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REVIEW ARTICLE

Advances in the understanding, detection and management of equine strangles

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Summary

Streptococcus equi subspecies *equi* (*S. equi*) is the causative organism of the upper respiratory disease of equids, strangles, characterised by pyrexia, lymphadenopathy and mucopurulent nasal discharge. Strangles was first reported over 750 years ago and continues to be of significance in equine populations across the globe. This review discusses how *S. equi* has adapted, the clinical manifestation of strangles, and how clinicians and caregivers can tackle the disease in the future. *S. equi* evolved from the commensal, and occasionally opportunistic pathogen, *Streptococcus equi* subspecies *zooepidemicus* refining its capabilities as it became host restricted. The success of *S. equi* can be attributed to its ability to cause both acute and persistent infection, the latter occurring in about 10% of those infected. In this carrier state, *S. equi* persists in the guttural pouch without causing clinical signs, intermittently shedding into the environment, and encountering naïve animals. Insight into the *S. equi* genome and lifestyle has led to advances in diagnostic assays and the development of a safe and efficacious recombinant-fusion vaccine, giving clinicians and caregivers the tools to better combat this infection. Alongside rigorous biosecurity protocols and pragmatic control measures such as screening new arrivals for exposure and carrier status, these new technologies demonstrate that strangles can be an increasingly preventable infection.

KEYWORD
horse, strangles, *Streptococcus equi*

INTRODUCTION

Strangles was first described in 1256 (Ruffo, 1256), although the disease and its causative organism *Streptococcus equi* subspecies *equi* (*S. equi*), first identified by Schütz (1888), are believed to have been infecting equids for much longer. In the 17th century, strangles was considered an inevitability; indeed, it was suggested that the disease was transmitted in utero due to the high numbers of horses that contracted the infection across varied backgrounds, genetic profiles and management systems (Paillot et al., 2017; Solleysel, 1664).

As was long suspected (George et al., 1983) and later confirmed (Newton, Wood, Dunn, et al., 1997; Timoney et al., 1998), *S. equi* persists in the guttural pouch, without causing clinical disease in a proportion of animals. *S. equi* survives in this low nutrient state, intermittently shedding into the environment, allowing the organism to spread to naïve individuals; indeed, its success as a pathogen can be attributed to the ability to cause both acute and persistent disease. Chronically infected equids rarely show clinical signs, presenting a major obstacle to the prevention and control of outbreaks (Verheyen et al., 2000). The challenges associated with detecting

carriers are a key reason for the perpetual spread of *S. equi* (Pringle, Venner, et al., 2020).

STREPTOCOCCUS EQUI

Pathogenesis

Contact with infected equids represents the primary cause of strangles infection; although, *S. equi* has been shown to persist in the environment for up to 34 and 13 days in wet and dry sites, respectively, and environmental persistence is an additional source of contagion (Durham et al., 2018). Equids become infected via the oronasal route, likely through ingestion of contaminated material (Boyle et al., 2018). Upon entry, *S. equi* attaches to the crypt cells of the lingual and palatine tonsillar tissue, before translocating to regional lymph nodes (Timoney & Kumar, 2008).

Virulence factors act to mitigate the effects of the host immune response: the hyaluronic acid capsule aids immune evasion (Woolcock, 1974), IgG endopeptidases are secreted to cleave antibodies (Lannergard & Guss, 2006) and antiphagocytic binding proteins such as Se18.9 are secreted (Tiwari et al., 2007). Additionally, SeM surface proteins block immune activity by binding to fibrinogen and immunoglobulin (Meehan et al., 2009; Timoney et al., 1997). High morbidity is achieved through this antiphagocytic activity, resulting in intra- and extracellular multiplication in tonsillar and lymphoid tissue, including regional lymph nodes (Timoney & Kumar, 2008). Additionally, *S. equi* can produce a microscopic biofilm with potential adhesive functions (Steward et al., 2017) that may play a role in persistence (Figure 1).

If visible lymph node abscessation occurs, it is not until 3–5 days after their infiltration, as large numbers of neutrophils are attracted to the site through the interaction of complement-derived factors and pathogen-associated molecular patterns such as peptidoglycan (Muhktar & Timoney, 1988). The ability of *S. equi* to import iron has been linked to its growth within these abscesses, with the secreted molecule equibactin facilitating this acquisition (Harris et al., 2015; Heather et al., 2008). If abscesses occur, they rupture into the airways, guttural pouches or through the skin 7–28 days after initial infection (Waller, 2014): abscesses of the retropharyngeal lymph nodes typically rupture into the guttural pouches, draining into the nasopharynx and subsequent nasal passages resulting in copious mucopurulent discharge.

