SYSTEMATIC REVIEW

The incidence of vaccine-associated sarcomas in cats: a systematic review and meta-analysis

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Objectives: Feline injection-site sarcoma is a rare but serious adverse event associated with vaccination in cats. Published estimates of feline injection-site sarcoma incidence vary widely, contributing to uncertainty in clinical decision-making and incidence communication.

Materials and Methods: We conducted a systematic review and meta-analysis to estimate the incidence of feline injection-site sarcoma following vaccination in cats and to assess the certainty of the evidence. MEDLINE (*via* Ovid), CAB Abstracts and Web of Science were searched from database inception through January 2026 using terms related to cats, vaccination, sarcomas and adverse vaccine events. Eligible studies reported quantitative estimates of feline injection-site sarcoma incidence, including incidence, incidence rate or measures of association. Two reviewers independently screened studies, extracted data and assessed study quality using the Joanna Briggs Institute checklist for prevalence studies. Incidence estimates were calculated using random-effects meta-analysis. Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation framework.

Results: Eight studies met inclusion criteria, representing 14,059,036 vaccinations and 411 reported feline injection-site sarcoma cases. Study-level incidence estimates ranged from near zero to substantially higher values per vaccination. The incidence was 8.8 feline injection-site sarcoma cases per 100,000 vaccinations (95% CI 0.8 to 100.6), equivalent to approximately 1 feline injection-site sarcoma per 10,000 vaccinations. Between-study heterogeneity was very high ($I^2 = 99.61\%$), reflecting differences in study design, surveillance systems and reporting methods. Subgroup analyses comparing studies conducted before and after 2000 found no significant difference in feline injection-site sarcoma incidence; although lower incidence estimates were observed in later studies, suggesting that the introduction of non-adjuvanted vaccines may have reduced feline injection-site sarcoma incidence. Overall certainty of evidence was rated as very low due to high risk of bias and imprecision.

Clinical Significance: Feline injection-site sarcoma remains a rare adverse event associated with vaccination in cats. Current evidence supports a low absolute incidence and reinforces the importance

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of routine feline vaccination while underscoring the need for improved surveillance and higher quality epidemiologic studies.

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INTRODUCTION

In cats, vaccination is the foundation of preventive care and is associated with preventing morbidity and mortality associated with common diseases like panleukopenia and calicivirus infection (Richards et al., 2006). Acute vaccine-associated adverse events, including anaphylaxis, are rare but well documented (Moore et al., 2007). One of the most rare but serious adverse events that can occur post-vaccination in cats is feline injection site sarcoma (FISS), a late onset but potentially life-threatening complication (Hartmann et al., 2015). FISSs are aggressive, malignant tumours that develop at sites of vaccination or other injections in cats and are characterised by extensive local invasion and have reported metastasis rates ranging from 10% to 28% (Hershey et al., 2000).

Since it was first described in the 1990s, FISS has been reported globally; however, its true frequency, particularly in association with vaccinations, remains uncertain. Incidence has been estimated to range anywhere from 0.3 to 4 in every 10,000 vaccinated cats (Hartmann et al., 2015). These estimates vary widely and are influenced by factors such as surveillance intensity and diagnostic criteria (Kass, 2018). Accurate estimation is further complicated by the diversity of injections administered to cats (not restricted to vaccines), as well as inconsistent reporting of injection sites in relation to subsequent FISS development. Additionally, since FISS is such a rare event, individual studies are often underpowered and produce imprecise incidence estimates. This limitation highlights the value of pooling available data to enhance precision and strengthen overall estimates.

Despite considerable research into the potential pathogenic mechanism linking vaccination with FISS development, a causal relation is still not well established (Kass et al., 1993). One hypothesis is that chronic inflammation following vaccination may contribute to FISS development (Hartmann et al., 2015). In particular, vaccine adjuvants like aluminium have been identified in FISS biopsy samples and have been hypothesised to play a role in the pathogenesis of FISS (Hershey et al., 2000). Similarly, some studies have reported an association between adjuvanted rabies vaccinations and FISS development when compared to non-adjuvanted or recombinant rabies vaccinations (Kass et al., 1993; Sirvio et al., 2025); however, these findings are inconsistent (Gaskell et al., 2002).

To help address some of these uncertainties in the existing literature, we conducted this systematic review and meta-analysis to synthesise available data on the incidence of FISS in vaccinated cats and to assess the quality of the existing studies. Specifically, our objectives were to identify studies which estimate and pool the incidence of FISS following vaccinations, and to explore the incidence for adjuvanted and rabies vaccine types where data permitted.

MATERIALS AND METHODS

Protocol registration

A copy of the protocol developed for this project is publicly available in the University of Guelph's institutional research repository, which provides permanent archiving and a time-stamped record to ensure transparency and reproducibility of the study methods ("Feline injection site sarcoma: a systematic review and meta-analysis protocol", n.d.). This study was developed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Welch et al., 2012), and a populated PRISMA checklist is available in Appendix S1 (Table S1).

