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Vaccination and Seasonality as Risk Factors for Development of Meningoencephalitis of Unknown Origin in 172 Dogs

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ABSTRACT

Background: Meningoencephalitis of unknown origin (MUO) is a neuroinflammatory disease that is suspected to be immune-mediated. Vaccination and season inconsistently have been reported as risk factors for development of MUO in dogs, but limited prospectively collected data is available to evaluate these potential risk factors.

Objective: Prospectively evaluate the association between vaccination and season and the development of MUO in dogs.

Animals: A total of 172 client-owned dogs diagnosed with MUO.

Methods: Dogs were enrolled prospectively from August 2021 through July 2023. Signalment, body weight, vaccination history, and season of onset of neurologic signs were recorded. The incidence rate ratio (IRR) of MUO within various post-vaccination windows was statistically compared to a referent window of 451–560 days post-vaccination. The incidence rate (IR) of MUO in each season was compared statistically.

Results: Of dogs vaccinated within the previous 450 days, MUO IRR was highest in the first 0–45 days (IRR = 9.14; confidence interval [CI] = 4.04–20.71), followed by 46–90 days (IRR = 4.86; CI = 2.01–11.71) and 91–180 days (IRR = 4.86; CI = 2.15–10.96) post-vaccination compared to the 451–560 day post-vaccination referent window. The MUO IR was slightly more common in the spring (28.5%) and least common in the summer (19.8%). No significant difference in IR between seasons was identified.

Conclusions and Clinical Importance: In dogs with potential vaccine-associated MUO, the highest risk to develop MUO may be in the first 45 days post-vaccination. A slowly developing immune response to vaccination over 3–6 months may occur in some dogs. There is no apparent association between season and the development of MUO.

1 | Introduction

Immune-mediated inflammatory disease accounts for up to 25% of central nervous system (CNS) disease in dogs [1]. Granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME), and necrotizing leukoencephalitis (NLE) are neuroinflammatory conditions of unknown etiopathogenesis that fall under the umbrella of meningoencephalitis

Abbreviations: AAHA, American Animal Hospital Association; ACIP, Advisory committee on Immunization Practices; AEFI, adverse events following immunization; CNS, central nervous system; CSF, cerebrospinal fluid; DAPP, distemper, adenovirus, parvovirus, parainfluenza virus; DAPPL, distemper, adenovirus, parvovirus, parainfluenza virus, leptospirosis; EAE, experimental autoimmune encephalomyelitis; GBS, Guillain-Barré syndrome; GME, granulomatous meningoencephalomyelitis; IMHA, immune-mediated hemolytic anemia; IR, incidence rate; IRR, incidence rate ratio; ITP, immune-mediated thrombocytopenia; MMR, measles-mumps-rubella; MRI, magnetic resonance imaging; MS, multiple sclerosis; MUO, meningoencephalitis of unknown origin; NLE, necrotizing leukoencephalitis; NME, necrotizing meningoencephalitis; SRMA, steroid-responsive meningitis-arteritis; VAPA, vaccine-associated polyarthritis.

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of unknown origin (MUO) [1–4]. Infectious agents, toxicants, and environmental factors are known triggers for immune-mediated neuroinflammatory diseases in humans, but similar triggers have yet to be identified in dogs [1–3, 5–13]. Vaccination inconsistently has been reported as a trigger for multiple autoimmune diseases in humans and dogs [7, 14–19]. Guillain-Barré syndrome (GBS) has been associated with influenza vaccination in people, and the measles-mumps-rubella (MMR) vaccine has been associated with the development of immune-mediated thrombocytopenia (ITP) in children [20–22]. Increased risk for development of multiple sclerosis (MS) has been associated with recent hepatitis B vaccination [23]. Despite these findings, controversy remains about the association between vaccination and onset and risk of relapse of immune-mediated diseases in humans [18, 20, 21, 24–29].

Limited studies have suggested that recent vaccination, defined as vaccine administration within 4–6 weeks preceding clinical signs [17, 24], has been associated with development of immune-mediated hemolytic anemia (IMHA) [17] and vaccine-associated polyarthritis (VAPA) in dogs [30]. Relapse of IMHA and VAPA also has been reported after vaccination [30, 31]. A conflicting study showed no association between vaccination and development of IMHA [32]. No association has been identified between vaccination and development of GME [7], steroid-responsive meningitis-arteritis (SRMA) [14], and ITP in dogs [24] in retrospective studies. Veterinary studies evaluating the association between vaccination and development of immune-mediated disease are limited by small patient numbers and retrospective design, which carries inherent case selection bias and lesser ability to determine cause and effect.

Our objective was to prospectively investigate the association between vaccination window and development of MUO. A second objective was to prospectively evaluate whether there is a seasonal predilection for development of MUO. We hypothesized that vaccination within the previous 45 days would be significantly associated with development of MUO and that significantly fewer dogs would be presented during the winter.