Severity is dose-dependent with around 10,000 colony-forming units required to cause disease in a mature and immunocompetent equid (Boyle et al., 2018). Increasing the number of colony-forming units will result in more severe disease and a shorter incubation period, which can vary from 1 to 28 days (Boyle et al., 2018).

Shedding of *S. equi* typically commences 1–2 days after the onset of pyrexia and persists for 2–3 weeks; equids can remain infectious for over 6 weeks after purulent nasal discharge has resolved (Boyle et al., 2018).

Streptococcus equi evolution

Streptococcus equi is a host-restricted pathogen of equids, thought to have evolved from the opportunistic pathogen *Streptococcus equi* subspecies *zooepidemicus* (*S. zooepidemicus*) (Harris et al., 2015; Holden et al., 2009; Waller et al., 2011). *S. equi* and *S. zooepidemicus* are closely related, sharing over 97% of their DNA (Holden et al., 2009).

Streptococcus equi and *S. zooepidemicus* have many structural and functional differences (Bannister et al., 1985; Holden et al., 2009; Lindmark et al., 2001) but share a common phage pool; their divergent evolution is a result of functional loss, pathogenic adaptation and genetic exchange (Holden et al., 2009). The deletion of the clustered regularly interspaced short palindromic repeats (CRISPR) locus in *S. equi* is thought to have favoured the acquisition of genetic elements, at the expense of genome stability (Waller & Robinson, 2013). A notable difference between the two genomes is the presence of the equibactin locus in *S. equi*, involved in iron acquisition (Heather et al., 2008), which may have been the speciation event that distinguishes *S. equi* from *S. zooepidemicus* (Harris et al., 2015; Heather et al., 2008; Holden et al., 2009).

The *S. equi* genome is larger than that of *S. zooepidemicus*, partly because of its plasticity and the procurement of many mobile genomic elements, which have been crucial in the development of *S. equi* as a pathogen (Holden et al., 2009). The loss of genes not required to cause strangles has reduced the ancestral capabilities of *S. equi*, leading to host restriction (Waller et al., 2011); as a result, *S. equi* is only able to cause disease in equids, whereas *S. zooepidemicus* can infect a wide variety of mammalian hosts (Blum et al., 2010; Las Heras et al., 2002; Pelkonen et al., 2013; Pisoni et al., 2009; Priestnall et al., 2010; Salasia et al., 2004).

Streptococcus equi genome changes during persistent infection

Streptococcus equi has been characterised as possessing a dynamic genome with the ability to diversify and decay; mutations relating to metabolic streamlining and the loss of virulence have been noted in chronically infective isolates (Harris et al., 2015). The endemicity of *S. equi* can, in part, be attributed to its ability to persist in the guttural pouch following an infection, surviving in a low-nutrient state, yet intermittently shedding and thus exposing naïve animals to bacteria.

Genomic decay during persistent infection may reduce transmissibility and result in a lessened ability to cause severe acute disease, such as with the deletion of the equibactin locus, which is linked to the development of lymph node abscesses; although, the organism undoubtedly remains infectious (Harris et al., 2015). Individuals with residual immunity such as equids that are older or vaccinated, and foals with maternal antibodies can develop a milder form of disease, termed 'atypical' strangles (Prescott et al., 1982). This presentation may be caused by a reduction in virulence in isolates where deletions

