yano et al., 2010a). These studies clearly identified the most effective antibiotics for use against DD treponemes as penicillin, penicillin derivatives (such as amoxicillin and ampicillin) and the macrolides erythromycin, azithromycin and gamithromycin. Treponemes were least susceptible to sulphamethoxazole, trimethoprim, cefalexin and colistin, and those antibiotics with intermediate susceptibility values included lincomycin, spectinomycin, oxytetracycline, ceftiofur and gentamicin (Evans et al., 2009a, 2012a; Yano et al., 2010a).

Since many commonly used/licensed DD antibiotic treatments have only intermediate treponeme antimicrobial susceptibility values, whilst some healing does occur likely resulting from limited activity against treponemes and destruction of secondary invaders, it is unsurprising that DD frequently recurs. Indeed the newly described DD disease stage (M4.1) is specifically associated with the topically applied, frequently used, antibiotics oxytetracycline and lincomycin (Berry et al., 2010, 2012) with intermediate DD treponeme susceptibilities (Evans et al., 2009a). Thus, M2 lesions treated with such products can result in M4 lesions which can reactivate to M4.1 lesions (Berry et al., 2010, 2012).

In Tables 3 and 4, antibiotic clinical trials are compared with DD treponeme antimicrobial susceptibilities and treatments of human treponematoses. In agreement with DD treponeme antimicrobial susceptibility data, penicillin and azithromycin have been used effectively to treat the human treponematoses, syphilis and yaws, with nearly 100% clinical cure and little recurrence. Long acting penicillin was used to nearly eradicate yaws by the world health organisation (WHO) in the 1960s and now azithromycin is being used by the WHO to finally achieve eradication (Giacani and Lukehart, 2014).

Given the success of human treponeme treatments with antibiotics, it has been proposed that comparable clinical trials with these antibiotics could effectively cure DD (Evans et al., 2012a). As shown in Tables 3 and 4, some known treatment approaches for human treponematoses have been repeated in cattle, although either with different application methods, shorter treatment durations or substantially reduced antibiotic quantities. These sub-optimal bovine treatment trials were likely to have been driven by growing concerns about antibiotic overuse in farm animals and to minimise the quantity of milk that needs to be discarded

according to relevant legislation. However, given that these treatments are very effective against human trepanematoses with little or no disease recurrence (Tables 3 and 4), the data suggests it is highly likely they should be efficacious in cattle.

For human treponematoses, only antibiotics with the highest treponemal susceptibilities are commonly used either by systemic injection or oral administration. For DD the most common antibiotic treatment is topical with antibiotics of intermediate susceptibilities. The time at/above a microorganism's inhibitory concentration is a key pharmacodynamic parameter for β-lactam activity against another pathogenic spirochaete, *Borrelia burgdorferi* (Wormser and Schwartz, 2009). In treatment of human treponematoses, the aim is to maintain a minimum serum penicillin concentration of 0.03 U/mL for 7-10 days in early infections (and 15-20 days in latent infections) (WHO, 1982). Aqueous procaine penicillin G (APPG) provides appropriate penicillin serum levels in humans when 600,000 U (~10,000 U/kg) a day are administered; hence, a 10 day course for syphilis is used (Table 3). However, penicillin preparations with slower absorption rates have been used preferentially in humans, as they only require single doses.

Two preparations, procaine penicillin G in oil with aluminium monostearate (PAM) and benzanthine penicillin G (BPG), provide the correct prolonged serum penicillin dosage with single injection for treatment of the human treponematoses. Whilst PAM is no longer widely available, BPG has become the antibiotic of choice for human syphilis (2.4 million units, effective levels 3-4 weeks) and yaws (1.2 million units, effective levels, 1 week) (WHO, 1982). If these treatments and criteria are then compared with those of β-lactam field trials against DD, the studies of Read and Walker (1998), which showed good cure rate but substantial recurrence rate, used too short a treatment, only using 3 days of APPG or ceftiofur. It might be anticipated that, if

used at an appropriate concentration for longer periods (7-10 days), these treatments might provide a more optimal cure with little recurrence. In that study, the superior results of APPG over ceftiofur are in agreement with reported in vitro data, where ceftiofur requires a higher concentration to be bactericidal (Evans et al., 2012a). Further evidence supporting prolonged penicillin use is a study using cefquinome, another β-lactam, where a 5 day rather than 3 day treatment resulted in a more effective treatment of DD (Laven, 2006) with the authors suggesting further injectable antibiotic studies were needed and a subsequent case report which reported potential eradication with long acting ceftiofur (Bell, 2011).

