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EVIDENCE REVIEW

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Treatment of equine sarcoids: A systematic review

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Abstract

Background: The sarcoid is the most common equine cutaneous neoplasm. Evidence-based treatment of this condition is often lacking, and selection of treatment modality based on clinical experience or anecdotal evidence.

Objectives: To assess the quality of the currently available best evidence regarding the treatment of the equine sarcoid.

Study design: Systematic review.

Methods: In compliance with PRISMA guidelines, literature searches were performed in PUBMED, Web of Science, CAB Abstracts, EMBASE (Ovid) and Scopus in April 2021. Included papers were required to describe an interventional study examining sarcoid treatment strategy, of level 4 evidence or greater. The case definition required confirmation of at least some included lesions on histopathology, and a minimum of 6 months of follow-up was required on treated cases. Studies were assessed by two independent reviewers (KO, CD). Data extraction was performed manually, followed by risk of bias assessment. Methodological quality was assessed using the GRADE system.

Results: In total, 10 studies were included in the review. Case definition was confirmed via histopathology in all included lesions in 60% of papers. Time to follow-up was variably reported. Overall risk of bias ranged from 'some concerns' to 'critical'. Reported sarcoid regression rate ranged from 28% to 100% on an individual sarcoid level, and 9%–100% on a whole horse level. Transient local inflammation was reported following most treatment strategies, with further adverse events reported infrequently.

Main limitations: Review methodology excluded a large proportion of available literature regarding the equine sarcoid. Significant heterogeneity between included studies prevented quantitative synthesis and most included papers were at significant risk of bias, indirectness, and imprecision.

Conclusions: There is insufficient evidence currently available to recommend one sarcoid treatment over another. There is an urgent need for sufficiently powered, randomised, placebo-controlled trials in order to allow more definitive comparison of the efficacy of different treatment strategies.

KEYWORDS
cutaneous, evidence, neoplasia, sarcoid

1 | INTRODUCTION

The equine sarcoid is ubiquitous worldwide and is the most common equine cutaneous neoplasm, diagnosed in approximately 46% of neoplastic equine cutaneous biopsy samples.[1] The condition has an owner reported prevalence in the United Kingdom of 5.8% and, although rarely metastatic, may be life-limiting due to locally aggressive invasion and secondary ulceration and/or infection.[2,3] Sarcoids, therefore, have a significant influence on the welfare and function of affected equids.

There is currently no uniformly effective therapy for the treatment of sarcoids. Reported success rates between studies are widely variable and recurrence post-treatment occurs frequently.[4] Multiple treatment protocols are reported, including sharp, or laser surgical excision,[5–11] cryosurgery,[6,12] topical or intratumoural chemotherapy,[5,13–17] and immunotherapy.[5–7,18] Further techniques, such as interstitial brachytherapy or plesiotherapy and local electrochemotherapy, are commonly reported but may have limited practical availability.[19–25]

The range in treatment modalities is primarily due to widely variable lesion clinical behaviour. Traditionally, selection of treatment modality for this condition has often been based on clinical experience, or anecdotal evidence and case series. Evidence based treatment of this condition is currently lacking and is severely limited by the lack of prospective, double-blinded trials.[26]

The question posed by this systematic review is: 'in equids with sarcoids (P) what effect do reported treatments (I) have on lesion resolution (O)?' We assessed the quality of the currently available best evidence, in an attempt to develop guidelines for the treatment of sarcoids in equids and highlight gaps in the current evidence.

2 | METHODS

2.1 | Eligibility criteria

Criteria for inclusion eligibility in this review were to be an interventional study examining a sarcoid treatment strategy. The study was required to be of Level 4 evidence and above, that is, at least a case series or case-controlled study in the hierarchy of evidence.[27] The case definition (i.e. of 'sarcoid') required confirmation on histopathology in at least some of the cases included, and a minimum of 6 months of follow-up was required on treated cases. A publication date restriction of 1970 onwards was applied.

2.2 | Exclusion criteria

Studies where the full text was not available, single case reports, or case series lacking a comparator group, non-systematic review articles, book chapters, newspaper articles and other documents not containing original data, and papers not available in the English language were excluded.

2.3 | Search strategies

Literature searches were performed in April 2021 in the following electronic search databases; PUBMED, Web of Science, CAB Abstracts, EMBASE (Ovid), Scopus. Search strategies/strings are available in Supplementary Item 1.

2.4 | Selection process

All retrieved titles were deposited in EndNote reference manager.[28] Duplicates were removed manually. They were then screened in an unblinded manner, first by title and then abstract, for relevance. Studies fulfilling the inclusion criteria, or in which fulfilment of the criteria could not be established from the abstract, were retrieved as full texts. Two independent reviewers (Katie S. Offer, Claire E. Dixon) then assessed the full contents of each study for inclusion in analysis (Supplementary Item 2).

2.5 | Data collection process

A data extraction sheet was developed based on the Cochrane Consumers and Communication Review Group's data extraction template.[29] Data were extracted manually from each report by the first author (Katie S. Offer), and then checked by the second (Claire E. Dixon). Disagreement was resolved by a third party (David G M Sutton). An example of the data extraction sheet is available in Supplementary Item 3.

Information was extracted regarding: study design, year of publication and source(s) of funding, the number of cases examined, sarcoid type and location, full details of the treatment, the number of repeat treatments and total treatment time, any adverse effects associated with treatment and the presence or absence of untreated/placebo treated control or, if not available, the treatment group used for comparison. The primary clinical outcome measure was the rate of complete regression, recorded both per horse and per lesion treated. This was defined as the percentage of sarcoids resolved or horses sarcoid free at the time of follow-up, as specified by each individual study. Further secondary outcomes included the rate of tumour recurrence, and where available objective measures such as reduction in tumour volume or area.