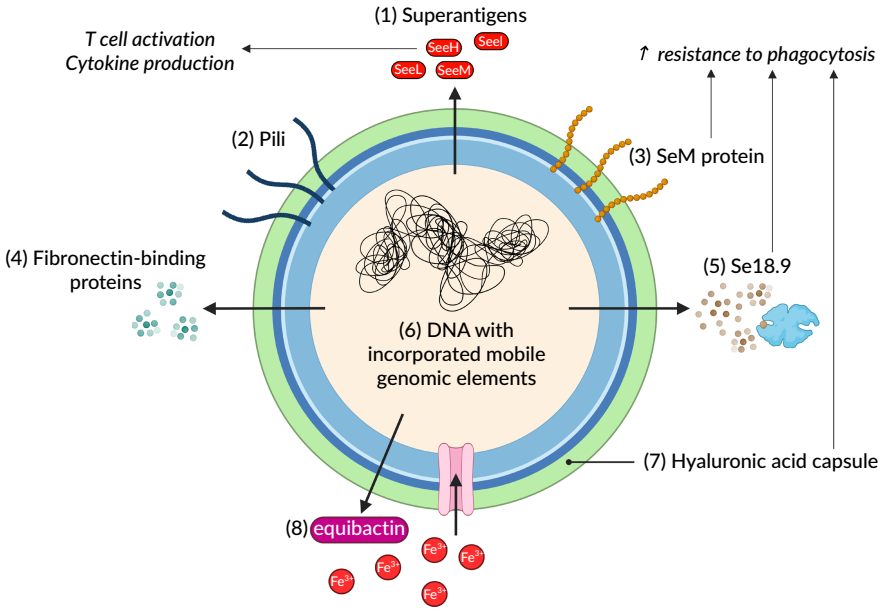

FIGURE 1 Virulence factors of *Streptococcus equi*. (1) Superantigens (SeeL, SeeH, SeeI, SeeM): Cross-link MHC class II and the T cell receptor generating an inappropriate activation of the immune response; (2) Pili: Longer pili compared to *S. zooepidemicus* to penetrate the capsule and bind to collagen more effectively; (3) SeM protein: Bind to fibrinogen and immunoglobulin, inhibiting C3b complement deposition. Targeted by the single and dual ELISA serological tests; (4) Se18.9: Secreted protein that binds to Factor H and interferes with complement activation; (5) Fibronectin-binding proteins (SFS, FNE): Assists with selectively binding to equine tissue and interferes with the attachment of competing pathogens such as *S. zooepidemicus*; (6) DNA and mobile genomic elements: The genome has acquired mobile genomic elements, such as prophage, increasing pathogenicity; (7) Hyaluronic acid capsule: Increased capsule depth compared to *S. zooepidemicus* enhancing resistance to phagocytosis, but reducing mucosal adherence; (8) Equibactin: Siderophore involved in iron acquisition, linked to the development of lymphadenopathy. Not present in *S. zooepidemicus* and lost in some carrier isolates. Created in BioRender.com by Luke McLinden.

in the genome are present (Waller, 2016), as with the outbreak described by Tscheschlok et al. (2018) where the strain of *S. equi* had a deletion in the SEQ_0402 gene, which likely attenuated it.

Morris et al. (2021) analysed the genomes of 35 *S. equi* isolates recovered from horses in Pennsylvania and Sweden to investigate changes that might explain long-term persistence in recovered horses. Whilst no consistent changes in the genomes of isolates from carrier horses were identified, the genomes of some individual isolates recovered from persistently infected horses were found to contain deletions in SeM and the citrate locus. Therefore, Morris et al. (2021) provides further evidence of genome decay in isolates from persistently infected horses that differs from one carrier to another, potentially reflecting the varied selective pressures that are exerted on *S. equi* as this organism persists within the guttural pouch.

A complex interplay between the host and causative agent is suggested (Harris et al., 2015; Morris et al., 2021) in which genomic plasticity could play a central role; this is an opportunity for further research with an emphasis on understanding host, as well as pathogenic, factors such as immunity.

Global endemicity

Equids are widely used and transported between geographic regions and strangles continues to spread as rapidly as ever (Leadon et al., 2008; Mitchell et al., 2021). Strangles is endemic worldwide, with only Iceland remaining free from the disease, due to a self-imposed import ban of equids and geographical isolation (Björnsdóttir et al., 2017). Population analysis of 670 isolates from 19 countries (Mitchell et al., 2021) revealed the extent of the international transmission that results in the endemicity of strangles across the world. The international transmission of *S. equi*, as demonstrated by Mitchell et al. (2021), is in accordance with the first criterion of the World Organisation of Animal Health listing of terrestrial animal diseases. The other three criteria are demonstrated elsewhere (Björnsdóttir et al., 2017; Boyle et al., 2018); therefore, it was recommended strangles be added to this listing (Mitchell et al., 2021).

CLINICAL MANIFESTATION

Acute *Streptococcus equi* infection

Strangles is characterised by sudden pyrexia, mucopurulent intermittent nasal discharge and the abscessation of the submandibular and retropharyngeal lymph nodes (Timoney et al., 1998). Less common clinical signs include respiratory signs, pharyngeal swelling, lethargy, inappetence, dysphagia, depression and the presence of chondroids (Rendle et al., 2021). Although strangles has a low mortality rate,

severe swelling of abscesses in the lymph nodes can lead to significant inflammation, asphyxia and, ultimately, death.

As abscesses form and subsequently rupture, empyema of the guttural pouch or upper respiratory tract can occur. Intermittent expulsion of this thick highly infectious pus is important for the resolution of the infection and removal of bacteria (Boyle et al., 2018); it results in mucopurulent nasal discharge and a cough, present in around half of equids with guttural pouch empyema (Judy et al., 1999). Abscessation and pharyngitis can obstruct the upper respiratory tract, resulting in dyspnoea and dysphagia, alongside potential temporary laryngeal hemiplegia (Boyle et al., 2018).

