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RESEARCH ARTICLE

Density matters: How population dynamics of house mice (*Mus musculus*) inform the epidemiology of *Leptospira*

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Abstract

1. Rodents are maintenance hosts of numerous pathogens, and both their density and the pathogen prevalence determine the risk they pose to other animals or humans. However, density is often overlooked. We investigated a capture-mark-recapture-sampling strategy to study introduced mice (*Mus musculus*) and *Leptospira* as a model and demonstrate the advantages of a combined approach.
2. We estimated population density and *Leptospira* prevalence in mice in a replicated longitudinal survey conducted between 2016 and 2018. Capture-mark-recapture sessions were undertaken at two sites in Spring and Autumn and blood and kidney samples were collected at the end of each session. Mouse density and areas of activity were estimated using spatially explicit capture–recapture (SECR) models and both were compared between *Leptospira* positive and negative mice. *Leptospira* exposure and shedding status were estimated using Microscopic Agglutination Test, and a combination of culture and *lipL32* PCR on kidneys.
3. *Leptospira* prevalence was higher in spring (83%–86%) than in autumn (31%–37%) and mouse densities simultaneously varied from 3.6 to 55.9/ha. However, despite these variations in prevalence and density, the density of infected animals remained relatively constant over time (3–8/ha). Shedding or being seropositive was also associated with the activity of mice. Shedding or seropositive mice had a larger activity area, and seropositive mice were trapped on average 1 day earlier than seronegative mice.
4. *Synthesis and applications*: Our results show how understanding the population dynamics of pathogen-carrying rodents is critical in epidemiology. The wider movement patterns and easier encounters of positive mice highlight the possibility of biases in classical prevalence surveys and have implications for disease transmission within and between species. Importantly, and quite counter-intuitively, *Leptospira* prevalence was negatively associated with mouse density, resulting in a constant density of shedders that contradicts the conventional view of higher exposure risk at high rodent density. More broadly, such sampling designs can improve animal and disease control policies and better inform modelling studies by providing more parameter estimates than classical prevalence surveys.

KEYWORDS
abundance, disease ecology, hybrid mixture model, *Leptospira borgpetersenii* serovar Ballum, micromammals, negative density dependence, wildlife disease surveillance

1 | INTRODUCTION

Population density is a fundamental parameter in epidemiological studies but is often unknown when studying wild populations and, therefore, an overwhelming majority of epidemiological studies only investigate disease prevalence. Studies using capture-mark-recapture and seroprevalence data have focused on the force of infection but not the density of infected animals (Gamble et al., 2020; Lambert et al., 2022). The fluctuations in densities of maintenance hosts of zoonotic pathogens are as important to consider as the prevalence, as both can affect the level of environmental contamination or human and other animal species contact rates and exposure (Plowright et al., 2017). These fluctuations also impact the capture rate in a studied population and can lead to overconfidence in prevalence estimates, as bias and variance of the latter increase when the capture rate is low (Walton et al., 2016).

Disease transmission is a complex process with multiple modes and routes, unmeasurable directly, and usually modelled assuming either frequency- or density-dependent transmission. In density-dependent models, contact rates and hence transmission are expected to be low at low densities, with resulting low prevalence. Frequency-dependent models assume that contact rates and transmission are rather impacted by changes in the proportion of infected individuals (i.e. prevalence), as in sexually transmitted infections. The choice of an approach can be challenging and field observations are critical to build appropriate models (Antonovics, 2017; Borremans et al., 2017).

Leptospirosis, a zoonosis caused by pathogenic *Leptospira* bacteria, is most often acquired by direct contact with urine of infected mammalian hosts or indirect contact with contaminated water environments. New Zealand has a higher leptospirosis incidence than other temperate countries (Thornley et al., 2002) with eight of over 300 globally recognised serovars identified: *Leptospira borgpetersenii* serovars Hardjobovis, Ballum, Balcanica, Tarassovi, Pacifica; and *L. interrogans* serovars Pomona, Copenhageni and Canicola (Wilkinson et al., 2023). The country's mammalian diversity, almost entirely comprised of introduced animal species including pets and farm animals or invasive 'pest' species like rodents and possums, provides a unique ecological context for leptospirosis. Leptospirosis in New Zealand has been associated with farm and meat workers most often infected by livestock-maintained serovars Hardjobovis and Pomona, although targeted by livestock vaccination, they have decreased in incidence and other serovars like Tarassovi and especially Ballum are emerging (Benschop et al., 2021; Marshall & Chereshsky, 1996; Nisa et al., 2020). Recent studies suggest vaccinated livestock can shed other serovars, including Ballum, albeit at a low rate (Yupiana, 2019). Research on Ballum in its wild hosts is rare (Moinet et al., 2021) but 1970s studies showed that mice *Mus musculus*, black and brown rats *Rattus rattus* and *R. norvegicus* and hedgehogs *Erinaceus europaeus* could harbour this serovar (Brockie, 1977; Brockie & Till, 1977; Hathaway et al., 1981). The potential for spillover from wild maintenance hosts to livestock has been proposed (Moinet et al., 2021, 2023), with competitive population dynamics among both *Leptospira* serovars and introduced mammals (especially rodents) likely playing an important role in disease dynamics and transmission. Epidemiological studies could thus benefit greatly from an ecological perspective on disease dynamics. Similarly, studies investigating mouse densities in New Zealand have only focused on forest and scrub habitats in the context of conservation, rather than public health (Moinet et al., 2021), and a true 'One Health' perspective may be better-attained by addressing ecological and epidemiological parameters simultaneously.

We conducted a long-term population dynamics study on mice in a New Zealand farm previously identified as a high-risk site for leptospirosis in livestock and humans. We concomitantly investigated the temporal fluctuations in mouse densities and the dynamics of *Leptospira* infection in mice using spatially explicit capture–recapture (SECR) methods. We also investigated if *Leptospira* infection was associated with mouse fitness by comparing activity areas and capture probabilities between infected and uninfected mice.