Eligibility criteria

To be included in this review, studies had to provide an estimate of sarcoma incidence in vaccinated cats (Table 1). For full-text screening, one additional screening criterion was used: studies were required to either report the overall incidence of FISSs in vaccinated cats or provide sufficient raw data (*i.e.* the number of FISS cases and total vaccinated population) from which incidence could be calculated. We specifically focused on studies reporting absolute measures of frequency (*e.g.* incidence or cumulative incidence) rather than requiring comparative measures (*e.g.* risk ratios or odds ratios), due to the limited availability of appropriate comparator groups across studies.

Search strategy and information sources

The search strategy was developed by a veterinary infectious disease specialist (JSW) (Appendix S2, Tables S2–S4). MEDLINE (*via* OVID), CAB Abstracts and Web of Science were searched from inception to 9 January 2026 using terms related to cats, vaccination, sarcomas and adverse vaccine events. No language or date restrictions were applied. Reference lists of included studies and relevant reviews were manually screened to identify additional citations. While grey literature was not specifically searched, relevant grey literature identified during hand searching of reference lists was included for full-text screening.

Study selection

All retrieved citations were deduplicated and screened in Covidence (Veritas Health Innovation, 2026). Two reviewers (FE, JSW)

Table 1. Summary of inclusion and exclusion criteria used for title and abstract screening and full text screening

	Criteria	Inclusion criteria	Exclusion criteria
Title and abstract screening	Population	The study reports on a population of cats	The study did not report on the population of interest (*e.g.* focuses on other animal species or humans)
	Exposure	The study evaluates vaccination with any type of feline vaccine as the exposure of interest	The study did not assess vaccination as an exposure (*e.g.* focuses on non-vaccine injections, trauma or unrelated medical procedures)
	Outcome	The study reports on FISSs in cats	The study did not report on injection site sarcomas (*i.e.* reported on other tumour types or lacks a clear link to vaccination)
	Study design	Study quantitatively evaluates the effect of an intervention, including case-population, cohort, case–control, cross sectional or surveillance-based incidence studies	The study was qualitative, a review, editorial, opinion piece, case report, conference abstract without data or otherwise did not provide quantitative assessment
Full text screening	Outcome	At full-text level we further assessed whether studies reported the outcome as: 1. FISS incidence in vaccinated cats as a rate, odds ratio, risk ratio or other measure and confidence intervals 2. The raw data from which incidence could be calculated (*i.e.* the number of FISS cases and total vaccinated population of cats)	Studies were excluded if they did not report sufficient data to calculate FISS incidence, if the outcome was not clearly attributable to vaccination or if they focused on FISS outcomes (*i.e.* prognosis).

independently screened titles and abstracts, followed by full-text assessment for eligibility. Disagreements were resolved by consensus.

Data extraction

Data were extracted independently by two reviewers (FE, SN) into a tailored Excel extraction form, which was first tested on two studies (Appendix S3, Table S5). Any conflicts were resolved through consensus. Researchers extracted study identifiers, study design, surveillance method (active, passive, self-reported) and vaccine information (*i.e.* adjuvanted *vs.* non-adjuvanted, rabies *vs.* non-rabies, where available) if reported. Any missing data were recorded on extraction forms, and authors of included studies were contacted twice to provide missing data using the corresponding author's emails or public emails found by searching the web.

Outcomes

To be included, studies needed to report on the primary outcome of interest: the incidence or cumulative incidence of FISSs associated with cat vaccinations (or other proxy), as defined by the study authors. Incidence refers to the occurrence of FISS per vaccination event (*i.e.* cumulative incidence at the vaccination level), and is not a comparative measure of risk between exposed and unexposed groups (Lane, 2013). Although included studies varied in design (cohort, case-population, cross-sectional or surveillance), all extracted outcomes were back-calculated to reflect incidence at the vaccination level. This allowed comparability across study designs while ensuring that estimates represent cumulative incidence rather than prevalence measures. Additionally, since most studies did not include a time component, we could not calculate incidence rate. Eligible studies were required to present either a quantitative estimate of FISS occurrence (*e.g.* cases per 10,000 vaccinated cats or incidence rate) so that the numerator and denominator could be back calculated or the raw data used to estimate FISS occurrence (*i.e.* number of FISS cases and total number of vaccinated cats).

Where available, we also recorded secondary outcomes such as the relative incidence of FISS by vaccine type (*e.g.* adjuvanted *vs.* non-adjuvanted vaccines), vaccine site or number of vaccinations administered. To allow comparability across studies, only studies evaluating vaccination as the primary exposure of interest were included. Studies that compared different exposures (*e.g.* surgical site sarcomas or injection site reactions unrelated to vaccination) or different outcomes (*e.g.* suspected FISS incidence among cats with sarcomas) were excluded, as were studies lacking sufficient data to estimate incidence.