For macrolide DD studies (Table 3), systemic erythromycin (injection) was comparable with the efficacy of footbath erythromycin (Laven, 2006). However, whilst considered efficacious, erythromycin footbaths resulted in significant improvement of DD lesions in only 60% of animals (Laven and Proven, 2000). In human beings, a minimum of 20 g erythromycin distributed over 10 days orally were required for effective cure of syphilis (Fernando, 1969). Subsequently, a recent study has shown azithromycin in single oral dose at 30 mg/kg has an excellent cure rate against yaws. Unfortunately, this highly efficacious dose is a three-fold increase per kg on the only erythromycin systemic trial in cattle thus far (Laven, 2006). It is clear that further trials are needed for reappraisal of antibiotic selection, application, dose, treatment time and licensing.

If treatments are not effective on all animals on a farm, then lesion recurrence might represent reinfection or treatment failure. In syphilis and yaws, all patient contacts are treated, which is interesting if considering housed dairy cattle, where all animals might be considered contacts, especially given the high stocking densities on many farms. For treatment of yaws, the

WHO treats the entire population if the active case prevalence is > 10% (WHO, 1982). Given that DD is endemic in many countries and the prevalence is typically 20-30% in each herd (Holzhauer et al., 2006; Capion et al., 2008; Barker et al., 2009; Cramer et al., 2009), this suggests whole herd treatment is required on many farms regionally to allow effective treatment and to stop reinfection. Furthermore, in human treponematoses, both clinical and serological cure are generally used in treatment criteria/outcomes (Brown, 1985; Parkes et al., 2004).

When DD was first reported in the UK and USA, there was clear serological distinction between infected and naïve animals, even on the same farms (Walker et al., 1997; Demirkan et al., 1999). However, more recent studies suggest that all the animals in a herd are frequently exposed and seroconvert (Vink et al., 2009). Thus, if we only treat active clinical manifestations, microorganisms may be present in other animals subclinically and their serological status may indicate if treatment is recommended.

In most studies on topical antibiotic treatments, cure rates after 1 month for topical antibiotic treatments of DD tend to be ~60-70% (Holzhauer et al., 2011). One recent study reported no significant difference between DD treatment with lincomycin or oxytetracycline (73 and 68% cure, respectively) (Berry et al., 2010). Whilst this could be considered efficacious, this is not comparable to success rates in treating human treponematoses. Furthermore, rates of recurrence of ~50% have been reported in cattle with DD during 12 month follow up (Berry et al., 2012). In addition, the underlying tissue pathology of many considered cured lesions at 1 month after treatment were suggestive of disease reinitiation (Berry et al., 2010).

Clearly, current antibiotic use with only intermediate susceptibilities from topical (not systemic) applications will only maintain DD lesions, since they are not properly treated and are likely to result in maintenance of an M4/M4.1 infection reservoir and therefore increase disease spread. Historically, it is understandable how topical antibiotics have come to be commonly used, as they demonstrate some efficacy, are not as environmentally polluting as footbaths and, at least for oxytetracycline, are not considered to enter the animal's milk (Britt et al., 1999). However, given the general failure of current treatments to reduce DD on farms, resulting in the disease's endemic status in many countries globally, clinical trials are needed to demonstrate whether the common treatments for human treponematoses may work, even if they do not immediately translate to actual farm use due to milk withdrawal times. From such a benchmark, there could then be development of novel antibiotics not entering the animal's milk supply that are effective against DD. Given the continual use of relatively ineffective antibiotic treatments and how much DD costs financially, if an eradication program farm by farm or region by region could be considered, this might be the best way to control this disease and, in the long term, would be more beneficial for environment, animal welfare and economically. However, given the WHO includes macrolides as a 'highest priority' critically important antimicrobial (CIA) for human medicine and penicillin as a CIA also (WHO, 2011), the veterinary antimicrobial prescriber currently faces a substantial challenge in terms of the routine treatment of DD with these most relevant antimicrobials.