2 | MATERIALS AND METHODS

2.1 | Study site

A 2-year longitudinal study was conducted on a dairy farm in New Zealand's coastal Manawatū-Whanganui region, previously investigated for *Leptospira* infection in humans (Benschop et al., 2017) and livestock (Yupiana et al., 2019) following a leptospirosis outbreak, and where mice were the dominant introduced rodent. The farm spans 130 ha of lowland exotic grass pastures and is adjacent to a commercial pine forest plantation. The terrain is flat (average elevation: 20 m) with patches of recently cut (1–5 years) pine trees around pastures (Figure 1). The dairy herd is moved to a new paddock twice daily on a rotation length of 17.5 days, and the grass kept low (<15 cm) by grazing. Around pastures, grass or vegetation is cropped infrequently and can reach up to 50 cm. Rodent control around farm buildings is irregular and was not implemented just before or during this study. Poison baiting operations targeting introduced common brushtail possums (*Trichosurus vulpecula*) had been conducted in the neighbouring forest before this study began and were repeated once in the months preceding the last sampling session.

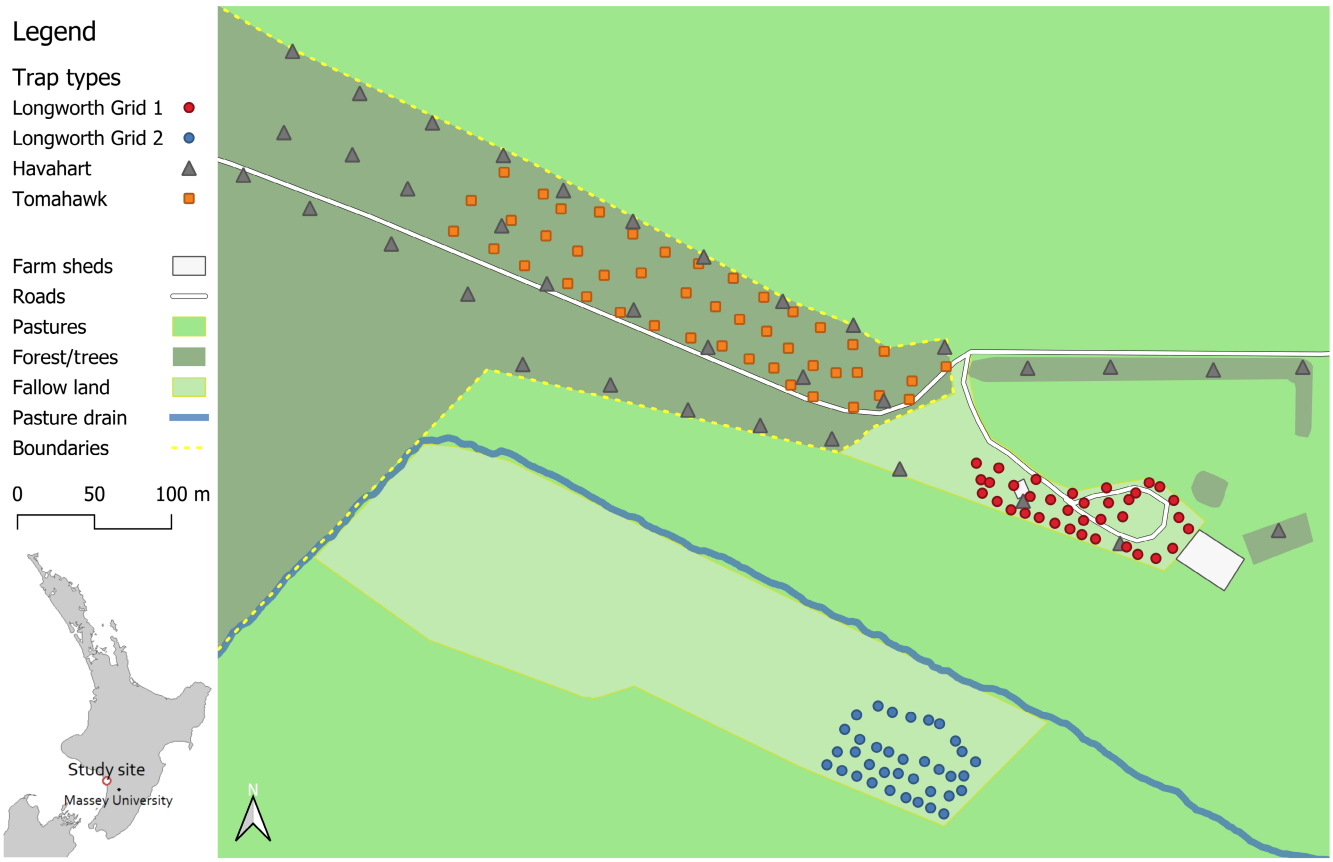

FIGURE 1 Map of farm study site and trap layout.

2.2 | Capture and sampling

From Spring 2016 to Autumn 2018, four live-trapping sessions (A1–A4) were organised, using Longworth small mammal live-traps (Penlon Ltd., Oxford, UK) set on two grids (Grid1 and Grid2) located outside pastures to avoid the risk of livestock interference and flooding (Figure 1). Grids consisted of 36 traps with ~10 m spacing approximately 175 m apart and were separated by a pasture with a drain running in the middle. Traps were set for 10–12 nights per session with peanut butter and pieces of apple covered with a mix of sugar and cinnamon as baits and checked every morning. To target larger introduced mammals such as common brushtail possums, hedgehogs, black and brown rats and feral cats, additional Tomahawk and Havahart live-traps were set around the farm (Figure 1 and Supporting Information). Procedures performed on animals were approved by Massey University Animal Ethics Committee under protocol 16/93.

In Phase I–CMR (Capture-Mark Recapture, first five nights) mice were anesthetised using isoflurane (Attane, Bayer) insufflated in a plastic bag, ear-tagged (Mouse eartag Style 1005–1, National Band & Tag Company, Newport, KY, USA), weighed and released. In Phase II–Removal (subsequent five to seven nights), mice captured or recaptured were anaesthetized, blood-sampled and euthanized to retrieve serum and kidneys for *Leptospira* serology, PCR and culture. Urine samples were also collected opportunistically during both sessions. In both phases, weight, sex, age and an estimation of the reproductive status (immature/active) were recorded. In phase II, other body measurements (tail length, total body length and hind leg length) were also noted. We used a 50 g Pesola® scale and weighed mice to the nearest 0.5 g, a 40 cm ruler to measure the tail and total length to the nearest mm, and a calliper to measure the hind leg to the nearest 0.1 mm.