2.5.1 | Risk of bias assessment

The risk of bias for each included study was assessed using the Cochrane group's 'Risk Of Bias In Non-randomized Studies of

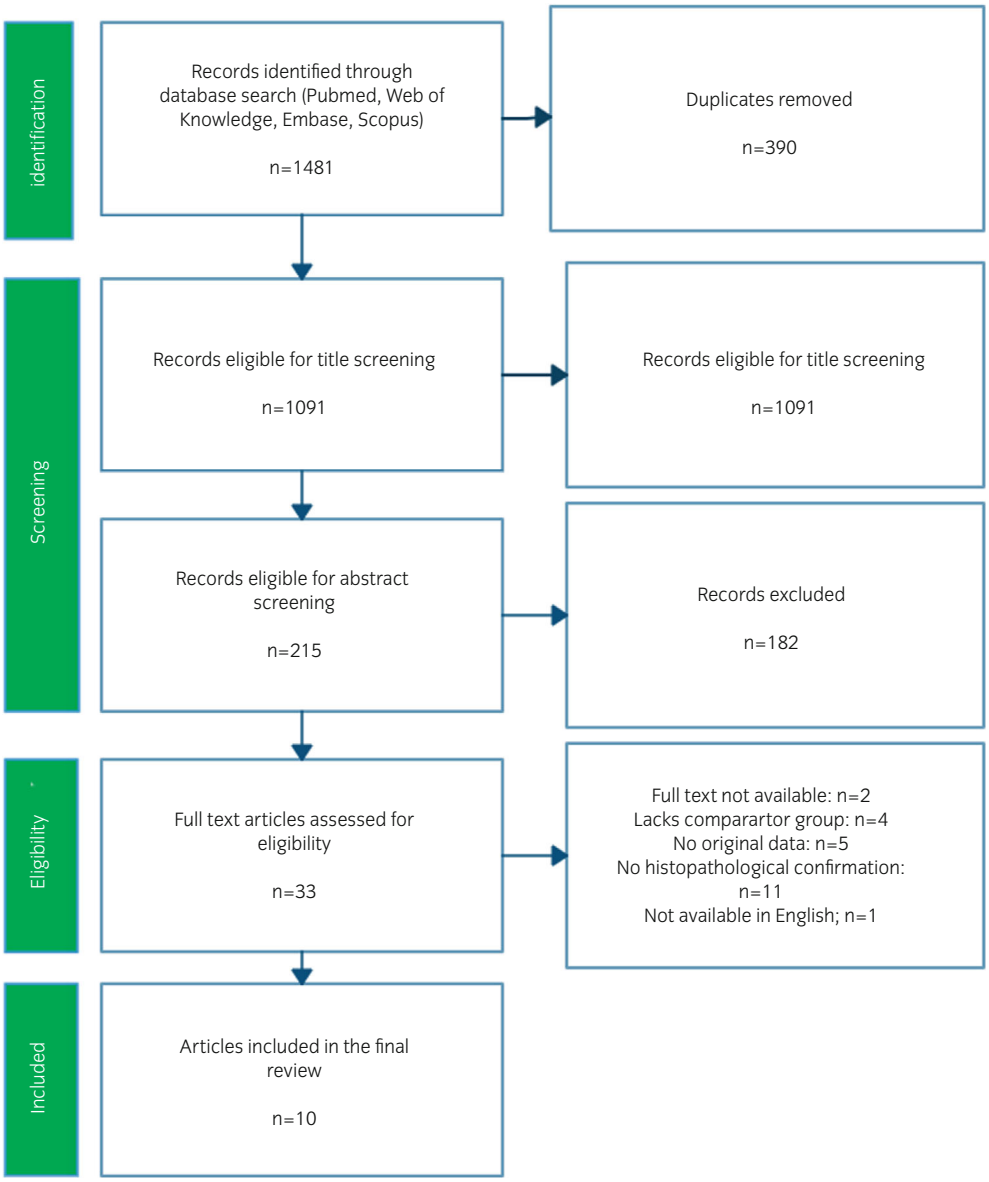

FIGURE 1 PRISMA flow diagram of studies included and excluded from the review.

Interventions (ROBINS-I)' tool for non-randomised trials, or the RoB 2.0 tool for randomised controlled trials (RCTs).[30,31] The Robvis tool was used to illustrate this assessment.[32]

2.5.2 | Assessment of methodological quality

Methodological quality was then assessed using the GRADE system.[9] For outcomes explored by RCTs, rating started at 'high', and non-RCTs started at 'low'. Studies were downgraded for risk of bias, inconsistency, indirectness, imprecision or publication bias. Quality of evidence was able to be upgraded where a large magnitude of effect of a treatment was present, a strong dose response to treatment was indicated, or where the effect of all plausible confounding factors would be to reduce the effect (where an effect is observed) or suggest a spurious effect (when no effect is observed).

2.5.3 | Data synthesis

Meta-analysis was not productive due to significant heterogeneity between studies. Data analysis was therefore descriptive. Where possible, results were combined utilising synthesis without meta-analysis (SWiM) guidelines.[33] Studies were grouped by treatment protocol in order to compare clinical success rates.

3 | RESULTS

3.1 | Study selection

In total, 1481 records were retrieved. Figure 1 describes the results of the search and selection process. The most common reasons for study exclusion included the lack of histopathological confirmation of diagnosis, review articles containing no original data, or case series lacking

TABLE 1 Methodological characteristics of included studies in the systematic review of equine sarcoids.