2 | Materials and Methods

We prospectively enrolled dogs diagnosed with MUO over a 2-year (730-day) period from August 1, 2021 to July 31, 2023. All dogs were required to have complete medical records and detailed vaccination history over the previous 2 years for inclusion in the study. The diagnosis of MUO was made based on standard ante-mortem diagnostic criteria including magnetic resonance imaging (MRI) findings of T2-weighted and fluid attenuation inversion recovery (FLAIR) hyperintense lesions [33] and cerebrospinal fluid (CSF) cytology (mononuclear pleocytosis, total nucleated cell count > 5 cells/μL) as previously described [1–3, 33]. All owners signed informed consent for enrollment in the study.

We recorded the following data on presentation: age, breed, sex, body weight, date of onset of neurologic signs, and date of presentation. Records then were retrospectively reviewed to record date of vaccinations over the past 2 years (and up to 5.5 years) and time from most recent vaccination to onset of clinical signs. We recorded administration data of the following vaccines: rabies; leptospirosis; canine influenza virus; coronavirus; Lyme; Bordetella (including intranasal, injectable, and oral); the combination vaccine distemper, adenovirus, parvovirus, parainfluenza virus (DAPP); and the combination vaccine distemper, adenovirus, parvovirus, parainfluenza virus, leptospirosis (DAPPL). Season of year clinical signs developed (Winter: December, January, February; Spring: March, April, May; Summer: June, July, August; Fall: September, October, November) was recorded.

Statistical analysis was performed using commercial software [STATA SE, v.18.0, StataCorp LLC, College Station, TX]. Numerical data were summarized as median (range) because of nonparametric distributions. Time in days between the most recent vaccination(s) and the onset of clinical signs was categorized in time intervals of 0–45, 46–90, 91–180, 181–270, 271–360, 361–450, 451–540, and > 540 days. Comparison of incidence rates (IR) of MUO in time windows after the most recent vaccination were calculated as incidence rate ratios (IRR) between time intervals using conditional fixed effects Poisson regression [34]. The referent was a 90-day window from 451 to 540 days, which was chosen to exclude time periods up to and around the time for annual booster vaccinations. The chi-square test of independence was used to compare seasonal rates of MUO diagnosis. Values of $p < 0.05$ were considered significant.

3 | Results

3.1 | Signalment

One-hundred and seventy-two dogs were included in the study. The median age at first onset of clinical signs was 5 years (range, 0.18–15.3 years). Median body weight was 15.9 kg (range, 2.1–72.6 kg). Seventy-four dogs (43%) were female (11 intact, 63 spayed) and 98 dogs were male (57%; 12 intact, 86 neutered). Fifty-six breeds were represented. Labrador or Labrador mixes were most common (13/172; 7.56%) followed by French Bulldogs (12/172; 7%) and Chihuahua or Chihuahua mixes (12/172; 7%). The total list of breeds is available in Table S1

3.2 | Disease Subtype

Of the 172 cases, necrotizing lesions were suspected on MRI in four Pugs with possible NME and one Yorkshire Terrier with possible NLE. Given the small number of cases with necrotizing lesions, these dogs were not separated from the total for statistical comparison.

3.3 | Vaccination Data

Time since last vaccination with any vaccine for all dogs ranged from 0 to 1787 days, with a median of 191 days. More dogs received no vaccines in the previous 450 days (44/172; 25.6%) compared with any other vaccination window. The IRR of diagnosis of MUO after the first two 45-day and following 90-day time intervals post-vaccination compared to a reference window of 451–560 days post-vaccination is listed in Table 1. Of dogs

vaccinated in the previous 450 days, the IRR to develop MUO was highest in the first 45 days post-vaccination (IRR = 9.14; 95% CI = 4.04–20.71; $p < 0.001$; Figure 1). Although too small in number to make any reliable statistical comparison, two of the five dogs with potential necrotizing lesions on MRI had been vaccinated in the previous 45 days, one was vaccinated 10 months before, and two were vaccinated > 1 year before.

The number of vaccine antigens administered at the last vaccine encounter ranged from 1 to 7 (median, 4) and included 1 in 67 (35.1%) dogs, 2 in 19 (10.0%) dogs, 3 in 4 (2.1%) dogs, 4 in 21 (11.0%) dogs, 5 in 35 (18.3%) dogs, and 6 in 28 (14.7%) dogs. This distribution was similar for the 32 dogs that received a vaccine in the 45 days preceding neurological signs. Vaccines most frequently administered in the 45 days preceding neurological signs were DAPP alone (8/32; 25.0%), Bordetella alone (6/32; 18.8%), Leptospira alone (6/32; 18.8%), Rabies + DAPPL + Bordetella (3/32; 9.4%), Leptospirosis + Bordetella (3/32; 9.4%), and Rabies alone (2/32; 6.3%).

TABLE 1 | Incidence rate ratio (IRR) of diagnosis of meningoencephalitis of unknown origin (MUO) in dogs for various post-vaccination time windows.

Time since last vaccination (days)	IRR	95% CI	*p*-value
0–45	9.14	4.04–20.71	< 0.001
46–90	4.86	2.01–11.71	< 0.001
91–180	4.86	2.15–10.96	< 0.001
181–270	2.14	0.87–5.26	0.096
271–360	3.43	1.48–7.96	< 0.001
361–450	0.86	0.29–2.55	0.782
451–560[a]	1.00	NA	NA

[a]Referent window.