2.3 | *Leptospira* infection status determination

The presence of antibodies against *Leptospira* spp. was tested using the Microscopic Agglutination Test (MAT) as described in (Moinet et al., 2023), at dilutions 1:24 to 1:3072, with a panel representing all five serogroups known to circulate in animals in New Zealand: Sejroe, Ballum and Tarassovi (*Leptospira borgpetersenii* serovars Hardjobovis, Ballum and Tarassovi) and Pomona and Icterohaemorrhagiae (*Leptospira interrogans* serovars Pomona and Copenhageni). In addition, the direct presence of *Leptospira* spp. in the kidneys was tested by culture in three serial dilutions of EMJH+5-fluorouracil (first two sessions), later replaced by a unique mix of EMJH+STAFF (Sulfamethoxazole, Trimethoprim, Amphotericin B, Fosfomycin and 5-Fluorouracil; Chakraborty et al., 2011) to avoid contamination (two last sessions). Cultures were checked weekly to fortnightly under a dark field microscope

for 14 weeks. In some instances, leptospires were visible but could not be isolated. Cultures were considered positive for those animals. Finally, the presence in the kidneys of pathogenic *Leptospira* spp. DNA was tested by real-time PCR targeting the *lipL32* gene as described by (Galloway & Hoffmaster, 2015).

Mice with a MAT titre ≥48 for Ballum were considered 'seropositive'. Continuous excretion of leptospires in the urine has been described in mice experimentally infected by Ballum (Soupé-Gilbert et al., 2017), thus, all mice with a positive culture and/or PCR were considered to be 'shedding' leptospires. Finally, all mice positive with at least one method were considered to have been 'exposed' to *Leptospira*. Exact confidence intervals of observed prevalence and seroprevalence were calculated based on the binomial distribution (Dohoo et al., 2009).

2.4 | Sampling bias

Since some animals caught in phase I and released were not caught in phase II and, therefore, not tested, we also checked for the possibility of a selection bias in the time of sampling for *Leptospira* infection status. We used the χ^2 test (or Fischer's exact test when expected frequencies were insufficient) to test for an association with the age or sex of animals captured in phase I only, phase II only, or both; and a t-test to check if serological or shedding status influenced the day on which the animal was first captured.

2.5 | SECR modelling

Densities of mice were estimated using SECR models using R version 3.4.2 and package 'secr' version 3.2.0 (Efford, 2019b). Borchers and Efford (2008) give a detailed description of the statistical methods on which these models rely. To account for the removal of mice from the population, mice sampled in phase II (as well as seven accidental deaths or euthanasia cases during phase I) were assigned known capture histories of zero with probability equals one following removal (i.e. it is impossible to recapture a dead mouse).

The capture function was described as a half normal curve with two parameters, g_0 (probability to detect a mouse when home range centre and trap coincide) and σ (sigma, spatial scale over which this probability declines). The density *D* was derived from the capture and distribution functions (Borchers & Efford, 2008). As in (Russell, 2012), the parameter σ was interpreted as a proxy of the distance an animal moves from its home range centre, and, derived from it, the 95% circular probability density area of capture A (where $A=\pi[2.45\sigma]^2$) gave an indication of the area of animal activity.

We treated each grid (Grid1, Grid2) within trapping session (A1–A4) as a distinct 'session' (i.e. sessions 1–8) and used the season, year, grid and/or 'trapping session' number (i.e. A1–A4) as session covariates. Conditional likelihood methods allow inclusion of individual animal covariates, so we also included the age (adult/juvenile) and sex of all individuals. Furthermore, because the information on serological and/or shedding status of mice was missing for some individuals, hybrid mixture models were used to estimate *Leptospira* status differences in mouse detection. These mixture models combine known classes (e.g. sex or age) and a latent class, hence the name hybrid. They include a mixing proportion parameter, 'pmix', that was allowed to vary between trapping sessions and that represented the proportion of either seropositive or shedding mice in the population (Efford, 2019a).

To build the models we took a 3-stage approach. We first checked for effects of session covariates. We then investigated individual mouse covariates. Finally, we included the parameters in the hybrid mixture models, either with seropositivity or shedding status as a latent class. Only one individual parameter with two levels can be included in hybrid mixture models in secr v3.2.0, so no models with both shedding and seropositivity status were built. At all stages, candidate models were compared using an AIC framework (Borchers & Efford, 2008) with models retained based on lowest AICc (comparison of models between stages is not possible due to different likelihood functions).

3 | RESULTS

Across all sessions, 231 different mice were caught in a total of 345 captures (Table 1). Morphological summaries are given for adult mice in Supporting Information. Forty-four mice were caught only in phase I (the first five nights of release trapping). Of them, 12 were sampled: four died during anaesthesia and had all laboratory tests done, one had serology only, two were found dead in traps and had culture and PCR done but no serology, and four only had a urine sample submitted to culture. One mouse was preyed upon in the trap by a weasel in Spring 2017 and was counted in the capture history, but sex and *Leptospira* status could not be investigated.

Female and male mice and juvenile and adult mice were as likely to be caught in phase I only, in phase II only, or in both (respectively $\chi^2=0.62$, df = 2, *p*-value = 0.73 for sex and $\chi^2=3.05$, df = 2, *p*-value = 0.22 for age).

In total, 192 mice were tested for serology, PCR and/or culture (Table 1) and 104 were positive at least once (Table 2). All PCR assays with positive amplification had a cycle threshold value <37. All but one seropositive mice were positive for Ballum, and several also had titres against other serovars (Table 2). The seropositive mouse with no detectable antibodies against Ballum had a titre of 96 for Hardjobovis. This mouse, which also had a negative PCR and culture, was considered as seronegative in the subsequent analyses.