Non-antibiotic control strategies

A bacterin vaccine was developed based on a two treponeme phylotypes, which showed initial promise but subsequently produced poorer results and was withdrawn from market (Keil et al., 2002; Ertze et al., 2006). As we now know, DD lesions typically contain several (≥3-5)

429 treponeme phylotypes (Klitgaard et al., 2008; Nordhoff et al., 2008; Evans et al., 2009c), so it is
430 maybe not surprising that a dual phylotype vaccine failed. Given that some phylotypes remain
431 uncultivable, the use of targeted gene sequencing and recombinant vaccine production could
432 allow for a multivalent vaccine to be produced in the near future that is representative of multiple
433 treponeme phylotypes and therefore is more efficacious. However, given that it has been shown
434 that four *T. phagedenis*-like isolates from DD lesions varied in virulence and antigenicity *in vivo*
435 (Elliott et al., 2007) further studies are needed to characterise such diversity to ensure that any
436 vaccine candidate identified would allow for effective DD protection.
437
438 Towards using farm management to control DD, when taking risk factors (Table 2) into
439 consideration, many issues need to be addressed, including better on-farm housing hygiene,
440 access to pasture, a balanced diet, regular footbathing and hoof trimming with appropriately
441 disinfected equipment. Purchasing new stock from herds with no history of DD or ensuring
442 bought animals have no evidence of DD, whether active or healed, would help to reduce the risk.
443 Further characterisation of infection reservoirs and transmission routes in the future may allow
444 for even better farm management of DD or even removal of specific infection reservoirs.
445
446 Worries about antibiotic use in farm animals means that footbaths have been developed to
447 offer an alternative and their use is associated with a reduced risk of DD (Rodriguez-Lainz et al.,
448 1999). Given the lack of tissue penetration, it is unlikely footbaths can be used to eradicate DD;
449 however, together with other farm management practices, they may help to reduce transmission
450 and allow some healing. Table 5 shows a selection of commonly used footbath solutions with
451 associated efficacies. Copper sulphate is widely used and does show some efficacy. In one study,
452 copper sulphate was more effective than formalin (Teixeira et al., 2010), whilst another

453 demonstrated a comparable cure rate for both, but copper sulphate reduced risk of development
454 of new lesions (Holzhauer et al., 2012). More frequent treatment with copper sulphate has been
455 reported to increase efficacy (Speijers et al., 2012), as does treatment for a longer duration
456 (Logue et al., 2012).
457
458 Unfortunately, the widely used footbath chemicals copper sulphate and formalin are
459 environmentally damaging and carcinogenic respectively, with legislative bodies beginning to
460 ban/limit their use for these reasons, suggesting that they may have limited future capability. As a
461 result, several alternative products have been developed, some of which are comparable in
462 efficacy to copper sulphate (Teixeira et al., 2010; Smith et al., 2014). There is little data provided
463 on recurrence of DD with the use of footbaths (Table 5) and continual regular use is required to
464 keep the prevalence of DD as low as possible (Blowey, 2010). Interestingly, an in vitro method
465 has been developed to assay footbath solutions against DD treponemes (Hartshorn et al., 2013).
466 This study assesses the interaction of footbath solutions with both faeces and microbes, and could
467 be a useful tool in future product development. Interestingly, the efficacy of copper sulphate was
468 severely diminished in the presence of 20% manure, with several alternatives performing better
469 under this condition.
470
471 A variety of non-antimicrobial topical treatments other than footbath solutions have been
472 discussed in a previous relevant review, with many performing no better than tap water (Laven
473 and Logue, 2006) and the most efficacious being very labour intensive; for example triplicate
474 application for 21 days (Britt et al., 1996). Obviously, for any practical treatment, minimal labour
475 is required. Table 5 details recent studies showing the efficacy of several solutions with
476 corresponding regimens. Several treatments now give comparable or better results than topical

antibiotic spray. Unfortunately, follow up studies are not described for the majority of studies and recurrence may be considerable given tissue penetration problems with topical applications. Whilst most topical treatments involve antiseptics (Table 5), more recently there have been novel approaches, such inducing sloughing of necrotic skin with salicylic acid (Schultz and Capion, 2013) or increasing the general hygiene of cows with specifically designed washing systems (Thomsen et al., 2012).