Paper	Study design	Sarcoid types	Sarcoid locations	% Histo	Available for inclusion		Excluded		Lost to follow-up		Time to follow-up (months)	Treatment groups	Included	
					Horses	Sarcoids	Horses	Sarcoids	Horses	Sarcoids			Horses	Sarcoids
Christen-Clottu et al., 2010[34]	Prospective randomised blinded clinical trial	Occult-34% Verrucous-50% Nodular- 3% Fibroblastic-5% Mixed- 9%	Head- 12% Neck- 12% Prepuce- 6% Inner thigh- 6% Ventrum- 33% Axilla- 14% Thorax- 14%	79	53	163	11	34	17	48	12	Viscum album extract Placebo	23 13	72 43
Klein et al., 1986[18]	Prospective randomised clinical trial	Not stated	Head- 20% Leg- 26% Abdomen- 6% Breast- 20% Eye- 1% Anal- 9% Ear- 3% Groin- 14%	100	41	-	11	-	0	0	4–40	Live attenuated BCG vaccine BCG cell wall vaccine Cryosurgery	10 10 10	29 16 26
[b]Knottenbelt and Kelly, 2000[5]	Retrospective	Occult- 3% Verrucose-29% Nodular-36% Fibroblastic-16% Mixed- 13% Malignant-0.1%	Periorbital- 100%	12	445	-	-	-	[a]	[a]	Variably reported, ≤108	Benign neglect (Control) Surgical excision Cryosurgery Radiofrequency hyperthermia BCG immunomodulation Radiotherapy (Ir^{192}) Radiotherapy (Sr^{90}) Intralesional cisplatin Topical AW4 Topical 5% 5-fluorouracil	42[b] 28[b] 23[b] 2[b] 309[b] 66[b] 3[b] 18[b] 146[b] 9[b]	- - - - - - - - -
Martens et al., 2001[6]	Prospective clinical study	Occult- 5% Verrucose-25% Nodular-13% Fibroblastic-24% Mixed- 34%	Head- 16% Trunk- 76% Extremities- 8%	- (39% of horses)	95	453	-	256	4	-	6–60 [14]	Sharp excision CO_2 laser excision Cryosurgery Local BCG vaccination	22 28 14 27	57 81 18 30
McConaghy et al., 1994[7]	Retrospective	Not stated	Head- 33% Limbs- 59% Body- 8%	100	63	-	-	-	-	-	6–120	Sharp excision Cryotherapy	- - -	18 31 11

(Continues)

TABLE 1 (Continued)

Paper	Study design	Sarcoid types	Sarcoid locations	% Histo	Available for inclusion		Excluded		Lost to follow-up		Time to follow-up (months)	Treatment groups	Included	
					Horses	Sarcoids	Horses	Sarcoids	Horses	Sarcoids			Horses	Sarcoids
												BCG vaccination- Cell wall preparation		
												BCG vaccination- Attenuated vaccine	-	5
												Radiotherapy (Au^{198})	-	1
Pettersson et al., 2020[37]	Prospective clinical study	Occult- 21% Verrucose- 4% Nodular- 20% Fibroblastic- 38% Mixed- 16%	Head- 15% Axilla- 10% Distal limb- 13% Trunk- 15% Genitalia- 15% Neck- 3%	20	25	164	-	-	-	6	3	Topical Imiquimod 5%		45
												Topical *Sanguinaria canadensis* + zinc		16
												Control (untreated)		107
Spoormakers et al., 2003[36]	Prospective, randomised, clinical study	Occult- 4% Verrucose- 46% Fibroblastic- 35% Mixed- 15%	Girth/ventral abdomen/ genital- 17% Pectoral/neck- 20% Proximal limbs- 11% Distal limbs- 7% Head- 41% Back- 4%	100	36	-	-	-	-	-	12	5 days low dose intralesional IL-2	11	
												10 days low dose intralesional IL-2	10	
												Single high dose intralesional IL-2 + cisplatin	15	
Tamzali et al., 2012[25]	Retrospective	Occult- 8% Verrucose- 41% Nodular- 15% Fibroblastic- 18% Mixed- 18%	Head- 15% Neck- 5% Trunk- 30% Limbs 30% Genital/ paragenital 23%	100	48	194	14	-	[a]	[a]	48	Cisplatin ECT		110
												Cisplatin ECT plus surgical debulking		84
Théon et al., 1999[35]	Prospective, randomised, clinical trial	Not stated	Periorbital- 58% Pinna- 6% Trunk/neck- 9% Limbs- 17% Genitals- 2%	100	70	89	-	25	-	-	20–69 [47]	Perioperative ITC	-	32
												Postoperative ITC	-	32
Théon et al., 2006[15]	Prospective clinical trial	Not stated	Periorbital- 58% Face and pinnae- 11%	100	368	409	-	-	[a]	[a]	36	ITC alone	-	64
													-	47

TABLE 1 (Continued)

Paper	Study design	Sarcoid types	Sarcoid locations	% Histo	Available for inclusion		Excluded		Lost to follow-up		Time to follow-up (months)	Treatment groups	Included	
					Horses	Sarcoids	Horses	Sarcoids	Horses	Sarcoids			Horses	Sarcoids
			Trunk and neck- 10% Limbs- 17% Genitals- 4%									Perioperative ITC, open wound, gross residual disease after Sx		
												Perioperative ITC, closed wound, gross residual disease after Sx	-	99
												Postoperative ITC, open wound, gross residual disease after Sx	-	147
												Postoperative ITC, closed wound, microscopic residual disease after Sx	-	52

Note: '–' denotes no information. '[]' median. 'Available for inclusion' denotes the total number of horses/sarcoids initially presenting for inclusion in the study, 'Excluded' denotes the number of horses/sarcoids excluded on the basis of that study's inclusion criteria, 'Included' denotes the final number of horses/sarcoids included in the paper's analysis.

Abbreviations: % Histo, the percentage of included horses/sarcoids with a diagnosis confirmed via histopathology; BCG, Bacillus Calmette–Guérin vaccine; ECT, electrochemotherapy; ITC, intratumoural chemotherapy; Sx, surgery.