Across all sessions, the proportions of seropositive and shedding mice were significantly different in juveniles and adults. Adults were more likely to be seropositive (52/112 adults vs. 16/71 juveniles, $\chi^2=9.63$, df = 1, *p*-value = 0.0019) and to be shedders (69/118 adults vs. 26/73 juveniles, $\chi^2=8.53$, df = 1, *p*-value = 0.0035). No significant difference between sex was found among seropositives (23/62 females vs. 45/121 males, $\chi^2=7.71\ e^{-31}$, df = 1, *p*-value = 1) or shedding mice (32/66 females vs. 63/125 males, $\chi^2=0.0099$, df = 1,

TABLE 1 Numbers of house mice (*Mus musculus*) trapped in a New Zealand dairy farm environment and sampled for *Leptospira* detection between 2016 and 2018 per session and grid.

Trapping session	Season	Grid	Session	Trap nights	Detections[a]	Animals	Adults	Juveniles	Phase			Not sampled	MAT	Culture and/or PCR
									I only	II only	Both			
A1	Spring 2016	1	1	360	19	15	9	6	6	7	2	5	8	10
		2	2	360	22	17	14	3	2	12	3	3	14	13
A2	Autumn 2017	1	3	360	95	55	37	18	16	25	14	16	34	39
		2	4	360	82	48	17	31	8	24	16	8	39	40
A3	Spring 2017	1	5	432	12	11	9	2	1	9	1	1	10	10
		2	6	432	27	14	11	3	3	5	6	2	12	12
A4	Autumn 2018	1	7	432	45	37	26	11	3	30	4	1	35	36
		2	8	432	43	34	19	15	5	22	7	3	31	31
Total				3168	345	231	142	89	44	134	53	39	183	191

[a]Total number of captures.

TABLE 2 Session prevalence and seroprevalence for *Leptospira* infection assessed by Culture, Polymerase Chain Reaction (PCR) and Microscopic Agglutination Test (MAT) in a population of mice.

		Shedding status		Microscopic agglutination test (MAT)					
	#	Culture	PCR	Hardjobovis	Pomona	Ballum	Tarassovi	Copenhageni	Overall
A1–Spring 2016	24	10/24 42% [22, 63]	19/23 83% [61, 95]	7/22 32% [14, 55]	1/22 5% [0, 23]	13/22 59% [36, 79]	3/22 14% [3, 35]	2/22 9% [1, 29]	13/22 59% [36, 79]
A2–Autumn 2017	79	16/61 26% [16, 39]	23/74 31% [21, 43]	0/73 0% [0, 5]	0/73 0% [0, 5]	18/73 25% [15, 36]	0/73 0% [0, 5]	1/73 1% [0, 7]	18/73 25% [15, 36]
A3–Spring 2017	22	16/22 73% [50, 89]	19/22 86% [65, 97]	4/22 18% [5, 40]	1/22 5% [0, 23]	17/22 77% [55, 92]	0/22 0% [0, 15]	2/22 9% [1, 29]	17/22 77% [55, 92]
A4–Autumn 2018	67	21/67 31% [21, 44]	25/67 37% [26, 50]	1/66 2% [0, 8]	0/66 0% [0, 5]	20/66 30% [20, 43]	0/66 0% [0, 5]	3/66 5% [1, 13]	21/66 32% [21, 44]

Note: Numbers positive/tested, the % and [95% confidence interval] are indicated.

p-value = 0.92). Seroprevalence in animals captured in both phases (50% [24/48]) was significantly different from seroprevalence in animals captured in phase II only (32% [42/130], $\chi^2 = 4.70$, df = 1, p-value = 0.030).

No significant difference was found for adult versus juvenile mice in time of first capture—that is the number of days since the beginning of the session ($t = -0.76$, df = 201.05, p-value = 0.45), or female versus male ($t = -0.14$, df = 174.43, p-value = 0.89), or shedders versus non-shedders ($t = 0.23$, df = 188.77, p-value = 0.82). There was no significant difference in time of first capture for mice captured only in phase I, or in both phases (two-sample $t = -0.43$, df = 94.08, p-value = 0.67). There was a small but significant difference in the mean time of first capture for seropositive ($\overline{m} = 5.4$ nights, SD = 2.7) and seronegative ($\overline{m} = 6.6$ nights, SD = 2.7) mice (two-sample $t = -2.91$, df = 140.16, p-value = 0.0042), with seropositive mice being first captured on average a day earlier than seronegative mice.

Most of the non-shedding mice were captured during autumn sessions, and when both shedding and serological status were known, 36% (33/92) of the shedding animals were 'silent shedders' (i.e. had no detectable antibodies) (Figure 2 and Supporting Information). The proportion of silent shedders was as high as 71% for juvenile mice during autumn sessions (respectively 7/10 in 2017 and 5/7 in 2018).

Data on other sympatric wild mammals concurrently trapped and sampled appears in Supporting Information.

The session model that had the greatest AICc weight (55%) was the model where the probability g_0 to detect a mouse varied with year and σ, the spatial scale over which this probability declines, varied with the session (Table 3), followed by the model where both g_0 and σ varied with session (24%). We thus retained only the session and year covariates for the subsequent models. The individual model that had the greatest AICc weight (29%) was the model where the probability g_0 to detect a mouse varied with session and mouse age and σ, the spatial scale over which this probability declines varied with the session, followed by the model where both g_0 and σ varied with session and age (16%, Table 3). The hybrid mixture model including *Leptospira* seropositivity that had the greatest AICc weight (50%) was where g_0 varied with the session and age, σ varied with the session and seropositivity status, and the mixing proportion varied by trapping session. This was followed by a similar model where g_0 also varied with the seropositivity status (24%, Table 3). The hybrid mixture model incorporating *Leptospira* shedding with the highest AICc weight (42%) was also the one where g_0 varied with the session, age and shedding status, σ varied with the session and shedding status, and the mixing proportion varied by trapping session. Estimates of g_0, σ and the resulting densities and areas of activity are presented for the latter (Tables 4 and 5 and Figure 3). Juvenile mice had a lower g_0 than adult mice. Mice shedding *Leptospira* had a lower g_0 but a higher σ, and similarly, mice with antibodies against *Leptospira* had a higher σ (but