Conclusions

Bovine DD has been with us for at least 30 years and, unless drastic changes to treatment and control can be made, it is here to stay. Given associated animal welfare issues and substantial costs to farmers and the wider economy, substantially more research is needed into this severe infectious disease towards eradication. Studies into appropriate systemic antibiotic use might allow for eradication and stop the continued overuse of less efficacious antibiotics and environmentally damaging footbath solutions. Further studies are needed worldwide to allow for more comprehensive investigations of infection reservoirs and transmission studies. Genomics and proteomics studies are needed to identify relevant vaccine candidates. In the future, hopefully, we may be able to finally prevent this disease by vaccines, good farm practice and/or effective treatment.

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Table 1
Current bovine digital dermatitis scoring system with pathological descriptions.

Risk factors	Macroscopic description	Underlying pathology
M1	A small focal active red/grey circumscribed lesion < 2 cm wide with 1 mm wide red foci (Dopfer et al., 1997)	Partial epithelium loss; tissue degradation with fibrin islands; hyperplastic stratum corneum; acanthotic stratum spinosum; dermal perivascular infiltration with neutrophils and mononuclear cells located in the dermis and epidermis (Read and Walker, 1994, 1998; Dopfer et al., 1997)
M2	A painful large ulcerative, red/grey active lesion > 2 cm wide (Dopfer et al., 1997)	Stratum corneum now absent; haemorrhages at lesion edge; increased degradation and acanthosis; rete ridge formation; microabscesses; increased dermal perivascular infiltration; in the epidermis there are now mostly eosinophils and neutrophils (Read and Walker, 1994, 1998; Dopfer et al., 1997)
M3	A healing, painless brown scab; typically seen after treatment (Dopfer et al., 1997)	Not determined
M4	A chronic stage presenting as dyskeratosis or irregular proliferative hyperkeratotic overgrowths (Dopfer et al., 1997)	Highly proliferative epidermis with rete ridge formation and pronounced stratum corneum hyperplasia, acanthosis of the stratum spinosum; numerous horny columns surrounded by haemorrhages/cell detritus; stratum granulosum shows empty vacuoles, more neutrophils than mononuclear cells in epidermis, many plasma cells in dermis (Read and Walker, 1994, 1998; Dopfer et al., 1997)
M4.1	A chronic stage with active, painful M1 focus (Berry et al., 2012)	Not determined
M5 or M0	Healthy skin with no evidence of previous lesion (Berry et al., 2012)	Not determined