Summary effect measures for outcome

We extracted summary effect measures for the primary outcome, which were the incidence of vaccinations that result in new cases of FISS in cats. For each study, we extracted the raw data to calculate effect estimates [*e.g.* the number of FISS cases and the total number of vaccinated cats (or similar representative value *i.e.* cat visits) during the study period]. If effect estimates were reported (*e.g.* risk ratios, odds ratios or incidence rate ratios) comparing vaccinated and reference groups as defined by the study (*e.g.* unvaccinated cats, non-adjuvanted vaccines or other vaccine types), these values along with their 95% confidence intervals (CIs) were also extracted. We also extracted absolute incidence measures; specifically when vaccine-specific rates or incidence rates were reported, we back-calculated numerators and denominators using the raw data, assumptions or the analytic approach described by the original authors (Efthimiou, 2018). We did not independently verify vaccine attribution and assumed the authors' reported classifications were correct (Lane, 2013). If available, we also extracted any adjusted effect estimates and their corresponding covariates. Studies reporting multiple denominators, such as the number of FISS cases by both cat visits and number of cat vaccinations, were standardised to vaccination-level incidence where possible. If studies reported a range of FISS incidence estimates, the higher value was used as a conservative analytic

choice to avoid systematic bias of the effect estimate towards the null. This means the estimate represents an absolute measure of frequency rather than a comparative measure of epidemiological risk (Lane, 2013).

Risk of bias

Risk of bias was assessed independently by reviewers (FE, SN) using the Joanna Briggs Institute checklist for prevalence and incidence studies (Munn et al., 2015). The Joanna Briggs Institute checklist tool assesses risk of bias across nine domains, including sample representativeness, case ascertainment, diagnostic reliability and adequacy of denominator data. Each domain was rated as low, high or unclear risk. While the Joanna Briggs Institute checklist does not have built in overall assessment, a scoring system of low risk (7 to 9 "Yes" responses), moderate (4 to 6 "Yes" responses) and high (≤3 "Yes" responses) has been applied to other veterinary systematic reviews (Karshima et al., 2022), and this scoring system was used to make an overall risk of bias assessment for each study.

Data synthesis and statistical analysis

Study details were summarised narratively. The primary and secondary outcomes, incidence ratios and their corresponding 95% CI were calculated using random-effects models with maximum likelihood (ML) estimation and Hartung–Knapp adjustment (Röver et al., 2015). The use of random effects meta-analysis to pool study-specific incidences was considered appropriate given the rarity of FISS events and the heterogeneity and non-comparative nature of many included studies, where consistent estimation of relative effect measures was not feasible (Efthimiou, 2018; Lane, 2013). For both primary and secondary analyses, we assessed heterogeneity visually in the generated forest plots and using the I^2 statistic (which reflects between-study heterogeneity) and examined between-study variance using τ^2 (Higgins et al., 2003; Higgins & Thompson, 2002).

Additional analyses

A sensitivity analysis was conducted, which excluded two studies that reported incidence per cat rather than per vaccination (Coyne et al., 1997; Kliczkowska et al., 2015) and one study which captured a shorter time frame after vaccine exposure (only 1 to 2 years following vaccination for most cats captured in this study) which may not have been sufficiently long for FISS cases to develop (Moore et al., 2007). Subgroup analyses and sensitivity analyses were completed using the same methods described above. All analyses were performed using R statistical software (version 4.4.1, 2024) using the *meta* and *metafor* packages.

We also calculated incidence separately for adjuvanted and non-adjuvanted vaccines and for rabies and non-rabies vaccines using subgroup analyses. Our incidence estimates relied exclusively on vaccine-specific attributions as reported by the original authors; we did not independently verify vaccine exposure at tumour sites. Although injection-site sarcomas may develop months to years after vaccination and cats often receive multiple vaccines during this interval, clinical practice commonly assigns different vaccines to distinct limbs (*e.g.* rabies in the right hind) to facilitate later attribution. Nevertheless, misclassification of vaccine attribution remains possible. If non-differential, such misclassification would likely bias effect estimates towards the null.

Additionally, because feline vaccine-site recommendations changed in the early 2000s when the American Academy of Feline Medicine guideline advised that vaccines for feline leukaemia virus (FeLV) and rabies be given as distally as possible in the hind limbs (and core vaccines in the forelimbs) rather than in the interscapular region, we conducted a subgroup analysis comparing incidence in studies from before *versus* after 2000 (Stone et al., 2020). This change was not made specifically to prevent FISS; the intent was to facilitate more effective surgical management (including possible amputation) if a FISS were to occur, since sarcomas require large excision margins (Terry et al., 2017). However, around the same time, the production and use of non-adjuvanted rabies and FeLV vaccines occurred (Hartmann et al., 2015).

Finally, to explore potential methodological influences on reported incidence, we conducted a subgroup analysis comparing studies that identified FISS cases *via* self-reporting by veterinarians *versus* those that identified cases through chart review. We planned to apply the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN) tool to assess the credibility of any subgroup analyses if $P<.10$ (Schandelmaier et al., 2020).

Certainty of evidence and publication bias

The overall certainty of evidence for the primary outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We used GRADEpro software to generate a summary of findings table for our primary outcome of overall FISS incidence ("GRADEpro", n.d.) that presents both the quality of the evidence and corresponding effect estimates for overall FISS incidence. The potential for publication bias was assessed using a funnel plot which was visually examined for evidence of asymmetry which would suggest the presence of small-study effects.

Deviations from protocol

We focused on incidence (*i.e.* cumulative incidence per vaccination event) rather than incidence rate, as most included studies did not report person-time or an accurate time component. The Joanna Briggs Institute checklist for prevalence studies replaced the originally planned tools for risk of bias assessment which evaluates methodological quality and potential bias in studies reporting incidence or prevalence data (Munn et al., 2015).