3.4 | Seasonal Data

Forty-nine (28.5%) dogs developed neurologic signs in the spring, 34 (19.8%) in the summer, 45 (26.2%) in the fall, and 44 (25.6%) in the winter. No significant association was found between season and incidence of MUO ($p = 0.13$).

4 | Discussion

We found an increased risk (> 9 ×) to develop MUO in the first 45 days post-vaccination (in dogs vaccinated in the previous 450 days), lack of a specific antigenic trigger, and absence of seasonal risk. Vaccination is not a risk factor in many dogs with MUO because approximately 25% of dogs in our study were vaccinated > 450 days before the onset of clinical signs. The potential for vaccination to trigger induction or relapse of MUO is controversial and dictates recommendations for future vaccinations in dogs with immune-mediated diseases. Although the risk to develop MUO was highest in the first 6 weeks post-vaccination, an almost five-fold increased risk from 6 weeks to 6 months emphasizes the complexity of the immune response to vaccination and variability in different dogs.

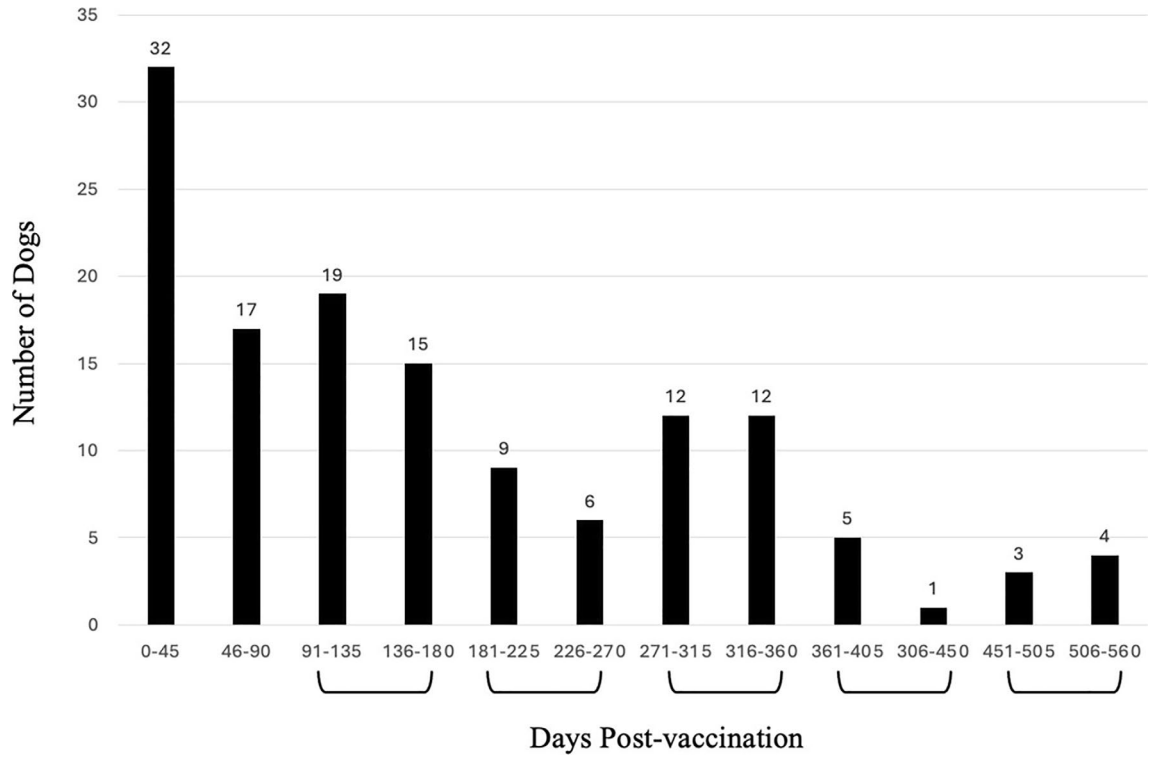

FIGURE 1 | Incidence of meningoencephalitis of unknown origin (MUO) in 45-day time windows post-vaccination. Some 45-day intervals were combined to form 90-day time windows, shown as brackets, for analysis.

The mechanisms by which vaccines potentially trigger autoimmune activation are not well understood, and evidence for an association between vaccines and autoimmunity in humans has been based largely on uncontrolled observational studies [35]. Generally, vaccines can cause immediate or delayed hypersensitivity reactions [36]. Immediate hypersensitivity reactions usually occur within 15 min of immunization and causality can more definitively be determined [36]. Delayed hypersensitivity reactions can occur weeks after vaccination, making establishment of causal association challenging [36]. Most delayed reactions are classified as Type IV reactions, mediated through activated CD4+ or CD8+ T cell mediated cytokine production or both, causing a hyperinflammatory environment [36]. Other proposed mechanisms for auto-immune reaction include molecular mimicry, where a similarity between vaccine components and host proteins causes the immune system to attack normal tissue; reaction to the chemical constituents of the vaccine; and acceleration of an underlying immune process by vaccinal viral epitopes [25, 26, 31, 37, 38].