Systemic and mucosal immune responses are evident 2–3 weeks of post-infection, and this immunity wanes over time (Boyle et al., 2018). Hamlen et al. (1994) showed that 75% of foals exposed to *S. equi* 6 months after recovering from strangles were protected from severe infection, corroborated by historical and contemporary literature (Boyle et al., 2018; Todd, 1910), although no animals were completely protected from clinical signs. The use of antimicrobial therapy early in acute strangles has been demonstrated to interfere with the persistence of humoral immunity (Pringle, Storm, et al., 2020).

The term 'atypical' strangles is used to describe a milder presentation of the disease, in which clinical signs are lessened or absent. The disease presentation may be milder due to an attenuated strain of *S. equi* (Tscheschlok et al., 2018), the presence of residual immunity (Hamlen et al., 1994), a low infective dose or a combination of these factors. Strangles can present with a range of clinical signs (e.g. pyrexia, lymphadenopathy and nasal discharge) and with different severities; therefore, classification as 'typical' or 'atypical' is misleading. Crucially, the severity of disease is not predictive of infectivity, as an animal with a milder presentation can still cause more severe disease in other animals.

Complications of *Streptococcus equi* infection

Streptococcus equi has the potential to spread haematogenously, via lymphatics, septic focus or by direct aspiration of purulent material (Boyle, 2017). Common sites include the lung, mesentery, liver, spleen, kidney and brain (Boyle et al., 2018; Sweeney et al., 1987); additional clinical signs are dependent on the location of abscesses. This presentation is known as metastatic or 'bastard' strangles and has been documented since the 17th century (Solleysel, 1664).

Streptococcus equi infection is the most common cause of purpura haemorrhagica, but vaccination with M-protein-containing vaccines, other bacteria, viruses and neoplasia can similarly result in purpura complexes and vasculitis (Mallicote, 2015).

Myopathies can be seen with *S. equi* infection, with three predominant presentations (Boyle et al., 2018): muscle infarctions (Kaese et al., 2005) and rhabdomyolysis with either acute myonecrosis or progressive atrophy (Sponseller et al., 2005; Valberg et al., 1996).

Persistent *Streptococcus equi* infection

Once ruptured, abscesses of the retropharyngeal lymph nodes typically drain into the guttural pouches, resulting in guttural pouch empyema. Most strangles cases are cleared within 6 weeks, but some animals can enter a carrier state, continuing to shed *S. equi* following the apparent resolution of an acute infection (Newton, Wood, & Chanter, 1997; Newton, Wood, Dunn, et al., 1997). If the purulent material is not cleared and loses fluid, this can form chondroids over time; both empyema and chondroids can act as chronic reservoirs of *S. equi* (Judy et al., 1999; Newton, Wood, Dunn, et al., 1997).

An average of 10% of infected individuals in an outbreak develop into carriers (Boyle et al., 2018; Sweeney et al., 2005); although, this figure may be an underestimate and is highly variable between outbreaks, with detection rates being limited by current diagnostic sensitivity (Pringle et al., 2019). Carriers intermittently shed bacteria into the environment, leading to recurrence and perpetuation of strangles within their herd as well as transmission to naïve individuals (Mallicote, 2015).

There is no consensus on the question of what constitutes a carrier animal, and the answer can be argued from a number of different perspectives. The gross appearance of the guttural pouches demonstrates a spectrum of persistence, from a grossly normal but microbiologically active biofilm (Steward et al., 2017) to the presence of purulent material or chondroids harbouring *S. equi*. Likewise, the chronicity of infection and presence of an observable immune response on a serological ELISA might determine the risk of infection propagation (Ivens & Pirie, 2021). The polymerase chain reaction (PCR) status and associated cycle threshold number, indicative of bacterial load, is often used to identify carriers, but this may be too simplistic in some cases as little is inferred about the viability and infectivity of the *S. equi* identified.

The following definition is proposed: a strangles carrier is an equid in which a viable population of *S. equi* persists and continues to shed, intermittently or continuously, following the apparent resolution of infection. These carriers can be divided into categories based on gross signs of infection (e.g. the presence of chondroids within the guttural pouch), immune status, serological status, chronicity of infection (e.g. short-term carriers that have recently been exposed and long-term carriers that have harboured *S. equi* for months/years) and bacterial load. For clinical practitioners, a division based on gross signs of infection may be most appropriate with carriers being categorised as symptomatic or asymptomatic accordingly.

DIAGNOSIS OF STRANGLES

Diagnosis of acute *Streptococcus equi* infection

The diagnosis of strangles relies on a thorough understanding of an animal's history, in particular with respect to onset, management structures, and possible exposure, including the history of travel, or new arrivals to the equestrian facility (Boyle et al., 2018).