RESULTS

Study selection

The database search identified 13,926 records, of which 8506 duplicates were removed. Following title and abstract screening,

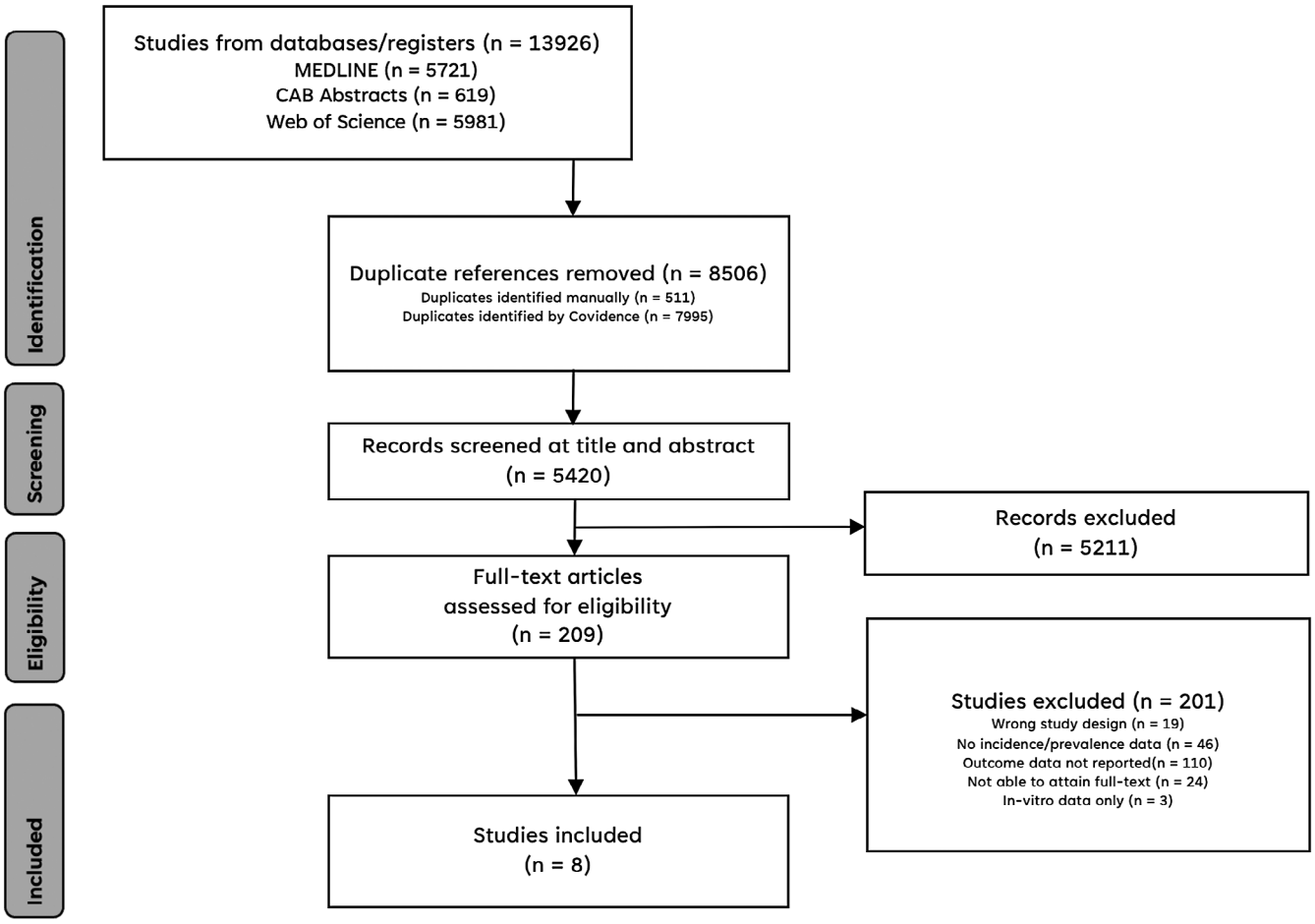

FIG 1. A PRISMA flow diagram depicting the study selection process and exclusion reasons.

5420 studies underwent title and abstract screening, of which 5211 were irrelevant. Two hundred and nine studies were assessed for full-text eligibility, and eight studies met the inclusion criteria for quantitative synthesis (Fig 1). One study in particular was excluded at full text because the authors did not provide numerator or denominator information or data to calculate these values (Valli, 2015).

Study characteristics

Included studies were published between 1993 and 2015, representing data from North America ($n = 5$) (Coyne et al., 1997; Gobar & Kass, 2002; Kass et al., 1993; Lester et al., 1996; Moore et al., 2007) and Europe ($n = 3$) (Dean et al., 2012; Gaskell et al., 2002; Kliczkowska et al., 2015). All studies were observational surveillance-based designs, which relied on veterinarians to self-report FISS cases ($n = 4$) (Coyne et al., 1997; Dean et al., 2012; Gaskell et al., 2002; Gobar & Kass, 2002) or FISS cases that were identified by searching veterinary records ($n = 4$) (Kass et al., 1993; Kliczkowska et al., 2015; Lester et al., 1996; Moore et al., 2007).