1061 **Table 2**
1062 Identified risk factors for bovine digital dermatitis (DD), with underlying pathobiological basis.
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Risk factors	Association with DD presence	Underlying pathobiological basis
Foot hygiene	Increased muddiness of environment associated with an increased risk of DD compared with less muddy environment (Rodríguez-Lainz et al., 1996a; Rodríguez-Lainz et al., 1996b).	Required maceration (continual exposure to moisture) of skin required to transmit DD in experimental model (Gomez et al., 2012; Read and Walker, 1996). Presence of digital dermatitis treponemes in the bovine GI tract suggests faecal shedding (Evans et al., 2012b)
	Increased animal hygiene associated with a reduced risk of DD (Hultgren and Bergsten, 2001)	As above
	Footbathing reduces the risk of DD compared to farms that do not footbath (Rodriguez-Lainz et al., 1999)	Decreases exposure of feet to unhygienic conditions. As above
Claw trimming	Lack of washing hoof trimming equipment between cows increased the risk of DD (Wells et al., 1999)	Disease considered highly contagious and transmitted through hoof trimming equipment (Wells et al., 1999). Presence of DD treponemes identified frequently on hoof trimming equipment (Sullivan et al., 2014a)
	Use of a primary hoof trimmer who trimmed cows hooves on other operations increases the risk of DD (Wells et al., 1999)	Disease considered highly contagious and transmitted through hoof trimming equipment (Wells et al., 1999). Presence of DD treponemes identified frequently on hoof trimming equipment even after disinfection in some cases (Sullivan et al., 2014a)
	Regular claw trimming twice a year reduces the risk of DD compared with longer durations between trimming (>7 months) (Somers et al., 2005)	Hoof trimming considered important for ruminant foot health since it reduces mechanical pressures (Toussaint Raven, 1985)
Housing and land access	Cows kept on pasture have a decreased risk of DD than cows housed indoors (Blowey and Sharp, 1988; and Rodríguez-Lainz et al., 1996b; Onyiro et al., 2008).	Increases exposure of cows to poor hygiene and moist foot conditions, which are a risk factor as above
	Cows with daily access to pasture in winter have a decreased risk of DD compared to those animals which do not (Wells et al., 1999)	Increases exposure of cows to poor hygiene and moist foot conditions, which are a risk factor as above
Heifer replacement	Buying in new heifers increases the risk of DD (Rodriguez-Lainz et al., 1996; Wells et al., 1999)	Since DD is considered to be a contagious infectious disease, it can be introduced with affected heifers (Read and Walker, 1998). DD asymptomatic animals harbouring DD treponemes in rectal tissues may shed DD treponemes and therefore transmit infection (Evans et al., 2012b). Macroscopically healed lesions may reactivate and cause subsequent spread (Berry et al., 2012; Berry et al., 2010)
Flooring type	Grooved concrete > Smooth/slatted concrete > Textured concrete for increased risk of DD (Wells et al., 1999)	Abrasiveness or slipperiness of concrete (Wells et al., 1999)
	Increased risk of DD from solid floor compared to use of rubber-slatted flooring (Hultgren and Bergsten, 2001)	Improved hygiene at the rear end of cows due to optimal flooring allowing drainage of urine and faeces (Hultgren and Bergsten, 2001)
	Increased risk of DD from solid floor compared to use of slatted flooring with scraper system (Somers et al., 2005)	Regular removal of manure reduces unhygienic moist conditions (Somers et al., 2005)
Nutrition	Cows receiving maximum concentrate supplement 2 weeks after calving are at increased risk of DD compared to those receiving their maximum concentrate supplement at 3 weeks (Somers et al., 2005)	Excessive concentrate shortly after calving may enhance the postnatal metabolic imbalance. Higher metabolic stress increases susceptibility to diseases and therefore DD (Enevoldsen et al., 1994)
	Feeding of by-products (Somers et al., 2005)	By-products are typically protein-rich and may cause an inappropriate diet with excessive protein intake identified as a potential risk factor for DD previously (Somers et al., 2005)
	Animals with a body condition score too high or low have a higher risk of developing DD (Schopke et al., 2013)	Inappropriate diet weakens immune system, resulting in an increased susceptibility to infectious diseases (Schopke et al., 2013)
Parity	First parity cows have increased risk of DD (Read and Walker, 1998; Rodriguez-Lainz et al., 1999; Somers et al., 2005)	Primiparous cows exposed to severe changes in nutrition and environment in the period surrounding calving (Somers et al., 2005) and considered to have less immunity (Blowey et al., 1994; Read and Walker, 1998)
Lactation	Increased risk of DD during lactation than dry period (Read and Walker, 1998; Murray et al., 2002; Somers et al., 2005)	Lactating cows frequently shed more liquid faeces due to diet, whereas dry cows excrete solid faeces, since they are fed a higher proportion of roughage. Liquid faeces are associated with more unhygienic and moist floor conditions (Somers et al., 2005)

Table 3

Comparison of bovine digital dermatitis (DD) treatment clinical trials, DD treponeme antibiotic in vitro susceptibility data and known effective treatments for human trepanemotoses: Systemic treatment.