[a]Indicates that only horses with available follow-up were included in the study.

[b]It is unclear from the original manuscript whether these numbers refer to individual sarcoids, or if horses received a combination of treatments and are included in multiple categories. They have been included as horses rather than individual sarcoids throughout this review.

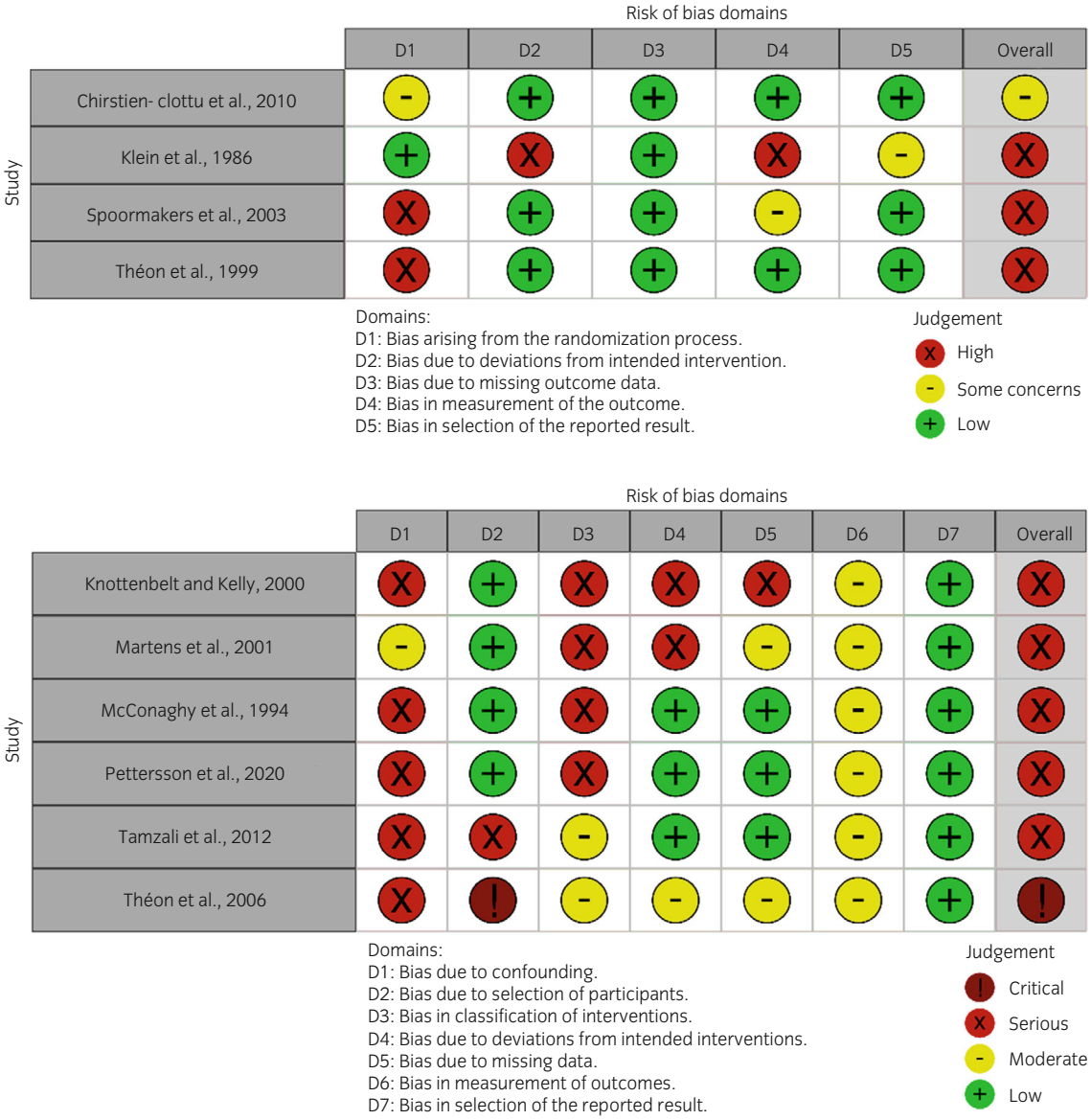

FIGURE 2 RoBvis diagrams of risk of bias in included (A) Randomised clinical trials; and (B) Non-randomised studies of interventions regarding the treatment of equine sarcoids.

comparator groups. Ten papers met the criteria for eventual inclusion in this review.

3.2 | Study characteristics

Four randomised clinical trials were identified, in addition to three prospective, non-randomised clinical studies and three retrospective studies. Methodological characteristics of included studies, with sarcoid type, location, treatment strategies and outcome at follow-up, are described in Table 1.

Case definition was confirmed via histopathology in all included lesions in 60% of papers. All but two papers lacked untreated or placebo controls, and in only one paper were those administering treatment blinded to the treatment protocol.[34] Only one paper included a power calculation.[35] Time to follow-up was variably reported but was up to 120 months in some cases.[7] Included sarcoid types varied between studies, but generally included all clinical morphological categories and, with the exception of Knottenbelt and Kelly on all regions of the body.[5]

3.3 | Risk of bias in studies

The risks of bias in individual studies are presented via the Robvis outputs below (Figure 2). Overall risk of bias ranged from 'some concerns',[34] to 'critical'.[15] In the RCTs, primary concerns arose regarding bias in the randomisation process and/or lack of blinding. In the non-randomised studies, bias arose from confounding, particularly baseline confounding, and from lack of blinding in the assessment of

TABLE 2 Complete regression rates by sarcoid and by horse for each included treatment, accompanied by the certainty in the evidence following GRADE assessment.