Denominators varied substantially. Six studies reported FISS per number of vaccinations either sold or administered, and two reported per number of cat visits (Coyne et al., 1997; Kliczkowska et al., 2015). Several studies estimated the number of vaccines administered from hospital records or based on sales data (Lester et al., 1996; Moore et al., 2007). Case confirmation was typically histopathological (Dean et al., 2012; Gobar & Kass, 2002; Kliczkowska et al., 2015), although several studies relied on veterinarians to self-report FISS cases (Dean et al., 2012; Gobar & Kass, 2002). Histopathological results were not always verified (Dean et al., 2012). Vaccine type and adjuvanted status were inconsistently reported; only one study stratified results by adjuvanted *versus* non-adjuvanted vaccines (Gobar & Kass, 2002), and only two stratified results by rabies *versus* other vaccines (Gobar & Kass, 2002; Kass, 2018). Of the studies that reported FISS incidence associated with rabies vaccination, only one study (Gobar & Kass, 2002) further distinguished between adjuvanted and non-adjuvanted rabies vaccine formulations (Table 2). Vaccine manufacturers were rarely reported.

Risk of bias

Seven of the eight studies included in this review were judged to be at high risk of bias (Coyne et al., 1997; Dean et al., 2012; Gobar & Kass, 2002; Kass et al., 1993; Kliczkowska et al., 2015; Lester et al., 1996), with only one (Moore et al., 2007) assessed

Table 2. Characteristics of studies included in this review

General information	Last name first author, year of publication	Gobar 2002	Coyne 1997	Dean 2013	Gaskell 2002	Kass 1993	Kliczkowska 2015	Lester 1996	Moore 2007
	Study design or type of report	Observational	Observational	Observational	Observational report	Observational	Observational	Observational	Observational
	Country	United States and Canada	United States	United Kingdom	United Kingdom	United States	Poland	Canada	United States
	Date of publication	2002	1997	2013	2002	1993	2015	1996	2007
Vaccinations	Vaccine antigen (s)	Rabies, FeLV, FVRCP±C	Not reported	Not reported	Rabies, FeLV, FVRCP±C	Rabies, FeLV, FVRCP±C	Not reported	FeLV, Rabies	Not reported
FISS	Years data was collected	1998 to 2000	1992	2007	1995 to 1999	1991 to 1992	2008 to 2014	1982 to 1993	2002 to 2004
	Data from before or after 2000	Before 2000	Before 2000	After 2000	Before 2000	Before 2000	After 2000	Before 2000	After 2000
	How was the data collected	Web-based reporting system (self-reported by veterinarians)	A mail-based questionnaire was sent to members of the American vet association of feline practitioners reported by veterinarians (self-reported by veterinarians)	Small animal veterinary practices were asked to participate and could retrospectively submit cases or clinics were contacted after cases were diagnosed at a histopathology laboratory	Veterinarians could voluntarily report cases to a surveillance system (self-reported by veterinarians)	Cases identified retrospectively in charts	Cases were identified retrospectively by searching medical records	Cases were identified retrospectively by searching medical records	Cases were identified retrospectively by searching medical records
	Denominator value	Vaccinations administered	Used cat visits as a proxy for vaccinations	Vaccination visits	Estimated vaccinations administered	Estimated vaccinations administered	Cat visits	Vaccinations administered	Vaccinations administered
Total FISS incidence	FISS numbers	2	158	14	26[#]	185	8	18	0
	Denominator value	61,747	744,993 cat visits	58,516 vaccination visits	12,380,952	525,574	4894 cat visits	13,350	1,258,712 vaccine doses
FISS incidence rabies vaccines	FISS numbers	1	Not reported	Not reported	Not reported	45	Not reported	Not reported	Not reported
	Denominator value	21,033	Not reported	Not reported	Not reported	252,588	Not reported	Not reported	Not reported
FISS incidence non-rabies vaccine	FISS numbers	1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
	Denominator value	40,714	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

(Continues)

Table 2. (Continued)

FISS incidence adjuvanted vaccines	FISS numbers	1	Not reported	Not reported	Rate only reported – 0.053 to 0.011 per 10,000 for vaccines with aluminium-based adjuvants or inactivated vaccines with other adjuvants, respectively	Not reported	Not reported	Not reported	Not reported	Not reported
	Denominator value	48,894	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
FISS incidence non-adjuvanted vaccines	FISS numbers	1	Not reported	Not reported	Rate only reported – 0.009 per 10,000 vaccines	Not reported	Not reported	Not reported	Not reported	Not reported
	Denominator value	27,545	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

FVRCP±C Feline viral rhinotracheitis, feline herpesvirus-1, feline calicivirus and feline parvovirus (panleukopenia) with or without chlamydia [FVRCP±C], FeLV Feline leukaemia virus
[a]Reported as rates originally

as having a moderate overall risk of bias. The most frequent sources of bias stemmed from limitations in study design and outcome capture. Specifically, several studies relied heavily on voluntary veterinarian or laboratory reporting systems (Coyne et al., 1997; Kass et al., 1993; Lester et al., 1996) and estimated the total number of cats vaccinated (Dean et al., 2012; Gobar & Kass, 2002). Ascertainment was another concern across studies since FISS diagnoses were based solely on histopathology submissions to diagnostic laboratories and may miss cases where owners do not want to pursue sampling (Kass et al., 1993; Kliczkowska et al., 2015). Finally, most studies used convenience or voluntary sampling rather than random or consecutive methods (Moore et al., 2007). A summary of the overall risk of bias for each study is provided in Table 2, while domain-specific risk of bias is available in Appendix S4, Fig S1.