Clinical signs can be variable and nonspecific; indeed, not all animals develop clinical signs (Boyle et al., 2018; Tscheschlok et al., 2018). Nevertheless, they form a vital part of any clinical diagnosis, especially during an outbreak where the testing of all affected individuals may not be necessary (Rendle et al., 2021).

Pathogen identification historically relied on the culture of *S. equi* due to its low cost and wide availability (Waller, 2014). However, sensitivity can be as low as 30%–40% (Boyle et al., 2012; Lindahl, Båverud, et al., 2013; Pusterla et al., 2021), and other beta-haemolytic Streptococci such as *S. zooepidemicus* can complicate interpretation (Boyle et al., 2018). Low levels of bacterial shedding, the presence of host-produced growth inhibitors, sample site and poor sampling technique can also lead to false-negative results (Pusterla et al., 2021).

Advances in PCR (Baverud et al., 2007; Noll et al., 2020; Webb et al., 2013; Willis et al., 2021) and loop-mediated isothermal amplification (LAMP) assays (Boyle et al., 2018) have improved the sensitivity and specificity of the detection of *S. equi* and these assays are now regarded as the gold standard (Boyle et al., 2018). The first PCR assays for *S. equi* were designed to detect a part of the SeM DNA sequence (Timoney & Artiushin, 1997); however; a homologue of SeM is known to exist in *S. zooepidemicus* resulting in cross-reaction (Kelly et al., 2006). In addition, SeM is variably found within the *S. equi* genome, particularly in persistently infective isolates (Chanter et al., 2000; Harris et al., 2015), limiting the diagnostic value of assays that only target SeM. Other PCR assays detect non-SeM sequences (Baverud et al., 2007; Boyle et al., 2016) or have multiple gene targets such as the commercially available triplex assay, which targets two *S. equi* genes (SEQ_2190 and eqbE) and an internal control (Webb et al., 2013).

Polymerase chain reaction and LAMP assays detect DNA of live and dead bacteria indiscriminately; although efforts to determine the physiological state and viability of *S. equi* using molecular approaches show promise (Pusterla et al., 2018). Despite the potential for false-positive results, all positive PCR cases should be taken seriously, even if they are culture-negative (Boyle et al., 2018; Pusterla et al., 2018; Rendle et al., 2021; Waller, 2014). Identification of animals with clinical signs consistent with strangles, regardless of the PCR result, should result in strict movement restrictions and biosecurity protocols (Rendle et al., 2021; Willis et al., 2021).

Advances in diagnostics and surveillance are interlinked: techniques such as quantitative PCR (Webb et al., 2013), nested PCR (Noll et al., 2020) and LAMP assays (Boyle et al., 2021) are rapid and possess high sensitivities and specificities. These technologies allow for the creation of clinically valuable surveillance schemes (McGlennon, 2019), with both laboratory and veterinary contributors. Point-of-care assays have limitations in detection threshold, but have the potential to reduce diagnostic turnaround times and provide a simpler option to caregivers (Slovis et al., 2020). This would allow for the screening of high-risk animals, reducing diagnostic guesswork and ensuring well-timed enaction of biosecurity measures.

The successful identification of *S. equi*, whether through bacterial culture or molecular methods, is dependent on the stage of infection (Rendle et al., 2021) and the sampling site and technique used (Boyle et al., 2017). A single negative test result does not equate to the absence of infection and multiple different samples may be required to obtain a positive result (Boyle et al., 2018). *S. equi* is only present transiently on the nasal mucosa and is often undetectable in a nasopharyngeal swab or wash sample until the lymphoid abscesses rupture, which typically occurs 1–4 weeks after infection (Rendle et al., 2021). Similarly, guttural pouch washes will yield negative results in the initial stages of infection, until the retropharyngeal lymph node abscesses rupture (Boyle et al., 2018). Nasal swabs are only recommended when an equid has active mucopurulent nasal discharge (Lindahl, Båverud, et al., 2013). Aspiration of a mature lymphoid abscess can be used to confirm *S. equi* infection and is often optimal during this stage of the disease (Boyle et al., 2018).

Diagnosis of persistent *Streptococcus equi* infection

Carriers of *S. equi* do not differ clinically and cannot be diagnosed on the basis of inflammatory markers, including white blood cell counts and serum amyloid A (Christoffersen et al., 2010; Davidson et al., 2008; Pringle, Venner, et al., 2020); therefore, carrier status has little impact on systemic inflammation. There is conflicting evidence on the utility of endoscopy scoring and *S. equi* has been demonstrated to produce a microscopic biofilm, microbiologically positive but grossly normal, with potential adhesive functions (Steward et al., 2017). Many carriers have been shown to possess grossly normal guttural pouches at 6 months and beyond following an outbreak (Pringle, Venner, et al., 2020; Riihimäki et al., 2016). The timing of guttural pouch examination is likely to influence findings as Boyle et al. (2017) found distinct differences are visible in many carriers at a median time of 3 months after an outbreak.