DD Treatment	Response	Recurrence	MBC_{90} [a]	References	Human treponematoses treatment [b]	Response	Recurrence	References
Aqueous procaine penicillin G, IM, 3 days, 18,000 U/kg, twice daily	Highly responsive, all (100%) healed	Yes, in 25% of cases, 7-12 weeks after healing	0.1875	Read and Walker (1998)	Early syphilis: Procaine penicillin IM 600,000 units/day once daily for 10 days	Highly responsive (100% cured)	None	Idsoe et al. (1972)
					Early syphilis: Penicillin G benzanthine 2.4 MU, single injection	Highly responsive (97% cured)	1% after 2 years	Smith et al. (1956)
					Yaws: Penicillin G benzanthine 1.2 MU, single injection	Highly responsive (96% cured)	1.5% after 6 months	Grin et al. (1954)
Ceftiofur sodium, IM, 3 days, 2 mg/kg, daily	Highly responsive, with 87% healed	Yes, in 27% of cases, 7-12 weeks after healing	24	Read and Walker (1998)	-	-	-	-
Cefquinome, IM, either 3 days or 5 days 1 mg/kg	5 days cefquinome lesion scores better than 3 day use or erythromycin footbath	Not reported	Not reported	Laven (2006)	-	-	-	-
Erythromycin, IM, 10 mg/kg, day 1	Lesion scores comparable to erythromycin footbath but not as good as cefquinome	Not reported	0.1875	Laven (2006)	Alternative to penicillin for early syphilis: Erythromycin, oral, 500mg per 6 hours for 10 days (total 20g)	Highly responsive (100% cured)	None	Fernando (1969)
					Penicillin alternative for early syphilis: Azithromycin, oral, 1 g initially, then 500 mg daily for 8 days	Highly responsive (100% cured)	None	Gruber et al. (2000)
					Also note recently reported penicillin alternative for yaws: Azithromycin, oral, 30 mg/kg, day 1	Highly responsive (96% cured compared to 95% in benzanthine Penicillin G group)	None	Mitja et al. (2012)

[a] Reported using in vitro susceptibility testing of DD treponemes as described by (Evans et al., 2009a, 2012a) whereby in those studies the cumulative susceptibility results across all BDD spirochaetes tested are expressed as MBC90, the concentration at which 90% of digital dermatitis associated spirochaetes are killed.

[b] Average weight of a mature Holstein Friesian cow is 680 kg and average weight of a human being is 62 kg.

Table 4

Comparison of bovine digital dermatitis (DD) treatment clinical trials, DD treponeme antibiotic in vitro susceptibility data and known effective treatments for human trepanemotoses: Topical treatment.

DD Treatment	Response	Recurrence	MBC_{90} [a]	References	Human treponematoses treatment [b]	Response	Recurrence	References
Oxytetracycline, single treatment with bandage, 5 mL applied at 100 g/L	Cure rate at day 29 was 13·8% for primiparous and 38·7% in multiparous cows	Not described	6	Nishikawa and Taguchi (2008)	Oxytetracycline, 2 g orally for 5 days	Highly responsive, Clinical cure at 3 months	Not described	Loughlin et al. (1951)
Oxytetracycline, day 1 with bandage, 5 mL applied at 100 g/L, treatment repeated day 6 and new bandage removed 2 days later	Cure rate 87% at 32 days after treatment	Not described	6	Manske et al. (2002)	As above			
Lincomycin (10 g) or oxytetracycline (10 g) paste, single treatment with bandage (day 1), bandage removed day 4	Cure rates 73% at day 14 and 68% at day 30; no significant difference between antibiotics	Not described but 50% of cured lesions at day 30 were histologically considered active or incipient	48 or 6	Berry et al. (2010)	-	-	-	-
Lincomycin (10 g) paste, single treatment with bandage (day 1), bandage removed day 4, cows checked and retreated monthly for 1 year	-	High recurrence rate (54%) during 1 year follow up	48	Berry et al. (2012)	-	-	-	-
Lincomycin 0.5 g/L and spectinomycin 1.0 g/L (50:50), spray once daily for 10 days	Only 1.0 g/L showed significant improvement day 12 and significant cure compared to control (66%) at days 30 and 90	Not described	48/48 and a resistant isolate (> 12,288)	Berry and Maas (1997)	-	-	-	-
Erythromycin footbath (0.035 g/L), day 1	Assessed day 4 and lameness and several lesion scores were significantly better than control	Not described	0.1875	Laven and Proven (2000)	See oral erythromycin and azithromycin above.	-	-	-

Table 5

Comparison of recent non-antibiotic bovine digital dermatitis (DD) treatment clinical trials.