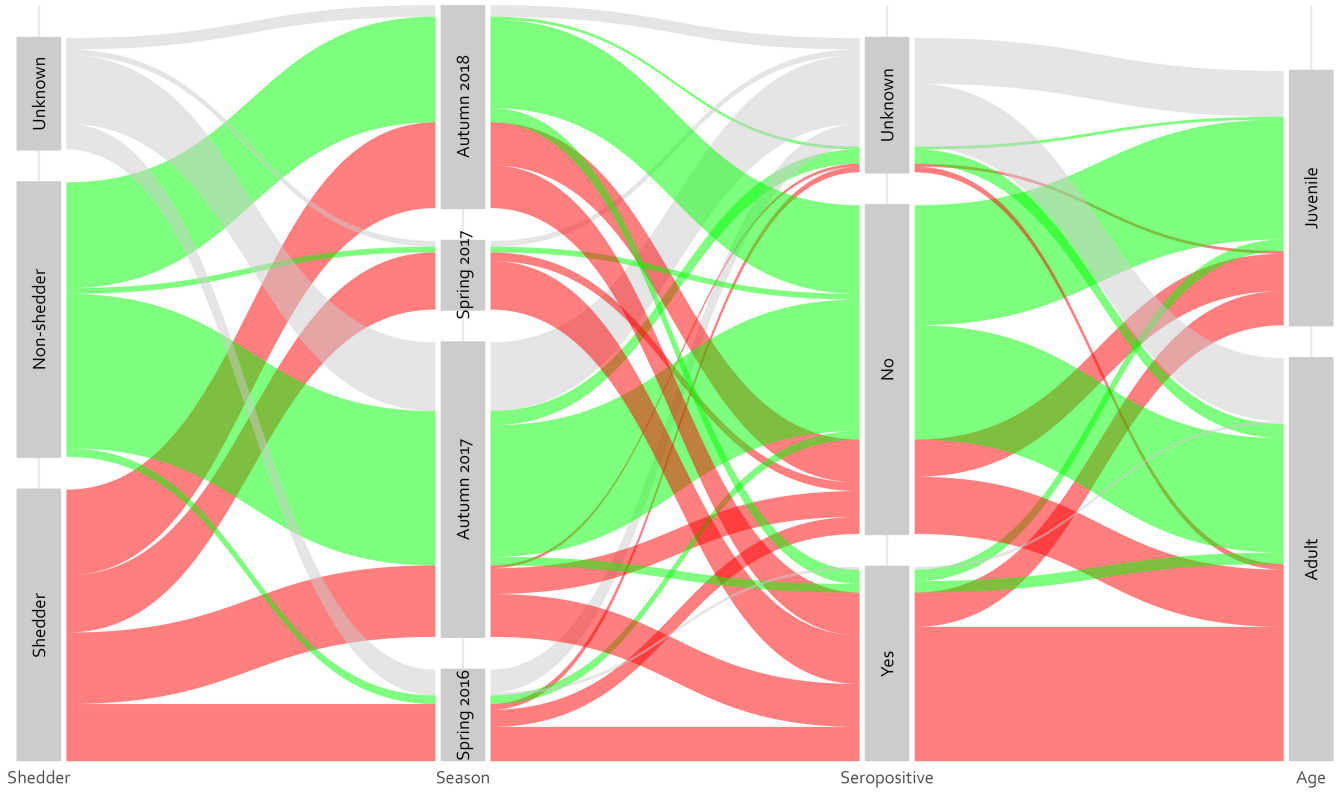

FIGURE 2 Breakdown of mice captured by shedding status (PCR and/or Culture positive), season, serological status and age, shown as a parallel sets plot. The band colouring highlights the proportion of shedders and non-shedders in the population studied.

TABLE 3 SECR conditional likelihood models with session covariates initially built (a), individual covariates (b) and hybrid mixture models built including seropositivity (c) or shedding status (d) as a mixture class. Respectively, only the top 3, 3, 3 and 4 ranked models with an AICc weight (wt) > 0.1 are listed, including factors affecting the probability to detect a mouse when home range centre and trap coincide (g_0), the spatial scale over which this probability declines (σ) and a latent mixture class (pmix) representing the proportion of positive mice in the population.

	npar	logLik	AIC	AICc	dAICc	wt
(a) Initial session covariate models						
$g0 \sim$ year sigma ~ session	11	−1362.12	2746.23	2747.44	0	0.55
$g0 \sim$ session sigma ~ session	16	−1357.28	2746.56	2749.11	1.67	0.24
$g0 \sim$ season + year sigma ~ session	12	−1362.11	2748.22	2749.66	2.22	0.18
(b) Individual covariate models						
$g_0 \sim$ session + age $\sigma \sim$ session	17	−1349.55	2733.09	2735.98	0.00	0.29
$g_0 \sim$ session + age $\sigma \sim$ session + age	18	−1348.96	2733.92	2737.16	1.18	0.16
$g_0 \sim$ year + age $\sigma \sim$ session	12	−1355.96	2735.92	2737.36	1.38	0.14
(c) Hybrid mixture model (pmix = seropositivity)						
$g_0 \sim$ session + age $\sigma \sim$ session + h2 pmix~ts + h2	22	−1443.26	2930.52	2935.40	0.00	0.50
$g_0 \sim$ session + age + h2 $\sigma \sim$ session + h2 pmix~ts + h2	23	−1442.75	2931.49	2936.85	1.45	0.24
$g_0 \sim$ year + age $\sigma \sim$ session + h2 pmix~ts + h2	17	−1450.37	2934.73	2937.62	2.22	0.16
(d) Hybrid mixture model (pmix = shedder)						
$g_0 \sim$ session + age + h2 $\sigma \sim$ session + h2 pmix ~ ts + h2	*23*	*−1455.39*	*2956.78*	*2962.14*	*0.00*	*0.42*
$g_0 \sim$ year + age + h2 $\sigma \sim$ session + h2 pmix~ts + h2	18	−1461.96	2959.91	2963.16	1.01	0.25
$g_0 \sim$ year + age $\sigma \sim$ session + h2 pmix~ts + h2	17	−1463.75	2961.49	2964.38	2.24	0.14
$g_0 \sim$ session + age $\sigma \sim$ session + h2 pmix~ts + h2	22	−1457.84	2959.69	2964.58	2.43	0.12

Abbreviations: AIC(c), Akaike's information criterion (corrected for a small sample size); dAICc, differences in AICc; h2, mixture term for pmix; logLik, log likelihood; Npar, number of parameters; ts, trapping session.

similar g_0 since g_0 varied only with session and age in the most-supported model).