Treatment	Paper	Complete regression rate (%)		Timing of follow-up (months)	Number of participants		Certainty in the evidence (Grade)	Comments
		Per sarcoid	Per horse		Sarcoids	Horses		
Sharp excision	Knottenbelt and Kelly, 2000[5]	-	18	≤108	-	28	Very low	Periocular, superficial verrucose or Type A nodular sarcoids only.
	Martens et al., 2001[6]	82	72	6–60 [14]	57	25		Surgical margins 8–16 mm
	McConaghy et al., 1994[7]	28	-	6–120	18	-		Surgical margins 5–10 mm. Base cauterised with electrosurgical unit.
CO_2 Laser excision	Martens et al., 2001[6]	89	71	6–60 [14]	81	28	Very low	Surgical margins 8–16 mm
Cryotherapy	Klein et al., 1986[18]	100	100		26	10	Very low	'Very large' tumours first frozen, then debulked, then 2 freeze–thaw cycles repeated at 2–3 weekly intervals between 1 and 5 times.
	Knottenbelt and Kelly, 2000[5]	-	9	-	-	23		Periocular, <2 cm^2 verrucose or occult lesions. Three freeze–thaw cycles, once only.
	Martens et al., 2001[6]	78	73	6–60 [14]	18	15		Debulked surgically prior to 2 freeze–thaw cycles, once only.
	McConaghy et al., 1994[7]	42	-	6–120	31	-		Debulked surgically prior to 3 freeze–thaw cycles, once only.
BCG immunotherapy (live attenuated vaccine)	Klein et al., 1986[18]	83	60	4–40	29	10	Very low	0.25 ml/cm^2, repeated after 12, 35 and 56 days.
	Knottenbelt and Kelly, 2000[5]	-	69	-	-	300		Periocular only. Variable protocols reported.
	Martens et al., 2001[6]	70	67	6–60 [14]	30	27		Ulcerated, fibroblastic sarcoids debulked to the level of the skin prior to treatment.
	McConaghy et al., 1994[7]	80	-	6–120	5	-		Surgically resected to skin level prior to treatment.
BCG immunotherapy (cell wall vaccine)	Klein et al., 1986[18]	69	70	4–40	16	10	Very low	0.25 ml/cm^2
	McConaghy et al., 1994[7]	82	-	6–120	11	-		Surgically resected to skin level prior to treatment. 5 ml/3 cm^2 tumour
Gamma radiotherapy-Ir^{192}	Knottenbelt and Kelly, 2000[5]	-	100	12	-	66	Very low	Periocular sarcoids only. Average dose 7000–9000 rads.
Gamma radiotherapy-Au^{198}	McConaghy et al., 1994[7]	-	100	6–120	-	1	Very low	Surgically debulked prior to treatment.
Beta radiotherapy- Sr^{90}	Knottenbelt and Kelly, 2000[5]	-	100	12–48	-	3	Very low	Periocular, single or few 'very small' verrucose/occult sarcoids only. 10 000 rads over 5 days.

(Continues)

TABLE 2 (Continued)

Treatment	Paper	Complete regression rate (%)		Timing of follow-up (months)	Number of participants		Certainty in the evidence (Grade)	Comments
		Per sarcoid	Per horse		Sarcoids	Horses		
Intralesional cisplatin	Knottenbelt and Kelly, 2000[5]	-	33	-	-	18	Very low	Periocular, fibroblastic or extensive nodular lesions only. 1 mg/cm^3 tumour
	Théon et al., 2006[15]	94	-	36	64	-		1 mg/cm^{3-} tumour, four times at 2 week intervals.
Surgery + perioperative intralesional cisplatin	Théon et al., 1999[35]	90 ± 6	-	20–69 [47]	32	-	Very low	1 mg/cm^3 four times at 2 week intervals, commencing at the time of surgery.
	Théon et al., 2006[15]	93	-	36	146	-		1 mg/cm^3 four times at 2 week intervals, commencing at the time of surgery.
Surgery + postoperative intralesional cisplatin	Théon et al., 1999[35]	85 ± 7	-	20–69 [47]	32	-	Very low	1 mg/cm^3 four times at 2 week intervals, commencing median 14 days postoperatively.
	Théon et al., 2006[15]	98	-	36	199	-		1 mg/cm^3 four times at 2 week intervals, commencing 2–3 weeks postoperatively.
Intralesional IL-2	Spoormakers et al., 2003[36]	-	14	12	-	21	Low	200 000 IU IL-2 Daily for either 5 or 10 days
Intralesional IL-2 and cisplatin	Spoormakers et al., 2003[36]	-	53	12	-	15	Low	1 mg/cm^2 cisplatin then daily 200 000 IU IL-2 treatment for 10 days
Topical 5-fluorouracil (5%) cream	Knottenbelt and Kelly, 2000[5]	-	67	-	-	9	Very low	Periocular, superficial occult or verrucose lesions away from the eyelid margins. Twice daily for 5 days, then once daily for 5 days.
Topical AW4	Knottenbelt and Kelly, 2000[5]	35	35	-	159	146	Very low	Periocular, small, previously untreated, superficial verrucose lesions only.
Topical imiquimod (5%)	Pettersson et al., 2020[37]	84	-	3	45	-	Very low	Three times weekly on non-consecutive days until remission or up to 45 weeks.
Topical *Sanguinaria canadensis* and zinc chloride	Pettersson et al., 2020[37]	75	-	3	16	-	Very low	Facial tumours excluded. 6 days of daily treatment then every 4th day until remission or up to 45 weeks.
Electrochemotherapy (cisplatin)	Tamzali et al., 2012[25]	91	-	48	110	-	Very low	Performed at 2 week intervals. Mean treatment number 2.6 ± 1.1
Electrochemotherapy (cisplatin) combined with sharp excision	Tamzali et al., 2012[25]	100	-	48	84	-	Very low	ECT done either at the time of surgery, or 2 weeks following surgery, then at 2 week intervals. Mean ECT treatment number 2.9 ± 1.4
Radiofrequency hyperthermia	Knottenbelt and Kelly, 2000[5]	-	0	-	-	2	Very low	Periocular sarcoids only.
Mistletoe extract (Viscum album austriacus)	Christen-Clottu et al., 2010[34]	37.5	28	12	72	32	Moderate	Three subcutaneous injections of 1 mL per week for 15 weeks.