Primary meta-analysis

Eight studies were included in the primary meta-analysis, comprising a total of 14,059,036 vaccination opportunities and 411 reported FISS cases. Individual study-level incidences of FISS ranged from almost zero per vaccination (Gaskell et al., 2002; Gobar & Kass, 2002; Moore et al., 2007) to substantially higher rates in some studies (Kliczkowska et al., 2015), indicating wide variation across studies but consistently low absolute incidence. Using a random-effects model with maximum-likelihood estimation for between-study variance and Hartung–Knapp adjustment for the confidence interval, the overall incidence of FISS per vaccination was estimated at 8.83 FISS cases per 100,000 vaccinations (95% CI 0.78 to 100.56) (Fig 2). Heterogeneity among studies was significantly high ($\tau^2 = 6.68$, $\tau = 2.58$, $I^2 = 99.61\%$, $P < .0001$), reflecting substantial between-study variability.

Sensitivity and subgroup analyses

Results from the sensitivity analysis were broadly consistent with the primary meta-analysis. The sensitivity analysis excluded two studies which reported FISS incidence per cat visits instead of vaccinations (Coyne et al., 1997; Kliczkowska et al., 2015) and one study with a shorter (1-year) follow-up period that captured no FISS cases (Moore et al., 2007). This analysis included five studies, comprising a total of 2,233,613 vaccination events and 62.9 reported FISS cases. Individual study-level incidences of FISS ranged from effectively 0 (Gaskell et al., 2002; Gobar & Kass, 2002) per vaccination to higher (Lester et al., 1996), again reflecting a very low absolute frequency of these events. The overall FISS incidence was estimated at 9.66 per 100,000 vaccinations (95% CI 0.42 to 223.69). Between-study heterogeneity remained high ($\tau^2 = 5.06$, $I^2 = 99.22\%$, $P < .0001$).

Subgroup analyses did not demonstrate a statistically significant difference in FISS incidence between rabies and non-rabies vaccines, although heterogeneity could not be calculated for non-rabies vaccines because only one study contributed data. We could not calculate the incidence for adjuvanted *versus* non-adjuvanted vaccines since only one study reported this data. There was also no statistically significant difference in FISS incidence between

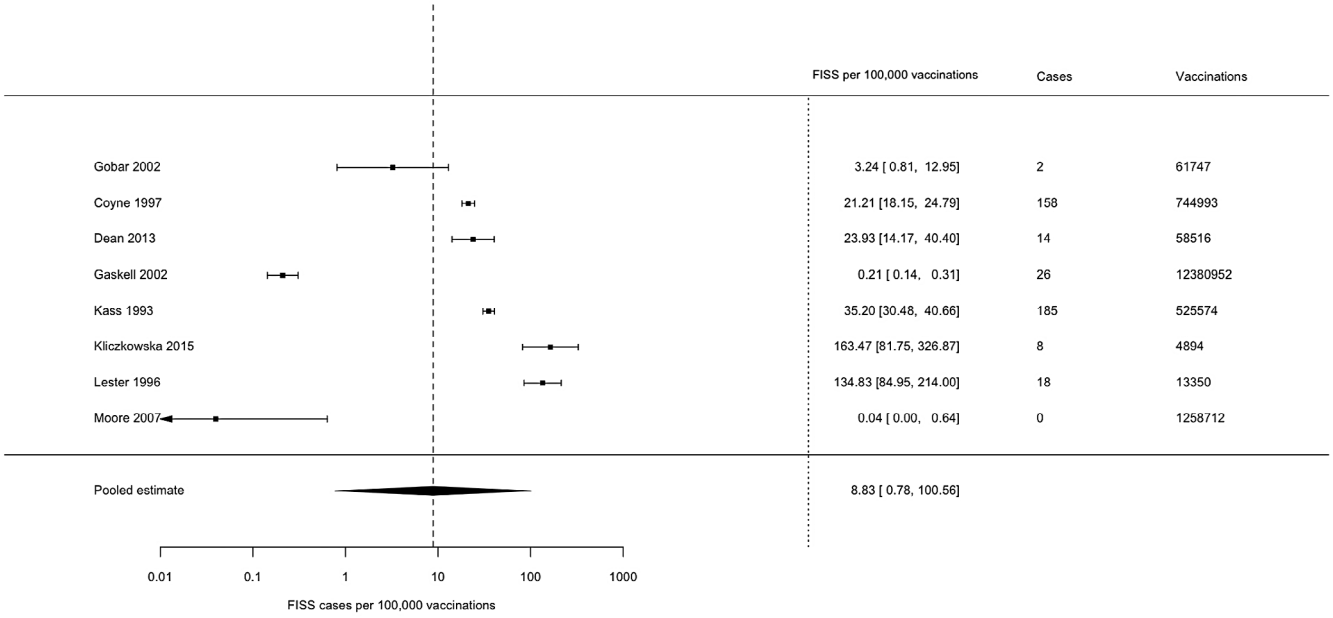

FIG 2. Forest plot of feline injection-site sarcoma incidence per 100,000 vaccinations using a random-effects model with Hartung–Knapp adjustment. The blue diamond represents the pooled estimate with a 95% confidence interval. The overall pooled risk of FISS per vaccination was estimated as 8.83 FISS cases per 100,000 vaccinations (95% CI 0.78 to 100.56).