Vaccines contain complex agents and adjuvants including aluminum, which remain in the body for an extended period of time [17, 23] and elicit an immune response weeks after inoculation [17]. Most studies in humans evaluating delayed hypersensitivity reactions and the development of immune-mediated diseases use a 6–12 week follow-up period [36, 39–43]. Guillain Barré Syndrome, Bell's Palsy, MS, and acute disseminated encephalomyelitis all have been reported as adverse events post-immunization [36]. Studies evaluating the risk of developing GBS after immunization report increased risk within 6 weeks after vaccination [39–43], but symptom onset can occur years after vaccination in some patients [39]. A prospective study evaluating the risk of development of MS after hepatitis B vaccination identified an increased odds ratio of 3.1 within the 3 years after vaccination [44]. It is challenging to accurately evaluate the potential for a vaccine reaction when the time frame necessary for a vaccine to stimulate the immune system and ultimately produce clinical signs is poorly understood. Time windows also may differ for various immune-mediated diseases. We opted to use time windows up to 450 days in our study to more accurately reflect immunological processes over an extended period of time. We anticipated the auto-immune activity in the first two 6-week time intervals may have been distinct. The following time windows from 3 to 6, 6 to 9, and 9 to 12 months were assumed to be more uniform and were therefore grouped together. Our results suggested the highest risk in the first 45 days post-vaccination, similar to what has been reported with some neuroinflammatory diseases of humans including GBS.

Vaccine-induced autoimmunity likely involves a combination of genetic and environmental factors in addition to stimulation of the immune system [37, 38]. Sequential vaccine administration may be necessary to incite chronic immune stimulation and subsequently trigger an autoimmune disease [24], and frequent, long-term vaccination may increase the chance of an aberrant immune response [45]. Dogs are frequently vaccinated starting at the age of 6–8 weeks and continue to receive vaccines every 2–4 weeks until > 16 weeks of age [46]. Dogs have the most vaccination visits before 9 months [47], but the American Animal Hospital Association (AAHA) recommends boosters every 3 years for the distemper, adenovirus, parvovirus, parainfluenza, and rabies vaccines, leading to vaccination of dogs throughout most of their lifetime [46]. Many dogs are vaccinated on a yearly basis for *Leptospira* and *Bordetella bronchiseptica* based on recommendations by AAHA and requirements for *B. bronchiseptica* vaccination before allowing dogs at boarding facilities, daycare, parks, and shows [46]. In contrast, the Advisory Committee on Immunization Practices (ACIP) in humans recommends more frequent vaccination with frequent boosters in the first 0–6 years of age with fewer vaccines between 7 and 18 years of age and the fewest vaccinations in adults ≥ 19 years of age [48]. The difference in vaccination frequency between dogs and humans may contribute to a different pathogenesis or increased relative risk of development of immune-mediated diseases in dogs, and the complexity of evaluating multiple vaccinations over years makes identifying a causal relationship challenging.

No seasonal predilection for MUO was identified, substantiating the results of a previous retrospective study in dogs with GME [7]. In contrast, multiple studies have substantiated a seasonal predilection for the development of MS [49–51], inflammatory bowel disease [52], Type 1 diabetes [53], and many other immune-mediated diseases in humans [54]. Similarly, seasonal predilections have been identified for non-neuroinflammatory diseases, such as IMHA in dogs [55]. Distinct seasonal weather patterns occur in this geographical location; seasonality may have a different impact in regions with less variability.

Certain breeds have a known predisposition to develop immune-mediated neuroinflammatory diseases [56–60]. French Bulldogs were the second-most common breed in our study, which may reflect both breed popularity and predisposition to develop MUO. However, French Bulldogs (0.56%) recently have surpassed Dachshunds (0.49%) in having the highest adverse event rate after vaccination [47]. Therefore, it is possible that vaccination in this breed carries a higher risk for development of MUO. There was a higher percentage of large-breed dogs in our cohort compared with some other MUO studies, which likely reflects breed popularity in the state (six of the eight top dog breeds are large or giant breed dogs).

Limitations of our study include lack of histopathological confirmation of MUO, a common problem in studies where patients respond well to treatment. Although we found significantly increased risk to develop MUO after vaccination in several time windows, the CI ranges are wide and therefore significance needs to be interpreted cautiously. No case-controls were included for univariate analysis or to serve as the referent, and future studies should consider including case-controls to strengthen the study design. Defining and finding an appropriate control group is a recognized challenge in human medical and veterinary vaccine safety studies, particularly when the adverse event outcome of interest is very uncommon or rare. The self-controlled case series design [34] was employed in our study to try and overcome the limitation of identifying an unvaccinated control group. We chose a referent time window of 451–540 days to evaluate time periods up to and around the time of annual booster vaccinations, but other referent time windows could be justifiable. Our study evaluated initial onset of neurological signs only; evaluating potential relapse after vaccination in a separate cohort would provide additional information as to the potential risk of repeat vaccination in dogs with previously diagnosed MUO. A

large-scale multidisciplinary prospective study documenting the development of immune-mediated disease (MUO and others) in vaccinated dogs would be another potentially better approach to determine the true incidence of MUO post-vaccination.