Endoscopically guided guttural pouch lavage followed by quantitative PCR is recommended for the detection of persistent infections (Boyle et al., 2018). This technique provides visualisation of the guttural pouch, allowing identification of chondroids, inflammation or empyema; although, contamination of equipment can result in false-positive results (Svonni et al., 2020). Guttural pouch lavage has been validated as superior to a single nasopharyngeal swab or lavage (Boyle et al., 2017). However, nasopharyngeal lavage on three separate occasions has been demonstrated to predict freedom from persistent infection (Pringle et al., 2022; Sweeney et al., 2005), with repeated testing mitigating the possibility of false negatives. Serological testing is unreliable in identifying carrier animals (Davidson et al., 2008; Durham & Kemp-Symonds, 2021; Pringle, Venner, et al., 2020), and does not replace these other more invasive, expensive, and time-consuming methods of detection. Guttural pouch lavage combined with quantitative PCR is considered the best, albeit imperfect, method for carrier detection (Boyle et al., 2018; Rendle et al., 2021; Svonni et al., 2020); although, economic and practical implications mean it is not always applicable.

Serological testing

Indirect ELISAs detect antibodies generated by the host: they are used for screening animals (Craig, 2021), identifying exposure following an outbreak (Rendle et al., 2021; Robinson et al., 2013), and diagnosing the complications of strangles (Boyle et al., 2009). Commercially available ELISAs detect antibodies produced against the SeM surface protein, or both antigen A (SEQ_2190, a non-SeM target) and antigen C (a fragment of SeM) of *S. equi*, the so-called dual-target ELISA (Boyle et al., 2018; Robinson et al., 2013). Carrier status cannot be determined using commercially available ELISAs (Durham & Kemp-Symonds, 2021; Van Maanen et al., 2021); however, the identification of recently exposed animals can be helpful in identifying animals to perform further diagnostics or in biosecurity plans that do not allow for blanket guttural pouch lavage for economic and/or practical reasons (Rendle et al., 2021). Biosecurity plans are always a balance of benefit versus risk and serology can play a role although its limitations should be clearly understood.

SeM-based ELISAs can be used to aid in the diagnosis of purpura haemorrhagica or metastatic abscessation (associated with titres ≥ 12,800), as well as identify animals predisposed to developing purpura haemorrhagica (titre > 1:3200) (Boyle et al., 2009, 2018). They can also be used to indicate recent infection (≥4-fold increase in titre between paired samples taken 10 days apart) (Boyle et al., 2009, 2018), although a single reading does not provide a measure of protection or active infection.

Cross-reactivity with a SeM homologue in *S. zooepidemicus* (Kelly et al., 2006) combined with the failure of the SeM-based ELISA to detect *S. equi* strains not containing SeM (Harris et al., 2015) led to the development of the dual-target ELISA (Duran & Goehring, 2021; Robinson et al., 2013). Following an outbreak, it is advised to use the dual-target ELISA to identify horses exposed to *S. equi* (Boyle et al., 2018; Duran & Goehring, 2021). The dual-target ELISA is reported to have similar sensitivity but greater specificity than the single target SeM-based ELISA (Robinson et al., 2013). It can be used to identify recent exposure, from as little as 2 weeks of postinfection, and has been used to determine exposure in populations across the globe (Ling et al., 2011; Štritof et al., 2021).

CLINICAL MANAGEMENT

Treatment of acute *Streptococcus equi* infection

Most equids with acute strangles exhibit non-specific signs of generalised respiratory infection with presentation depending on challenge dose and host immunity, often responding well with only supportive and nursing care (Rendle et al., 2021; Whitelegg & Saunders, 2021). Acute disease can quickly deteriorate into severe cases, emphasising the need for regular monitoring (Rendle et al., 2021).

Nursing for an animal with strangles is vital; good provision should include an environment that encourages rest, appropriate nutrition, regular monitoring (TPR), abscess management and a quarantine protocol (Whitelegg & Saunders, 2021). A soft, calorific and palatable diet alongside water, to facilitate deglutition, both provided from a height, can help equids with profound lymphadenopathy; assisted nutrition may be indicated (Rendle et al., 2021). The experience of individual equids must be considered during a strangles outbreak, as small changes in diet and environment can aid in assuaging the effects of infection with *S. equi*.