Although prevalence (Table 2) and densities (Figure 3) showed important changes over time, with prevalence varying between 31% and 86% and total densities varying between 3.6 and 56 mice/ha, the densities of shedding animals were more stable over time and varied only between 3 and 8 shedding mice/ha (Figure 3).

4 | DISCUSSION

Density of hosts and disease prevalence are two key parameters jointly required to fully understand disease dynamics and transmission of a pathogen. There are few studies describing the prevalence of *Leptospira borgpetersenii* serovar Ballum in wild mice, their maintenance host, and even fewer describing mouse temporal dynamics and the relationships between pathogen and population dynamics. We found evidence of temporal heterogeneity in prevalence consistent across populations of house mice in a dairy farm environment. Moreover, we found that the detection function—and hence mouse activity—was associated with exposure to leptospires, although the causal direction of this association remains unknown.

The dynamics of *Leptospira* in New Zealand's wild mouse populations remain understudied. Recent prevalence estimates for *Leptospira* infection in mice (Moinet et al., 2023) correspond to the lowest estimates in this study but surpass previous estimates, 22% to 38% versus 13% to 16% in (Brockie, 1977; Hathaway et al., 1981). The presence of 'silent shedders', with leptospires detected in their kidneys but no detectable antibodies, lowered the apparent seroprevalence across these studies. All were cross-sectional studies, giving single time-point estimates. Population density estimates were unavailable, a common limitation in wildlife studies. While relative trapping abundance indices were reported (captures per 100 trap nights), they do not provide robust estimates of population size as reliable as CMR methods (Sagar et al., 2022).

As is typical for rodent species, house mice densities fluctuate cyclically and the number shedding pathogens into the environment is, therefore, also expected to fluctuate (Hathaway & Blackmore, 1981). On the contrary we demonstrated that despite variations in population dynamics, with a higher prevalence during spring sessions when the population is mostly composed of winter-surviving adults, the density of infected (shedding) animals remained relatively constant over time. This result has several implications.

TABLE 4 Estimates of g_0 (probability to detect a mouse when home range centre and trap coincide) by age, *Leptospira* shedding status, trapping grid and season.

Season	Grid	Age	*Leptospira*	g_0	lcl	ucl
Spring 2016	Grid1	Adult	Non-shedder	0.036	0.009	0.127
			Shedder	0.016	0.005	0.051
		Juvenile	Non-shedder	0.015	0.004	0.056
			Shedder	0.007	0.002	0.022
	Grid2	Adult	Non-shedder	0.012	0.003	0.051
			Shedder	0.005	0.001	0.02
		Juvenile	Non-shedder	0.005	0.001	0.022
			Shedder	0.002	0.001	0.009
Autumn 2017	Grid1	Adult	Non-shedder	0.128	0.072	0.216
			Shedder	0.061	0.034	0.108
		Juvenile	Non-shedder	0.056	0.029	0.105
			Shedder	0.026	0.013	0.051
	Grid2	Adult	Non-shedder	0.146	0.086	0.236
			Shedder	0.07	0.035	0.138
		Juvenile	Non-shedder	0.064	0.037	0.109
			Shedder	0.03	0.014	0.062
Spring 2017	Grid1	Adult	Non-shedder	0.014	0.002	0.106
			Shedder	0.006	0.001	0.052
		Juvenile	Non-shedder	0.006	0.001	0.048
			Shedder	0.002	0	0.023
	Grid2	Adult	Non-shedder	0.241	0.096	0.487
			Shedder	0.124	0.058	0.245
		Juvenile	Non-shedder	0.114	0.042	0.273
			Shedder	0.054	0.024	0.117
Autumn 2018	Grid1	Adult	Non-shedder	0.044	0.018	0.104
			Shedder	0.02	0.007	0.052
		Juvenile	Non-shedder	0.018	0.007	0.047
			Shedder	0.008	0.003	0.024
	Grid2	Adult	Non-shedder	0.038	0.015	0.089
			Shedder	0.017	0.006	0.044
		Juvenile	Non-shedder	0.015	0.006	0.039
			Shedder	0.007	0.002	0.02

Note: lcl and ucl = lower and upper 95% confidence limits, respectively.

Firstly, if the number of shedders represents a constant source of contamination, only variations in shedding levels and subsequent pathogen survival in the environment will affect exposure risk and spillover probability to other species (including humans). The longer pathogens survive, accumulate and disperse in the environment, the less disease dynamics in the maintenance host species will predict the risk of spillover (Plowright et al., 2017). Experimental mouse infections showed that shedding of Ballum increased in the first 2 months after infection, and then remained constant throughout their lifetime (Soupé-Gilbert et al., 2017). Knowledge on Ballum survival in the environment is fragmented and mostly inferred from in vitro studies on other serovars or theoretical inference from genomic analyses with contradictory data (Moinet et al., 2021). Leptospires of the species *L. borgpetersenii* have lost genes important in survival outside of their host, theoretically limiting them compared to other pathogenic leptospires like *L. interrogans* or saprophytic strains from which they diverged (Bulach et al., 2006). In contrast, in vitro studies of *L. borgpetersenii* isolates demonstrated long survival (up to 144 days) under controlled conditions (Addamiano, 1959). If Ballum's environmental survival is sustained, precise knowledge of mouse infection dynamics may not be necessary to assess environmental exposure to *Leptospira*. However, if variations in levels of environmental shedding better explain the quantity of leptospires present in the environment, understanding factors affecting the density of shedders and individual shedding levels will be important to devise strategies to limit shedding.