5 | Conclusions

We found the highest risk to develop MUO to occur within the first 45 days post-vaccination (of dogs receiving vaccines in the previous 15 months). No significant association was found between seasonality and development of MUO. Further research is required to better understand the mechanisms and time frame of delayed immune reaction and potential for increased genetic risk for vaccination reaction in some breeds (e.g., French Bulldog).

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Authors declare no Institutional Animal Care and Use Committee (IACUC) or other approval was needed. Authors declare human ethics approval was not needed.

Conflicts of Interest

George E. Moore served as Consulting Editor for Experimental Design and Statistics for the Journal of Veterinary Internal Medicine. He was not involved in the review of this manuscript. No other authors have a conflicts of interest.

References

1. S. Vitale and K. Foss, "Immune-Mediated Central Nervous System Disease—Current Knowledge and Recommendations," *Topics in Companion Animal Medicine* 34 (2019): 22–29, https://doi.org/10.1053/j.tcam.2018.11.003.

2. J. R. Coates and N. D. Jeffery, "Perspectives on Meningoencephalomyelitis of Unknown Origin," *Veterinary Clinics of North America: Small Animal Practice* 44, no. 6 (2014): 1157–1185, https://doi.org/10.1016/j.cvsm.2014.07.009.

3. L. R. Talarico and S. J. Schatzberg, "Idiopathic Granulomatous and Necrotising Inflammatory Disorders of the Canine Central Nervous System: A Review and Future Perspectives," *Journal of Small Animal Practice* 51, no. 3 (2010): 138–149, https://doi.org/10.1111/j.1748-5827.2009.00823.x.

4. A. de Lahunta, E. Glass, and M. Kent, "10—Small Animal Spinal Cord Disease," in *De Lahunta's Veterinary Neuroanatomy and Clinical Neurology*, 5th ed., ed. A. de Lahunta, E. Glass, and M. Kent (W.B. Saunders, 2021), 267–311.

5. J. C. Wohlsein and A. Tipold, "Steroid-Responsive Meningitis-Arteritis: What Have We Learned Since 2010? A Narrative Review," *Veterinary Journal* 300–302 (2023): 106030, https://doi.org/10.1016/j.tvjl.2023.106030.

6. A. Kipar, W. Baumgärtner, C. Vogl, K. Gaedke, and M. Wellman, "Immunohistochemical Characterization of Inflammatory Cells in Brains of Dogs With Granulomatous Meningoencephalitis," *Veterinary Pathology* 35, no. 1 (1998): 43–52, https://doi.org/10.1177/030098589803500104.

7. H. L. B. Heller, M. N. Granick, M. E. Pinkerton, and N. S. Keuler, "Case–Control Study of Risk Factors for Granulomatous Meningoencephalomyelitis in Dogs," *Journal of the American Veterinary Medical Association* 254, no. 7 (2019): 822–825, https://doi.org/10.2460/javma.254.7.822.

8. E. J. O'Neill, D. Merrett, and B. Jones, "Granulomatous Meningoencephalomyelitis in Dogs: A Review," *Irish Veterinary Journal* 58, no. 2 (2005): 86–92, https://doi.org/10.1186/2046-0481-58-2-86.

9. J. B. Thomas and C. Eger, "Granulomatous Meningoence-Phalomyelitis in 21 Dogs," *Journal of Small Animal Practice* 30, no. 5 (1989): 287–293, https://doi.org/10.1111/j.1748-5827.1989.tb01558.x.

10. S. Schwab, C. Herden, F. Seeliger, et al., "Non-suppurative Meningoencephalitis of Unknown Origin in Cats and Dogs: An Immunohistochemical Study," *Journal of Comparative Pathology* 136, no. 2–3 (2007): 96–110, https://doi.org/10.1016/j.jcpa.2006.11.006.

11. R. M. Barber, Q. Li, P. P. V. P. Diniz, et al., "Evaluation of Brain Tissue or Cerebrospinal Fluid With Broadly Reactive Polymerase Chain Reaction for Ehrlichia, Anaplasma, Spotted Fever Group Rickettsia, Bartonella, and Borrelia Species in Canine Neurological Diseases (109 Cases)," *Journal of Veterinary Internal Medicine* 24, no. 2 (2010): 372–378, https://doi.org/10.1111/j.1939-1676.2009.0466.x.

12. R. M. Barber, B. F. Porter, Q. Li, et al., "Broadly Reactive Polymerase Chain Reaction for Pathogen Detection in Canine Granulomatous Meningoencephalomyelitis and Necrotizing Meningoencephalitis," *Journal of Veterinary Internal Medicine* 26, no. 4 (2012): 962–968, https://doi.org/10.1111/j.1939-1676.2012.00954.x.