Note: '–' denotes no information. '[]' median.
Abbreviation: BCG, Bacillus Calmette–Guérin vaccine.

outcomes. There was also concern regarding differences in co-interventions across groups, and regarding the selection of participants based on patient characteristics observed after the start of the study (e.g., exclusion of horses lost to follow-up).

A summary of sarcoid resolution rate expected with each treatment is provided in Table 2. Heterogeneity in study design and reporting meant that complete regression rate was not available by horse and sarcoid in every paper. It was also not possible to extract which individual sarcoids within each treatment or paper were histopathologically confirmed, and so all included lesions were combined. Significant methodological differences existed between papers within each treatment category, for example, surgical debulking prior to cryotherapy, the frequency and number of cryotherapy treatments, or the inclusion of only superficial sarcoids within a treatment category (Table 2). Certainty in the evidence (GRADE scoring) for each treatment outcome is also presented in Table 2. Complete regression rates are displayed graphically in Figure 3.

Reported adverse events with each treatment strategy are available in Supplementary Item 4. Transient local inflammation was experienced following nearly all reported treatments.[5,7,15,18,25,34–37] More significant adverse events were generally restricted to individual cases, but included cicatrisation of the upper eyelid following sharp excision,[5] septic arthritis of the tarsus following cryotherapy and sequestration of the underlying orbital bone following gamma radiotherapy of a periocular sarcoid.[5,7] One case of anaphylaxis was reported following live attenuated BCG vaccine administration which resulted in collapse, but this horse survived with appropriate treatment.[5] Accelerated growth of fibroblastic sarcoids was observed in 91% of lesions treated with cryotherapy by Knottenbelt and Kelly, and resulted in the euthanasia of 11 horses, and in one case the treatment of a periocular sarcoid with topical AW4 cream resulted in the loss of the eye.[5]

4 | DISCUSSION

This is the first evidence synthesis study providing an objective assessment of the relevant literature to support equine practitioners in the important and common clinical problem of selection of treatment modality for equine sarcoid treatment. There are challenges in the interpretation and comparison between all described treatments for equine sarcoids due to the significant risk of bias, methodological differences, and underpowered studies. Clinical decisions must therefore continue to be made on a case by case basis.

The most effective treatment regimens based upon this study are radiotherapy, cryotherapy, intralesional cisplatin or electrochemotherapy, with complete regression rates of >90% reported. We summarise the key considerations for these treatments.

4.1 | Radiotherapy

Radiotherapy has long since been considered the gold standard treatment for sarcoids.[5,38] Both the Ir^{192} and Au^{198} represent low-dose rate brachytherapy—a technique whereby radioactive wires or beads are inserted into the tumour and left in place until a total dose of 50-60Gy is administered.[19] There are a number of disadvantages to this approach; general anaesthesia is generally required for the implantation process, and the horse must be kept strictly isolated for several days. Accidental displacement of the implants represents a risk of exposure of personnel to high doses of radiation, and accidental ingestion of the implants by the horse may occur.[38] As such, this technique currently has very limited availability. Sarcoids treated by this approach were periocular (with the exception of one, where the location was not reported) or were surgically debulked prior to treatment.[7] This represents a major limitation of the technique—tumour response is inversely proportional to tumour volume and so the technique is best suited to small or superficial sarcoids only.[38]

There is one included report of strontium plesiotherapy included here by Knottenbelt and Kelly.[5] Limited further anecdotal reports exist in the literature,[38] and in one case series where treatment was not limited to the periocular region and all treated sarcoids resolved with variable time to follow-up.[20] The advantage of this treatment is that the β radiation supplied by the strontium probe is poorly penetrating, and so significant side effects are less likely to occur.[5] This treatment is currently limited by availability, but it may represent an effective treatment for carefully selected lesions going forward.

4.2 | Cryotherapy

Papers investigating cryotherapy as a treatment modality report success rates of up to 100%.[18] However, three of the four included papers citing 'cryotherapy' or 'cryosurgery' as a treatment protocol, do so after surgical debulking of the mass, and a significantly lower clinical regression rate of 9% is reported when cryotherapy was used as a sole therapy.[5] Case selection, anatomical site and sarcoid type likely contribute to this, and is variably described.[5–7] The number of freeze–thaw cycles applied to the tissue also varied between papers from 2 to 3 cycles per treatment, with variable repetition between 0 and 5 times at 2–3 weekly intervals.[5,7,18,39] The optimal number of freeze–thaw cycles in sarcoid treatment is unknown, however in human medicine it is accepted that repetitive freezing is crucial in the cryosurgical management of cancers, and that repetition of the freezing may increase the extent of the necrosis to up to 80%.[39]

4.3 | Cisplatin

Intralesional cisplatin demonstrated sarcoid regression rates of up to 98% when combined with surgical excision.[15] Success rates were comparable in this paper when used as a sole therapy (94%), but were as low as 33% in the Knottenbelt and Kelly paper.[5,15] Direct comparison is perhaps not entirely useful—drug formulations (almond oil vs. sesame oil emulsions) and concentrations (1 mg/ml vs. 3.3 mg/ml) were different between papers, as was sarcoid type and anatomical location. Théon et al. found that larger tumour size and prior use of