Individuals with visible lymphadenopathies require good supportive and nursing care, with a focus on facilitating the maturation and subsequent drainage of abscesses (Boyle et al., 2018). Surgical drainage may be required if the abscesses are not spontaneously rupturing, although care must be taken to ensure the abscess is mature to enable maximal drainage (Boyle et al., 2018). Once open, abscesses should be lavaged with saline or antiseptic solutions, followed by daily flushing so long as discharge persists (Rendle et al., 2021). NSAIDs can be employed to provide analgesia and reduce pyrexia; it has been suggested that their use can slow the development of abscesses, but this claim lacks evidence (Rendle et al., 2021). Paracetamol has also been recommended since it does not inhibit inflammation but possesses antipyretic and analgesic actions, resulting in improved appetite and welfare (Rendle et al., 2021). Phenylbutazone or flunixin meglumine could also be considered (Boyle et al., 2018).

Antimicrobial therapy has a role in combatting *S. equi* infections but must be prescribed responsibly and only when clearly indicated, with careful consideration to minimise the development of antimicrobial resistance (Boyle et al., 2018; Jaramillo-Morales et al., 2022). For most strangles outbreaks, antimicrobials are not indicated or required for mature horses. Antimicrobials may be indicated between initial exposure and abscessation (Boyle et al., 2018), but this window is not always adhered to since abscesses can develop within days (Timoney & Kumar, 2008).

Penicillin is the drug of choice for *S. equi* infection; however, population analysis (Morris et al., 2020) revealed that pbp2x mutations are emerging. This mutation is in the penicillin-binding site and is associated with penicillin resistance in *Streptococcus pneumoniae* (Maurer et al., 2012; Nichol et al., 2002). Although penicillin resistance has been observed in *S. equi* isolates (Fonseca et al., 2020), it is not typically seen (Clark et al., 2008; Johns & Adams, 2015) and further work is needed to determine the clinical implications of these conflicting findings. It is important that resistance is monitored, and that unusual results (Fonseca et al., 2020) are followed up in accordance with international standards (CLSI, 2020; EUCAST, 2023).

Treatment of persistent *Streptococcus equi* infection

Persistent infections of the guttural pouch are typically treated with combination of topical antimicrobials in combination with lavage (Boyle et al., 2018); systemic antimicrobial therapy is only indicated in a proportion of cases (Rendle et al., 2021). Administration of penicillin systemically and an endoscopically guided gelatin-penicillin mix topically, has been regarded as broadly successful (Verheyen

et al., 2000). The use of a reverse thermodynamic gel with benzylpenicillin presents an easier alternative to using a gelatin mix, where antimicrobial concentration is maximised since the gel can be retained in the guttural pouch for over 72 h (Bowen, 2017; Rendle et al., 2021).

The removal of purulent material and chondroids from the guttural pouches is required for the elimination of the carrier state (Boyle et al., 2018). Standing endoscopic intervention is preferable to general anaesthesia surgical intervention due to inherent anaesthetic risks, surgical dissection around vital structures, and *S. equi* environmental contamination (Boyle et al., 2018). Topical application of 20% acetylcysteine (w/v) solution can facilitate drainage of non-inspissated mucopurulent material through the nasal passages by disrupting disulphide bonds, thereby reducing mucus viscosity (Boyle et al., 2018).

Specific treatment methods depend on the individual presentation and the type of material within the guttural pouches. Many carriers do not present with empyema or chondroids, and it has been reported that the carrier state can self-resolve without treatment (Pringle et al., 2019).

Outbreak prevention and management

Strangles was once considered an inevitability (Solleysel, 1664), but has since been demonstrated to be a very preventable infection (Rendle et al., 2021). Outbreaks can be prevented by limiting exposure to the infectious agent, through enacting rigorous biosecurity protocols, using appropriate quarantining and screening facilities, and understanding of the pathogenesis of *S. equi* (Boyle et al., 2018). Outbreaks of strangles are controlled through the cessation of movement to and from the equestrian facility, isolating animals that are infected and where infection is suspected. A tiered 'traffic light' system with segregation based on exposure and no mixing between groups should be adhered to (Boyle et al., 2018). Following the outbreak, all animals should be tested for exposure and persistent infection.

Long-term control strategies should consider the vaccination of unexposed animals, the identification and treatment of carrier animals, and caregiver education on clinical signs associated with acute disease (Duran & Goehring, 2021).