The second implication is that different control strategies of maintenance hosts populations can differentially impact the

TABLE 5 Estimates of σ and derived area of activity A (with lower and upper 95% confidence intervals) for mice according to their *Leptospira* shedding status, trapping grid and season.

Season	Grid	*Leptospira*	σ	A	lcl	ucl
Spring 2016	Grid1	Non-shedder	15.56	0.46	0.07	2.91
		Shedder	36.93	2.57	0.53	12.41
	Grid2	Non-shedder	32.31	1.97	0.11	34.14
		Shedder	76.68	11.09	0.68	179.60
Autumn 2017	Grid1	Non-shedder	9.02	0.15	0.07	0.33
		Shedder	21.41	0.86	0.51	1.46
	Grid2	Non-shedder	8.33	0.13	0.08	0.20
		Shedder	19.77	0.74	0.25	2.16
Spring 2017	Grid1	Non-shedder	23.25	1.02	0.09	11.71
		Shedder	55.18	5.74	0.41	79.94
	Grid2	Non-shedder	9.37	0.17	0.04	0.65
		Shedder	22.24	0.93	0.35	2.50
Autumn 2018	Grid1	Non-shedder	12.11	0.28	0.10	0.76
		Shedder	28.74	1.56	0.39	6.26
	Grid2	Non-shedder	14.69	0.41	0.14	1.16
		Shedder	34.87	2.29	0.56	9.47

Note: A: 95% circular probability density area of capture (hectares) with $A=\pi[2.45\sigma]^2$; lcl and ucl: lower and upper 95% confidence limits of A, respectively.

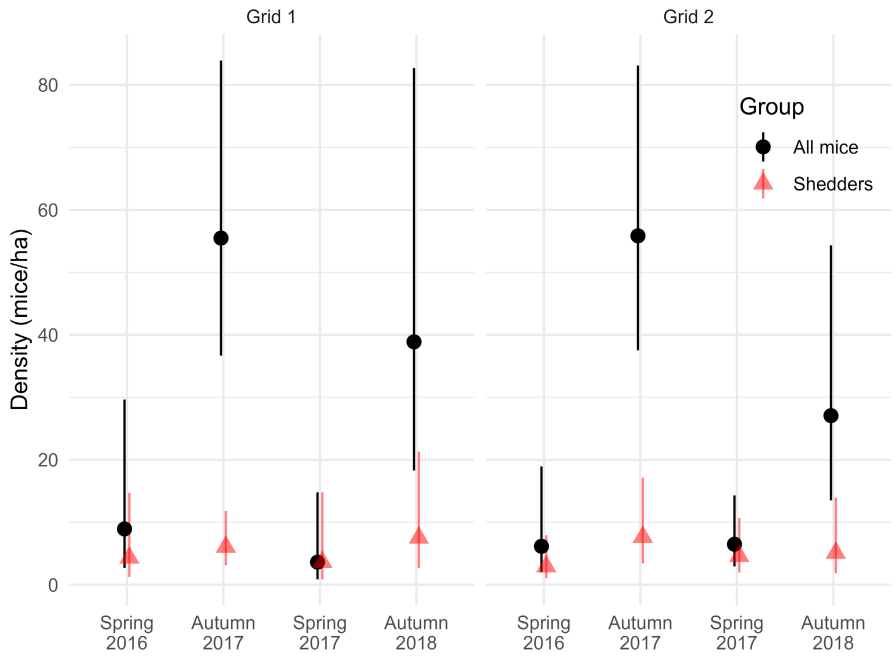

FIGURE 3 Densities of all mice, and mice shedding *Leptospira* derived from the hybrid mixture SECR model. Data presented in this graph are available in in Supporting Information.

pathogen epidemiology. Trapping or poisoning mice during winter or early spring, before densities are high and prevalence diluted by the recruitment of young uninfected individuals, will be more effective to decrease the prevalence and the density of infected animals. This period also poses the highest risk of direct contamination for people involved in trapping management. Appropriate personal protective equipment should be used to safeguard people in contact with mice or potentially contaminated water. Similar precautions should be extended to hedgehogs and rats that were not the target species of this study but were also shown to harbour Ballum.

Thirdly, these results inform potential disease models, providing parameter estimates and clues on the type of model(s) to favour. While Ballum is primarily transmitted sexually in laboratory mice (Hathaway et al., 1983), our results indicate simple frequency-dependent models may not be the most appropriate transmission models for wild mice, as observed for other sexually transmitted *L. borgpetersenii* serovars (Caley & Ramsey, 2001). More complex models incorporating density- and frequency-dependent transmission in a single equation (Hayman et al., 2022) or incapsulating indirect (environmental) transmission (Almberg et al., 2011; Espira et al., 2022) should be favoured to encompass different transmission routes.

Inverse density dependence observed in other host–pathogen systems with highly variable dynamics, like Sin Nombre virus, has been explained by a time lag between host density and pathogen prevalence (Luis et al., 2015), and a similar phenomenon may be at play for *Leptospira* dynamics in mice.

This study has shown that densities of mice in a farm environment were comparable with densities observed in other habitats in New Zealand, like forests and scrub (Murphy & Nathan, 2021). The *Leptospira* infection prevalence in mice was extremely high after the winter season, and this species therefore, represents a risk for people and animals in direct or, more commonly, indirect contact with this ubiquitous species. However, while inferences about disease dynamics from one location can be done (e.g. Bournez et al., 2020), they should be done with caution, and this is especially true for a multi-host multi-pathogen system like *Leptospira*. This study provided insightful information across time but it was limited in space and studies on *Leptospira* carriage in other habitats, such as forest and scrub conservation sites, are needed.

In 2016, the New Zealand government launched Predator Free 2050, a nationwide plan to eradicate stoats, rats and possums (Department of Conservation, 2016; Russell et al., 2015). Mice benefit from the removal of their predators and competitors (Caut et al., 2007; Goldwater et al., 2012), an advantage modelled to be higher in warmer forests (Walker et al., 2019), where Ballum is also likely to better survive in the environment. We did not detect an increase in prevalence of *Leptospira* with higher mouse densities (the number of shedders remained constant), but the situation may be different following predator control. Simultaneously targeting mice and rats for pest control is crucial for reducing the number of shedders.