Table 3. Subgroup meta-analysis examining differences in FISS incidence across vaccine type (rabies *vs.* non-rabies), study period (before *vs.* after implementation of the 2000 feline vaccination site guidelines) and by case ascertainment method (self-reported *vs.* chart review).

Subgroup comparison	Subgroup	Number of studies	Incidence of FISS per 100,000	95% confidence interval	I^2 (%)	τ^2	*P*-value for subgroup difference
Vaccine type	Rabies	2	33.3	0.06 to 398,000	0.0	0	.38
	Non-rabies	1	0.01	0.00 to 2.0	–	–	
Study period	Before 2000	5	11.0	0.03 to 440.0	99.6	6.65	.78
	After 2000	3	7.2	0.06 to 115.0	99.6	6.65	
Case ascertainment method	Self-reported	4	4.34	0.12 to 154.03	98.88	3.73	.507
	Chart review	4	17.26	0.04 to 6657.44	99.31	9.04	

studies conducted before and after the implementation of the 2000 feline vaccination site guidelines, or between studies that had veterinarians self-report FISS cases and those that conducted chart-based reviews to identify cases (Table 3).

Publication bias

The lack of clear symmetry in our funnel plot suggests the possibility of publication bias or small-study effects (Appendix S5, Fig S2). However, given the small number of included studies ($n = 8$) and the fact that FISS is a rare outcome, this pattern may also reflect sampling variability.

Summary of findings and grade assessment of certainty of evidence

The overall quality of evidence for FISS incidence following vaccination was judged to be very low (Table S6). Seven of the eight studies were assessed as high risk of bias, primarily due to study design limitations, data capture methods and sampling approaches. Most studies relied on voluntary reporting by veterinarians and/or estimated denominators through vaccine sales or cat visits (Coyne et al., 1997; Kass et al., 1993; Lester et al., 1996). Additionally, for most studies, FISS diagnoses were based on histopathology submissions alone, potentially missing cases where FISS was suspected, and histopathology was not pursued by owners (Kass et al., 1993; Kliczkowska et al., 2015). Statistical limitations, including the lack of confidence intervals, stratified analyses or adjustment for non-response, further reduce the certainty of the estimates. Consequently, the evidence was downgraded across multiple GRADE domains, including for risk of bias, imprecision (due to small sample sizes, sparse events and heterogeneity in reporting practices).

DISCUSSION

In our systematic review and meta-analysis of eight studies, contributing 14,059,036 vaccination opportunities for FISS, we found an incidence rate of 8.83 FISS per 100,000 cat vaccinations (95% CI 0.78 to 100.56 per 100,000; very low certainty); however, there are significant limitations in the

data based on the certainty of evidence, the typically indistinct reporting of vaccines and vaccination sites, and limited information about other types of injections that may have been administered. Excluding studies that reported per-cat incidence or had limited follow-up did not substantially change the estimate. Overall, our findings still support the rarity of FISS as an adverse vaccination event, which aligns with previous studies (Gobar & Kass, 2002; Kass et al., 1993), but the heterogeneity between the studies we identified suggests the observed variability in reported FISS incidence may reflect differences between studies rather than random error. This underscores the need for standardised case definitions, reporting time frames and consistent surveillance approaches across regions and vaccine types (Shaw et al., 2009).

Some studies reported slightly higher rates (Kliczkowska et al., 2015; Lester et al., 1996), exceeding 100 cases per 100,000 vaccinations. These rates may be due to smaller estimated numbers of cat vaccinations and biased reporting or surveillance systems. Some of the more recent large-scale surveillance studies (Moore et al., 2007) found near-zero rates, which could reflect improved vaccine formulations, better injection-site practices (Shaw et al., 2009) or be a reflection of improved surveillance systems. Our subgroup analysis found no significant difference in FISS incidence before and after 2000, suggesting that the introduction of vaccine site recommendations and changes in vaccine formulations may not have produced a detectable reduction in reported FISS cases at the population level (Hartmann et al., 2015; Shaw et al., 2009). However, like our primary analysis, the wide confidence intervals and high heterogeneity indicate substantial variability in study design. Further, data are not available about adoption of those changes, and anecdotally, use of older injection site practices and adjuvanted vaccines remains common.

Adjuvanted vaccines (including adjuvanted rabies vaccines) have been hypothesised to increase FISS incidence due to local inflammatory responses (Hershey et al., 2000). Concerns have been heightened by identification of aluminium, linked to adjuvants, at the site of sarcomas (Dean et al., 2012; Madewell et al., 2001). While we could not compare adjuvanted vaccines to non-adjuvanted vaccines, a subgroup meta-analysis of rabies *versus* non-rabies vaccines found no statistically significant difference in FISS incidence between the two vaccine types, although only two studies contributed vaccine-specific data. Although we did find the point estimate for rabies vaccines was numerically higher than that for non-rabies vaccines, this difference was accompanied by extremely wide confidence intervals and was driven by sparse data, including only a single study contributing to the non-rabies subgroup.