Vaccination

Vaccination as a tool for outbreak prevention has been limited by efficacy, safety, practicality, clashes with other vaccination schedules, geographical restrictions, differences in circulating *S. equi* strains and owner compliance (Boyle et al., 2018; Mitchell et al., 2021). Strangles vaccines should provide a high degree of protection against *S. equi*, a long duration of immunity, the ability to be administered intramuscularly safely, and permit the differentiation of infected from vaccinated animals (DIVA) (Waller & Jolley, 2007).

The first strangles vaccines were developed in the 1940s, using heat-killed bacteria, conferring a limited degree of protection but often resulting in adverse effects, including injection site reactions and pyrexia (Bazeley, 1940a, 1940b, 1942a, 1942b, 1943). Cell-free variations of this vaccine still exist (Waller, 2014), although the incidence of adverse reactions and the lack of DIVA capability have limited their use. A recent attempt to combine the *S. equi* bacterin and recombinant SeM protein in a vaccine yielded promising results in mice, with all demonstrating a humoral response (Rosa et al., 2021); evaluation of its safety and efficacy in horses is ongoing.

M-protein-containing extract vaccines have demonstrated some efficacy in reducing the frequency and severity of disease; although adverse reactions are common and they possess no DIVA capability (Hoffman et al., 1991). Commercially available options, although none are available in the UK, include Strepvax II (Boehringer Ingelheim), Equivac S (Zoetis New Zealand) and Strepguard (MSD Animal Health) (Duran & Goehring, 2021).

Live-attenuated vaccines have been at the forefront of strangles prevention since the early 21st century (Jacobs et al., 2000). The Equilis StrepE (MSD Animal Health) is administered submucosally, and the Pinnacle IN (Zoetis) is administered intranasally; they are commercially available in Europe and North America, respectively, as well as other countries intermittently (Duran & Goehring, 2021). Adverse reactions were reported upon intramuscular administration, and these live-attenuated vaccines possess no DIVA capability (Borst et al., 2011; Kemp-Symonds et al., 2007; Lanka et al., 2010; Livengood et al., 2016). Furthermore, the Equilis StrepE (MSD Animal Health) vaccine has been linked to *S. equi* replication, resulting in lymph node abscesses (Harris et al., 2015; Kelly et al., 2006; Kemp-Symonds et al., 2007; Mitchell et al., 2021).

Strangvac (Intervacc AB) is a recombinant fusion protein vaccine that is administered intramuscularly and has been shown to protect up to 94% (15 of 16) of ponies from clinical signs of disease, including the development of abscesses in the retropharyngeal or submandibular lymph nodes when challenged 2 weeks following third vaccination (Robinson et al., 2020). Strangvac has DIVA capability as the vaccine does not contain live *S. equi*, *S. equi* DNA nor the SeM and SEQ_2190 antigens that are targeted by culture, PCR, or ELISA diagnostic tests (Robinson et al., 2018). Future studies will be needed to evaluate the utility of Strangvac (Intervacc AB) in clinical practice.

Advancements such as the Strangvac vaccine represent a promising development, potentially allowing vaccination to become a more efficacious control measure. However, continued work is required from veterinary professionals to build trust with owners and caregivers over the use of any strangles vaccines due to past difficulties (White et al., 2021).

CONCLUSION

Understanding *S. equi* is crucial to combatting strangles, and much work has been carried out to characterise its evolution (Holden et al., 2009), genome (Harris et al., 2015), epidemiology (Mitchell

et al., 2021), survivability (Durham et al., 2018), resistance profile (Fonseca et al., 2020) and pathogenicity (Timoney, 2004; Timoney & Kumar, 2008). This increased understanding has enabled the development of more targeted diagnostic assays (Boyle et al., 2021; Noll et al., 2020; Webb et al., 2013; Willis et al., 2021), better outbreak prevention and management protocols (Rendle et al., 2021) and a safe and efficacious vaccine with DIVA capability (Robinson et al., 2020). These advances better equip clinicians and caregivers to treat and prevent strangles.

Further research is required to investigate the role of *S. zooepidemicus* as a primary respiratory pathogen in equids (Lindahl, Aspán, et al., 2013; Waller, 2017; Waller & Wilson, 2021), and to better understand the growing concern of antibiotic resistance in both *S. equi* and *S. zooepidemicus* (Fonseca et al., 2020; Johns & Adams, 2015). The success of *S. equi* as a pathogen can be attributed to the carrier state allowing infection to spread to naïve animals. Understanding the host and pathogenic factors that predispose equids to persistent infection and validating a gold-standard method of diagnosis will help prevent future outbreaks and safeguard animal welfare.

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L. McLinden conducted the literature review, created the figure and prepared the manuscript. All authors contributed to the design and revision of the manuscript. The final manuscript was approved by all authors.

CONFLICT OF INTEREST STATEMENT

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