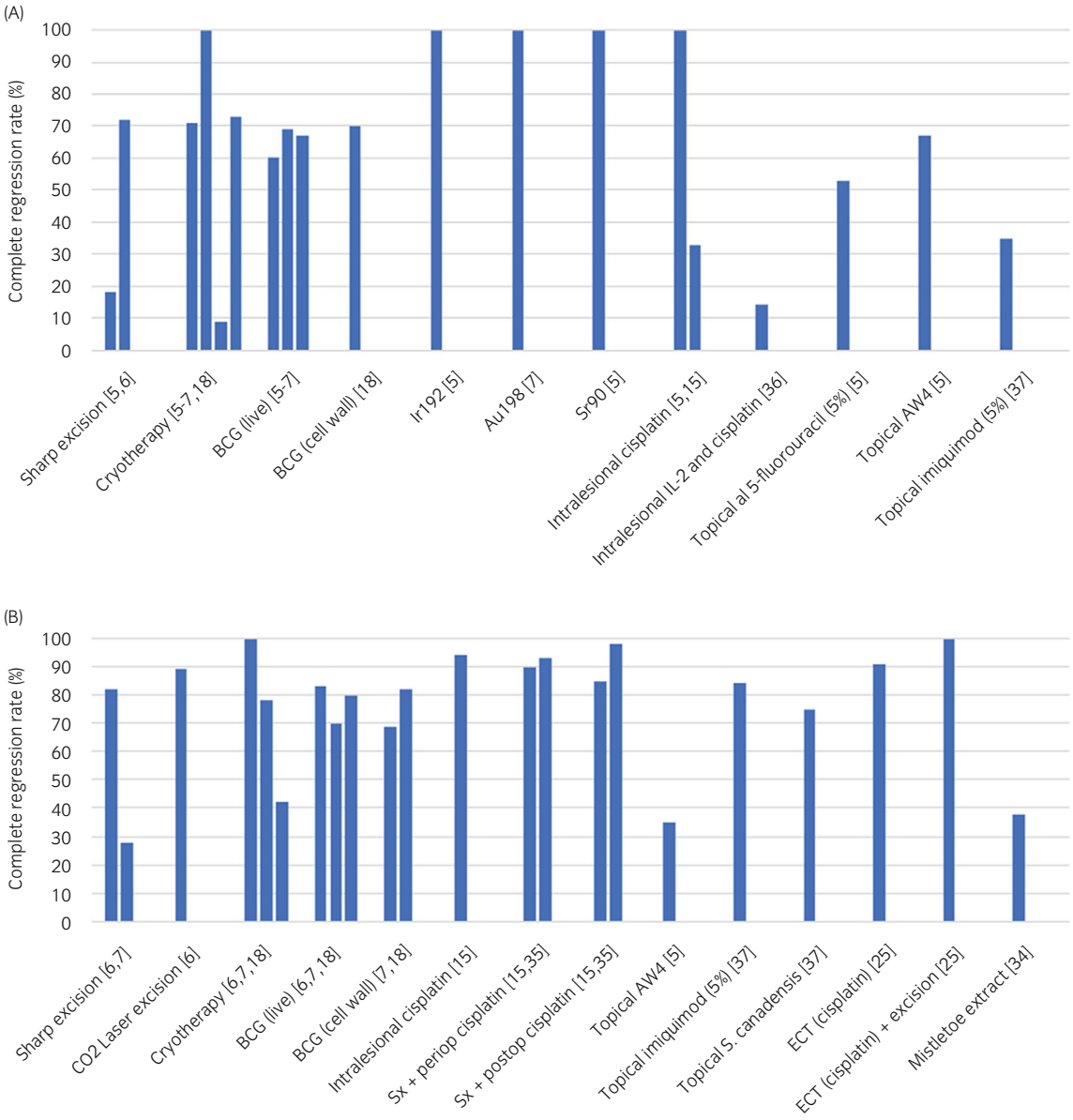

FIGURE 3 Complete sarcoid regression rates (A) per horse and (B) per tumour, reported with each treatment for equine sarcoids. Each bar represents an individual study (referenced in []) reporting that treatment). Due to the marked heterogeneity between studies review of the original manuscripts is recommended before using these figures solely for treatment selection. BCG, Bacillus Calmette–Guérin vaccine; ECT, electrochemotherapy; Sx, surgery.

other treatments negatively affected treatment efficacy,[15] possibly due to difficulty in achieving adequate drug concentrations throughout the tumour before its rapid metabolisation.[25] Cisplatin-containing biodegradable beads have been developed in order to address these limitations but as yet have not been compared with other treatment modalities.[40]

Cisplatin electrochemotherapy, either as a sole treatment or in combination with surgical excision of the mass, gave complete regression rates of 91%–100%.[25] Electrochemotherapy has the advantage of increasing a cytotoxic drug's intracellular concentration and cytotoxicity when compared with intralesional injection alone.[41] Surgical debulking did not significantly influence sarcoid regression rate, but for medium and large-sized tumours significantly reduced the number of treatments needed.[25] Surgical debulking should therefore be considered prior to ECT in cases with large or invasive tumours. Though this study examined the use of cisplatin with ECT, the most commonly used chemotherapeutic agent in other veterinary species receiving ECT is bleomycin.[42] A recent European Standard Operating Procedures of Electrochemotherapy study found no difference in cutaneous tumour response rate when comparing the use of cisplatin or bleomycin,[43] and so this may be considered in the future, given its low toxicity to non-tumour cells when compared with other chemotherapeutic agents.[13]

The above treatment modalities all have the disadvantage that they require, at the least, attendance to a veterinary facility. Given the

ubiquitous nature of sarcoids in horses,[2] it is often more feasible to pursue topical treatment options, which may be employed on the yard. Though topical imiquimod appears to have the best complete regression rate at the individual sarcoid level, this is not true when considering treatment success within the whole horse. No significant difference in regression rate was found between sarcoids treated with either topical imiquimod or *Sanguinaria canadensis* and zinc chloride by Pettersson et al, but small, fibroblastic tumours were more likely to respond favourably than larger sarcoids of other types (80% complete remission with either protocol).[37] The use of AW4 for the treatment of small, periocular sarcoids was less successful (regression rate 34%), though direct comparison between topical treatments should be made with caution given the extreme heterogeneity between studies.