Case–control studies have reported that cats vaccinated with adjuvanted rabies or FeLV vaccines had a significantly higher incidence of developing FISS, compared to the Feline Viral Rhinotracheitis (herpesvirus), Calicivirus and Panleukopenia (feline distemper) vaccines (Kass et al., 1993; Srivastav et al., 2012). However, the accuracy of these findings has been questioned based on limitations in the data and interpretations. The European Advisory Board on Cat Diseases reported that the introduction of recombinant non-adjuvanted rabies and FeLV vaccines did not significantly reduce the incidence of FISS, suggesting that other factors may contribute to tumour development (Hartmann et al., 2015). This finding highlights the low certainty and extremely rare nature of FISS, regardless of adjuvant or antigen type.

This review is limited by the small number of studies, inconsistent denominators (vaccinations *vs*. cat visits), and the overall high risk of bias across the captured studies. Additionally, multiple sources of bias may have influenced reported prevalence and incidence estimates, in both directions. Overestimation may occur because not all sarcomas arising at injection sites are necessarily caused by injections, and not all injection-site sarcomas are attributable to vaccination specifically, as cats may receive other injectable medications (Davidson & Lawrence, 2016). Some included studies may have captured FISS cases that developed before the study period or included cases without precise attribution to the observation window, which could also lead to overestimation (Davidson & Lawrence, 2016). Although the term FISS broadly encompasses sarcomas associated with injections, this review focuses primarily on vaccination as the most implicated and best-documented exposure, recognising that vaccination is likely the most common but not the only contributor to feline injection site sarcomas (Davidson & Lawrence, 2016). Conversely, under-reporting from general practice settings and a lack of comprehensive denominator data (*i.e.* poor estimations of the total number of cats vaccinated) could lead to underestimation of FISS rates. For example, different methods of case ascertainment were used across studies: self-reported *versus* chart-based identification. Although not statistically significant, studies which reviewed charts appear to report higher FISS incidence. Since the latency period between vaccination and tumour development is believed to be prolonged and remains poorly defined, unless studies follow cats for their entire lifespan, delayed-onset cases may not be captured within typical surveillance windows (Ladlow, 2013). Overall, the incomplete denominator data, voluntary reporting, inconsistent diagnostic confirmation and non-representative sampling frames suggest that available FISS incidence estimates may be imprecise and potentially inflated (Scherk et al., 2013). Finally, because our meta-analysis is based on incidence estimates rather than comparative effect measures, it does not allow direct estimation of causal relationships or relative risk between exposures; meaning incidence of FISS per vaccination event should not be interpreted as a comparative measure of risk between vaccinated and unvaccinated cats (Lane, 2013).

The incidence suggests that FISS is a rare outcome occurring after a small fraction of cat vaccinations. Although substantial heterogeneity and methodological weaknesses across studies mean that this estimate is of very low certainty, even the upper bound of the confidence interval (100.56 per 100,000 vaccinations, approximately 0.1%) represents a rare clinical event. Current data are inadequate to provide a confident assessment of the relative incidence from adjuvanted *versus* non-adjuvanted vaccines, different vaccine antigens or other potentially relevant factors. Continued surveillance will be essential to refine

incidence estimates and guide evidence-based vaccination policy for cats going forward (Squires et al., 2024; Stone et al., 2020). While the lack of studies identified by this review highlights the importance of continued monitoring and improved reporting of FISSs, the overall incidence of FISS should not deter standard vaccination practices in cats, which remain the cornerstone of feline preventive care (Richards et al., 2006).

Author contributions

F. Emdin: Conceptualization; methodology; formal analysis; writing – original draft; writing – review and editing. **N. Daneman:** Methodology; writing – review and editing; conceptualization; investigation. **S. G. Naro:** Methodology; formal analysis; writing – review and editing. **K. A. Brown:** Methodology; writing – review and editing; formal analysis; conceptualization. **J. S. Weese:** Conceptualization; methodology; investigation; data curation; validation; writing – original draft; writing – review and editing; project administration; supervision. **P. M. Hoang:** Conceptualization; methodology; writing – review and editing.

Conflict of interest

The authors do not have any competing interests to declare.

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AI disclosure statement

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Data availability statement

All data generated or analysed during this study are included in this published article and its Supporting Information files.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. PRIMSA checklist.

Table S1. Populated PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) checklist for recommended items to address in a systematic review and meta-analysis.
Appendix S2. Search strategy, OVID Medline.
Table S2. Search strategy, OVID Medline.
Table S3. Search strategy, CAB.
Table S4. Search strategy, Web of Science.
Appendix S3. Data extraction table.
Table S5. Extraction fields.
Appendix S4. Risk of bias.
Fig S1. Traffic-light plot for the risk of bias domains using Joanna Briggs Institute checklist for prevalence.
Appendix S5. Funnel plot.
Fig S2. Funnel plot of effect size (logit event rate) by standard error for studies included in the meta-analysis. Red dots represent studies published before 2000 and blue represent those published after 2000.
Appendix S6. GRADE.
Table S6. GRADE assessment of FISS incidence following vaccination in cats.