DD Treatment	Response	Recurrence [a]	Mode of action	References
Footbath				
Copper sulphate, 2% (w/v), daily for 7 days	Comparable to 2 days erythromycin footbath treatment in reducing lesion score	Not described	Bactericidal antiseptic/disinfectant	Laven and Hunt (2002)
Copper sulphate, 5% and 2% (W/V), hypochlorite 2% (W/V) weekly	Copper sulphate 5% (W/V) resulted in significantly less DD when compared with 2% (W/V) copper sulphate, hypochlorite or control	Not described	Bactericidal antiseptic/disinfectant	Speijers et al. (2010)
Formalin, 2.5% (W/V), daily for 7 days	Comparable to 2 days erythromycin footbath treatment in reducing lesion score	Not described	Bactericidal antiseptic/disinfectant	Laven and Hunt 2002)
Peracetic acid, 1% (V/V), daily for 7 days	Comparable to 2 days erythromycin footbath treatment in reducing lesion score	Not described	Bactericidal antiseptic/disinfectant	Laven and Hunt 2002)
Acidified copper sulphate, 4%, twice daily, 5 days a week; formalin 4%, 1 day each fortnight	Cure rates between treatments not different but risk of new lesions was three times less for copper sulphate	Not described	Bactericidal antiseptic/disinfectant	Holzhauer et al. (2012)
Dragonhyde, 5% (V/V), twice weekly for 4 weeks	Dragonhyde is comparable to copper sulphate and better than formalin when comparing the number of DD lesions in each group	Not described	Bactericidal antiseptic/disinfectant	Teixeira et al. (2010)
Commercial footbaths containing glutaraldehyde, organic acids or quaternary ammonium compounds, twice weekly for 8 weeks	Difference between treatment and control (in terms of cure and prevention) were not significantly different for any of the three treatments applied	Not described	Bactericidal antiseptic/disinfectant	Thomsen et al. (2008)
Organic acid footbath solution with tea tree oil, 3% (V/V), daily, 5 days a week for 9 weeks	Organic acid footbath solution with tea tree oil is comparable to copper sulphate 5% (V/V) in decreasing the proportion of M1/M2 lesions	Not described	Bactericidal antiseptic/disinfectant	Smith et al. (2014)
Direct topical treatment				
Salicylic acid, 10 g applied with bandage, day 1	Increased lesion healing and improvement when compared to chlortetracycline spray as a control	Not described	Sloughing of necrotic skin	Schultz and Capion 2013)
Protexin Hoof-Care (containing metallic salts and organic acids), days 1 and 4	Reduced lameness effectively; comparable to oxytetracycline spray	Not described	Bactericidal antiseptic/disinfectant	Kofler et al. (2004)
Water-based gel with activated copper and zinc chelate, 5 g applied on days 1, 3 and 7	Cure rate of DD lesions treated with gel chelate was significantly better than lesions treated with chlortetracycline	At day 7 all M2 cured but recurrence/reinfection at days 21 (2%) and 28 (8%)	Bactericidal antiseptic/disinfectant	Holzhauer et al. (2011)
Non-antimicrobial cream, day 1	Reduced DD significantly compared to control; comparable to lincomycin spray	Yes (percentage not clarified)	Bactericidal antiseptic/disinfectant	Moore et al. (2001)
Automated hoof washing with water and 0.4% soap solution, daily, for 64 days	Reduced DD significantly compared to no washing	Not described	Tackling general foot hygiene of animals	Thomsen et al. (2012)

[a] Recurrence in this review is whether lesions recur after treatment had finished (not during).