13. S. J. Schatzberg, N. J. Haley, S. C. Barr, A. de Lahunta, and N. J. Sharp, "Polymerase Chain Reaction Screening for DNA Viruses in Paraffin-Embedded Brains From Dogs With Necrotizing Meningoencephalitis, Necrotizing Leukoencephalitis, and Granulomatous Meningoencephalitis," *Journal of Veterinary Internal Medicine* 19, no. 4 (2005): 553–559, https://doi.org/10.1892/0891-6640(2005)19[553:pcrsfd]2.0.co;2.

14. J. H. Rose, M. Kwiatkowska, E. R. Henderson, N. Granger, J. K. Murray, and T. R. Harcourt-Brown, "The Impact of Demographic, Social, and Environmental Factors on the Development of Steroid-Responsive Meningitis-Arteritis (SRMA) in the United Kingdom," *Journal of Veterinary Internal Medicine* 28, no. 4 (2014): 1199–1202, https://doi.org/10.1111/jvim.12360.

15. J. F. McAnulty and R. G. Rudd, "Thrombocytopenia Associated With Vaccination of a Dog With a Modified-Live Paramyxovirus Vaccine," *Journal of the American Veterinary Medical Association* 186, no. 11 (1985): 1217–1219.

16. M. K. Axthelm and S. Krakowka, "Canine Distemper Virus-Induced Thrombocytopenia," *American Journal of Veterinary Research* 48, no. 8 (1987): 1269–1275.

17. D. Duval and U. Giger, "Vaccine-Associated Immune-Mediated Hemolytic Anemia in the Dog," *Journal of Veterinary Internal Medicine* 10, no. 5 (1996): 290–295, https://doi.org/10.1111/j.1939-1676.1996.tb02064.x.

18. S. Y and A. AM, "Vaccination and Autoimmunity—'Vaccinosis': A Dangerous Liaison?," *Journal of Autoimmunity* 14, no. 1 (2000): 1–10, https://doi.org/10.1006/jaut.1999.0346.

19. A. Langer-Gould, L. Qian, S. Y. Tartof, et al., "Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases," *JAMA Neurology* 71, no. 12 (2014): 1506–1513, https://doi.org/10.1001/jamaneurol.2014.2633.

20. L. H. Martín Arias, R. Sanz, M. Sáinz, C. Treceño, and A. Carvajal, "Guillain-Barré Syndrome and Influenza Vaccines: A Meta-Analysis," *Vaccine* 33, no. 31 (2015): 3773–3778, https://doi.org/10.1016/j.vaccine.2015.05.013.

21. R. S. Fadrique, L. M. Arias, J. A. Molina-Guarneros, N. J. Bulnes, and P. G. Ortega, "Guillain-Barré Syndrome and Influenza Vaccines: Current Evidence," *Revista Española de Quimioterapia* 32, no. 4 (2019): 288–295.

22. E. K. France, J. Glanz, S. Xu, et al., "Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children," *Pediatrics* 121, no. 3 (2008): e687–e692, https://doi.org/10.1542/peds.2007-1578.

23. H. Orbach, N. Agmon-Levin, and G. Zandman-Goddard, "Vaccines and Autoimmune Diseases of the Adult," *Discovery Medicine* 9, no. 45 (2010): 90–97.

24. A. A. Huang, G. E. Moore, and J. C. Scott-Moncrieff, "Idiopathic Immune-Mediated Thrombocytopenia and Recent Vaccination in Dogs," *Journal of Veterinary Internal Medicine* 26, no. 1 (2012): 142–148, https://doi.org/10.1111/j.1939-1676.2011.00850.x.

25. A. Schattner, "Consequence or Coincidence? The Occurrence, Pathogenesis and Significance of Autoimmune Manifestations After Viral Vaccines," *Vaccine* 23, no. 30 (2005): 3876–3886, https://doi.org/10.1016/j.vaccine.2005.03.005.

26. H. Qasim, A. Rahhal, A. Husain, et al., "Immune Thrombocytopenia Relapse in Patients Who Received mRNA COVID-19 Vaccines," *Journal of Blood Medicine* 14 (2023): 295–302, https://doi.org/10.2147/JBM.S396026.

27. J. G. Kelton, "Vaccination-Associated Relapse of Immune Thrombocytopenia," *Journal of the American Medical Association* 245, no. 4 (1981): 369–370.

28. B. Tackenberg, M. Schneider, F. Blaes, et al., "Acetylcholine Receptor Antibody Titers and Clinical Course After Influenza Vaccination in Patients With Myasthenia Gravis: A Double-Blind Randomized Controlled Trial (ProPATIent-Trial)," *eBioMedicine* 28 (2018): 143–150, https://doi.org/10.1016/j.ebiom.2018.01.007.

29. J. F. Rahier, M. Moutschen, A. Van Gompel, et al., "Vaccinations in Patients With Immune-Mediated Inflammatory Diseases," *Rheumatology* 49, no. 10 (2010): 1815–1827, https://doi.org/10.1093/rheumatology/keq183.

30. B. Kohn, M. Garner, S. Lübke, D. Bennett, L. Brunnberg, and B. Kohn, "Polyarthritis Following Vaccination in Four Dogs," *Veterinary and Comparative Orthopaedics and Traumatology* 16, no. 1 (2003): 6–10, https://doi.org/10.1055/s-0038-1632747.