Mice being well-adapted hosts, we expected little impact on fitness and no difference in activity areas. On the contrary, we found seropositive and shedding mice had larger areas of activity. These findings could be due to a true biological effect of *Leptospira*, to confounding by other un-measured factors, or due to sampling and measurement biases. Concerning the latter, one of the assumptions of SECR models is that the detection is homogeneous across animals and time. The determination of *Leptospira* status in this study required euthanasia of mice captured, and we had to choose a trade-off between CMR (phase I) and sampling (phase II). As a result, the status of most of the mice captured only in phase I remained unknown, and mice captured only in phase II were removed from the population at the first capture. However, we captured seropositive mice on average 1 day earlier than seronegative ones. A bias in the assessment of seroprevalence and density modelling is thus possible. Mice not sampled in phase I could have a higher proportion of seropositive than the rest of the animals sampled, and mice sampled during phase II (when the movement of animals between traps was not being assessed) could have a higher proportion of seronegative, with a negative impact on σ in that group. Despite this, we found no difference in sex, age and first day of capture between animals captured in phase I only and animals captured in both. We would expect no difference in their serological status either. In other words, mice captured in both phases—and, therefore, sampled—are expected to be a representative sample of mice captured in the first phase (whether phase I only or both phases). Randomly sampling a subset of mice throughout a single CMR study design (and assigning capture histories of zero with probability equals one for SECR analyses), rather than sampling in two distinct phases, would nonetheless prevent this possible bias, but simultaneous epidemiological sampling and CMR requires more workforce. The main difference between animals captured in both phases (seroprevalence = 50%) or in phase II only (seroprevalence = 32%) is the number of recaptures. The handling stress during the first phase may have elicited an enhanced immune response, and a better detection of antibodies in samples taken the following days, especially for animals with a titre close to the detection threshold (48). 'Wild immunology' is a recent discipline (Pedersen & Babayan, 2011) and there is a dearth of information on the impact of capture and handling on immune parameters, but it is likely this impact exists and remains to be quantified (Abolins et al., 2018; Pedersen & Babayan, 2011). Interestingly, like Byers et al. (unpublished, cited in Minter et al., 2019) noted in brown rats infected with *L. interrogans*, we found no significant association between infection status (i.e. shedding) and first day of capture.

Alternatively, confounding factors could explain the association observed between *Leptospira* infection and variation in capture probability and area of activity. For instance, animals with larger areas of activity are more likely to encounter traps and contaminated environments. Similarly, behavioural components like 'boldness' or 'wariness' could interact with both infection and capture probabilities, as illustrated by the association between the presence of wounds and *Leptospira* status described in brown rats (Himsworth et al., 2013; Minter et al., 2019). Lee et al. (2018) found that culling rats increased the odds that surviving rats carried *L. interrogans* and considered that culling could destabilise family groups and lead to enhanced opportunities for disease transmission by an increased number of fights and resulting wounds. We did not collect information on the presence of wounds on trapped mice, nor test for an effect of removal on prevalence.

Our results show that a difference in trappability could also bias early estimates of prevalence, especially if trapping sessions are too short to encompass the heterogeneity in capture probabilities in different groups. The long timespan of trapping in our study (10–12 nights) allowed this heterogeneity to be captured, but studies investigating prevalence in wild mice are usually shorter. The APHAEA project (harmonised Approaches in monitoring wildlife Population Health, And Ecology and Abundance, https://aphaea.org/cards/species/voles) recommends four to five days of capture to estimate population densities of wild mice. Studies assessing prevalence and seroprevalence in wild rodents should consider the possibility of such a sampling bias.

Mouse capture probability and areas of activity varied widely in our study without clear spatio-temporal (i.e. grid or season) patterns. Idiosyncratic external factors like the presence of predators, the change over time of vegetation cover or weather conditions were not included in the modelling but could also impact mouse detection.

The presence of a weasel on Grid1 during Spring 2017 impacted the number of captures and recaptures, but not the number of mice present, as almost as many mice were captured in Grid1 as in Grid2 after capture and removal of the weasel. The concept of 'landscape of fear' describes this change in behaviour in the presence of predators or competitors (Mahlaba et al., 2017). The vegetation cover remained relatively similar over the study, but weather conditions changed drastically. While A4 was conducted at the end of a particularly dry summer, after 4 months of water restrictions, A2 took place during cyclone Debbie, with heavy rain every day during the captures and the lower parts of pastures flooded in several places.

In summary, this study examined both disease prevalence and the density of infected animals using a unified ecological and epidemiological sampling design, shedding light on *Leptospira* dynamics. The density of infected animals remaining constant was more informative than the variations in prevalence or densities alone and held implications beyond leptospirosis, emphasising the importance of understanding population and disease dynamics simultaneously for effective risk assessment and disease control. Our sampling design furthermore provided evidence that disease status was associated with differences in trappability, highlighting the need for disease managers to consider potential sampling biases.

AUTHORS CONTRIBUTIONS

Marie Moinet, David A. Wilkinson, Emilie Vallée, Jackie Benschop and James C. Russell conceived the ideas and designed methodology; Marie Moinet, Carlos R. Abrahão, Vinícius P. O. Gasparotto, David A. Wilkinson and James C. Russell collected the data; Marie Moinet and James C. Russell analysed the data; Marie Moinet led the writing of the manuscript. All authors contributed critically to the drafts and gave final approval for publication.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data available via the Dryad Digital Repository: https://doi.org/10.5061/dryad.x69p8czsq (Moinet et al., 2024).

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SUPPORTING INFORMATION

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

Table S1. Session prevalence and seroprevalence assessed by Culture, PCR and MAT in other sympatric species sampled.

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Table S2. Average weight and body measurements of trapped mice (±SD).

Table S3. Breakdown of shedding and serological status by age and session in mice captured.

Table S4. Density estimates for all mice and mice shedding *Leptospira* derived from the top ranked hybrid mixture SECR previously selected.

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