Throughout the included studies, employing a multimodal approach to the treatment of sarcoids appears to provide an advantage in complete regression rate over single treatment modalities, though the significance of this cannot be determined. For example, the addition of surgical debulking prior to cryotherapy or electrochemotherapy, or the addition of intralesional cisplatin to intralesional IL-2 protocols. Although not included in these studies, recent advances in the understanding of the molecular basis of cryotherapy also suggests that this will be true for the addition of cytotoxic agents to cryosurgical techniques.[39] This has also been suggested by previous authors as a method to improve clinical regression rate and prognosis.[26]

4.4 | Limitations of evidence and review process

This methodology of the review itself introduces a number of potential biases. The exclusion of grey literature, single case reports and studies lacking any histopathological confirmation of diagnosis removed the majority of the literature regarding equine sarcoids. However, in only 60% of included papers were all included sarcoids confirmed histopathologically. It was not possible to extract only those confirmed lesions from these studies, and so unconfirmed lesions unfortunately had to be included. This compromise was made in order to maximise the scope, whilst maintaining the validity, of the review, but clearly introduces a significant source of bias.

Heterogeneity between included papers also limited the available synthesis, and so only a basic narrative synthesis was appropriate. This heterogeneity introduced an important source of bias in this review, variation in sarcoid type. For example, fibroblastic sarcoids were over-represented in the paper by Pettersson et al. compared with other articles (Table 1), and, in contrast to the majority of other included studies, verrucose sarcoids the least frequently treated.[37] The influence of sarcoid morphological type on behaviour has not been defined in the literature, though anecdotally, fibroblastic lesions are likely to be perceived as increasingly aggressive and locally infiltrative than other classifications.[2] Anatomical location of the included sarcoid was also very variable (Table 1). Only periorbital sarcoids were discussed by Knottenbelt and Kelly,[5] and were over-represented in both papers by Théon et al.[15,35] It has been suggested that sarcoids of the face and upper forelimb display an increased frequency of malignancy and more aggressive local invasion.[26] This cannot be confirmed by this review and may warrant further investigation, but likely influenced both treatment selection and tumour response in the included studies.

The most significant limitation in this review is the quality of available evidence. Included papers generally lacked power calculations or were underpowered,[35] and the persons administering the treatments were also unblinded to the treatment protocol in all but one of the included studies.[34]

Sarcoid resolution rate was selected as the outcome of interest in this review as it was the most consistently available outcome available between studies. However, this outcome is also complicated by significant bias. In only one paper was there an untreated control or placebo group included therefore the use of this outcome is problematic.[34] Spontaneous regression without treatment is reasonably frequently reported with sarcoids and may be expected in up to 48% of cases, particularly with young horses.[44] As above, comparison of different sarcoid types and anatomical location is often not valid given their widely different clinical behaviours.[26] The use of objective measures, for example, measured reduction in tumour area or volume compared with a matched, untreated control would be more desirable, but was not available in the literature.[44] The use of sarcoid recurrence rate would similarly be a more clinically significant outcome measure for this review, but available literature was widely variable in included follow-up times, and so again this comparison was not useful.

The GRADE rating protocol for the included outcomes suggests that the quality of this evidence is generally 'very low', and most included papers were at significant risk of bias, indirectness and imprecision.[45] This contributed to the large variation in sarcoid regression rates between studies looking at the same or similar treatment protocols. The confidence in the effect estimates (Table 2) is therefore so low that any recommendation of one treatment strategy over another is speculative, and in the majority of studies no significant difference between treatment modality was demonstrated.

Whilst the traditional pyramid of evidence places systematic reviews at the top of the hierarchy for evidence based medicine, this may be too simplistic in this case on account of the significant heterogeneity and risk of bias in the included papers.[46] More recently, a 'new evidence pyramid' has been suggested for medical evidence that views systematic reviews as a tool with which to examine and apply the available evidence, rather than evidence in their own right.[47] This may be more appropriate in this case, where there is significant uncertainly in the quality of the available evidence.

4.5 | Implications for practice/policy/future research

Given the above, it must be concluded in this review that there is insufficient evidence to routinely recommend one sarcoid treatment over another. We have identified an urgent clinical need for sufficiently powered, randomised, placebo-controlled trials to be

performed. This would facilitate the adoption of standardised treatment protocols, for example regarding dose of chemotherapeutic agent/cm^3 tumour or frequency and repetition of cryotherapeutic freeze/thaw cycles. All decisions regarding the most appropriate treatment for any sarcoid are conditional on the sarcoid type, location, size and other patient and owner factors, and should be made at the discretion of the attending veterinary surgeon. If available, radiotherapy should be considered a good treatment option, or if not available then a multimodal approach should be considered. When a topical treatment is necessary, the greatest evidence of efficacy exists for the use of topical imiquimod (5%) or *S. canadensis*.[37] Higher quality evidence is required to facilitate more definitive comparison of the efficacy of different treatment strategies for this common condition.

AUTHOR CONTRIBUTIONS

Katie S. Offer and Claire E. Dixon were involved in screening of titles, abstracts and papers, and in the data collection and synthesis process. Katie S. Offer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the preparation of the manuscript and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

Retrospective analysis of published data only, ethical committee oversight not required.

INFORMED CONSENT

Analysis of published data only, individual informed consent not required.

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SUPPORTING INFORMATION

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