31. A. Moon and J. Veir, "Vaccination and Associated Adverse Events in Dogs Previously Treated for Primary Immune-Mediated Hemolytic Anemia," *Journal of the American Animal Hospital Association* 55, no. 1 (2019): 29–34, https://doi.org/10.5326/JAAHA-MS-6868.

32. A. P. Carr, D. L. Panciera, and L. Kidd, "Prognostic Factors for Mortality and Thromboembolism in Canine Immune-Mediated Hemolytic Anemia: A Retrospective Study of 72 Dogs," *Journal of Veterinary Internal Medicine* 16, no. 5 (2002): 504–509, https://doi.org/10.1111/j.1939-1676.2002.tb02378.x.

33. G. B. Cherubini, S. R. Platt, T. J. Anderson, et al., "Characteristics of Magnetic Resonance Images of Granulomatous Meningoencephalomyelitis in 11 Dogs," *Veterinary Record* 159, no. 4 (2006): 110–115, https://doi.org/10.1136/vr.159.4.110.

34. H. J. Whitaker, C. P. Farrington, B. Spiessens, and P. Musonda, "Tutorial in Biostatistics: The Self-Controlled Case Series Method," *Statistics in Medicine* 25, no. 10 (2006): 1768–1797, https://doi.org/10.1002/sim.2302.

35. M. De Martino, E. Chiappini, and L. Galli, "Vaccines and Autoimmunity," *International Journal of Immunopathology and Pharmacology* 26, no. 2 (2013): 283–290, https://doi.org/10.1177/039463201302600201.

36. C. A. Stone, C. R. F. Rukasin, T. M. Beachkofsky, and E. J. Phillips, "Immune-Mediated Adverse Reactions to Vaccines," *British Journal of Clinical Pharmacology* 85, no. 12 (2019): 2694–2706, https://doi.org/10.1111/bcp.14112.

37. Y. Segal and Y. Shoenfeld, "Vaccine-Induced Autoimmunity: The Role of Molecular Mimicry and Immune Crossreaction," *Cellular & Molecular Immunology* 15, no. 6 (2018): 586–594, https://doi.org/10.1038/cmi.2017.151.

38. L. J. Gershwin, "Adverse Reactions to Vaccination: From Anaphylaxis to Autoimmunity," *Veterinary Clinics of North America. Small Animal Practice* 48, no. 2 (2018): 279–290, https://doi.org/10.1016/j.cvsm.2017.10.005.

39. E. Israeli, N. Agmon-Levin, M. Blank, J. Chapman, and Y. Shoenfeld, "Guillain–Barré Syndrome—A Classical Autoimmune Disease Triggered by Infection or Vaccination," *Clinical Reviews in Allergy and Immunology* 42, no. 2 (2012): 121–130, https://doi.org/10.1007/s12016-010-8213-3.

40. J. C. Kwong, P. P. Vasa, M. A. Campitelli, et al., "Risk of Guillain-Barré Syndrome After Seasonal Influenza Vaccination and Influenza Health-Care Encounters: A Self-Controlled Study," *Lancet Infectious Diseases* 13, no. 9 (2013): 769–776, https://doi.org/10.1016/S1473-3099(13)70104-X.

41. G. Sk, R. M, W. Es, et al., "Risk of Confirmed Guillain-Barre Syndrome Following Receipt of Monovalent Inactivated Influenza A (H1N1) and Seasonal Influenza Vaccines in the Vaccine Safety Datalink Project, 2009–2010," *American Journal of Epidemiology* 175, no. 11 (2012): 1100–1109, https://doi.org/10.1093/aje/kws195.

42. R. Y. S. Keh, S. Scanlon, P. Datta-Nemdharry, et al., "COVID-19 Vaccination and Guillain-Barré Syndrome: Analyses Using the National Immunoglobulin Database," *Brain* 146, no. 2 (2023): 739–748, https://doi.org/10.1093/brain/awac067.

43. D. A. Salmon, M. Proschan, R. Forshee, et al., "Association Between Guillain-Barré Syndrome and Influenza A (H1N1) 2009 Monovalent Inactivated Vaccines in the USA: A Meta-Analysis," *Lancet* 381, no. 9876 (2013): 1461–1468, https://doi.org/10.1016/S0140-6736(12)62189-8.

44. M. A. Hernán, S. S. Jick, M. J. Olek, and H. Jick, "Recombinant Hepatitis B Vaccine and the Risk of Multiple Sclerosis," *Neurology* 63, no. 5 (2004): 838–842, https://doi.org/10.1212/01.WNL.0000138433.61870.82.

45. O. A. Idowu and K. L. Heading, "Type 1 Immune-Mediated Polyarthritis in Dogs and Lack of a Temporal Relationship to Vaccination," *Journal of Small Animal Practice* 59, no. 3 (2018): 183–187, https://doi.org/10.1111/jsap.12774.

46. J. Ellis, E. Marziani, C. Aziz, et al., "2022 AAHA Canine Vaccination Guidelines," *Journal of the American Animal Hospital Association* 58, no. 5 (2022): 213–230, https://doi.org/10.5326/JAAHA-MS-Canine-Vaccination-Guidelines.

47. G. E. Moore, J. Morrison, E. K. Saito, N. Spofford, and M. Yang, "Breed, Smaller Weight, and Multiple Injections Are Associated With Increased Adverse Event Reports Within Three Days Following Canine Vaccine Administration," *Journal of the American Veterinary Medical Association* 261, no. 11 (2023): 1653–1659, https://doi.org/10.2460/javma.23.03.0181.

48. A. P. Wodi, N. Murthy, H. Bernstein, V. McNally, S. Cineas, and K. Ault, "Advisory Committee on Immunization Practices Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2022," *MMWR. Morbidity and Mortality Weekly Report* 71, no. 7 (2022): 234–237, https://doi.org/10.15585/mmwr.mm7107a2.

49. Ø. Torkildsen, N. Grytten, J. Aarseth, K.-M. Myhr, and M. T. Kampman, "Month of Birth as a Risk Factor for Multiple Sclerosis: An Update," *Acta Neurologica Scandinavica* 126, no. 195 (2012): 58–62, https://doi.org/10.1111/ane.12040.

50. L. D. Balbuena, R. M. Middleton, K. Tuite-Dalton, T. Pouliou, K. E. Williams, and G. J. Noble, "Sunshine, Sea, and Season of Birth: MS Incidence in Wales," *PLoS One* 11, no. 5 (2016): e0155181, https://doi.org/10.1371/journal.pone.0155181.

51. C. J. Willer, D. A. Dyment, A. D. Sadovnick, et al., "Timing of Birth and Risk of Multiple Sclerosis: Population Based Study," *BMJ* 330, no. 7483 (2005): 120, https://doi.org/10.1136/bmj.38301.686030.63.

52. G. Disanto, G. Chaplin, J. M. Morahan, et al., "Month of Birth, Vitamin D and Risk of Immune-Mediated Disease: A Case Control Study," *BMC Medicine* 10 (2012): 69, https://doi.org/10.1186/1741-7015-10-69.

53. T. Kimpimäki, A. Kupila, A. M. Hämäläinen, et al., "The First Signs of Beta-Cell Autoimmunity Appear in Infancy in Genetically Susceptible Children From the General Population: The Finnish Type 1 Diabetes Prediction and Prevention Study," *Journal of Clinical Endocrinology and Metabolism* 86, no. 10 (2001): 4782–4788, https://doi.org/10.1210/jcem.86.10.7907.

54. A. Watad, S. Azrielant, N. L. Bragazzi, et al., "Seasonality and Autoimmune Diseases: The Contribution of the Four Seasons to the Mosaic of Autoimmunity," *Journal of Autoimmunity* 82 (2017): 13–30, https://doi.org/10.1016/j.jaut.2017.06.001.

55. L. Kidd, R. Rasmussen, E. Chaplow, K. Richter, S. Hill, and P. G. Slusser, "Seasonality of Immune-Mediated Hemolytic Anemia in Dogs From Southern California," *Journal of Veterinary Emergency and Critical Care* 24, no. 3 (2014): 311–315, https://doi.org/10.1111/vec.12186.

56. A. Tipold and S. J. Schatzberg, "An Update on Steroid Responsive Meningitis-Arteritis," *Journal of Small Animal Practice* 51, no. 3 (2010): 150–154, https://doi.org/10.1111/j.1748-5827.2009.00848.x.

57. M. Lowrie, J. Penderis, M. McLaughlin, P. D. Eckersall, and T. J. Anderson, "Steroid Responsive Meningitis-Arteritis: A Prospective Study of Potential Disease Markers, Prednisolone Treatment, and Long-Term Outcome in 20 Dogs (2006–2008)," *Journal of Veterinary Internal Medicine* 23, no. 4 (2009): 862–870, https://doi.org/10.1111/j.1939-1676.2009.0337.x.

58. A. Tipold, R. Fatzer, A. Jaggy, A. Zurbriggen, and M. Vandevelde, "Necrotizing Encephalitis in Yorkshire Terriers," *Journal of Small Animal Practice* 34, no. 12 (1993): 623–628, https://doi.org/10.1111/j.1748-5827.1993.tb02598.x.

59. K. A. Greer, A. K. Wong, H. Liu, et al., "Necrotizing Meningoencephalitis of Pug Dogs Associates With Dog Leukocyte Antigen Class II and Resembles Acute Variant Forms of Multiple Sclerosis," *Tissue Antigens* 76, no. 2 (2010): 110–118, https://doi.org/10.1111/j.1399-0039.2010.01484.x.

60. I. Schrauwen, R. M. Barber, S. J. Schatzberg, et al., "Identification of Novel Genetic Risk Loci in Maltese Dogs With Necrotizing Meningoencephalitis and Evidence of a Shared Genetic Risk Across Toy Dog Breeds," *PLoS One* 9, no. 11 (2014): e112755, https://doi.org/10.1371/journal.pone.0112755.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.