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Pathogen biology

Urban rat exposure to anticoagulant rodenticides and zoonotic infection risk

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Anticoagulant rodenticides (ARs) deployed to control rodent pest populations can increase the risk of pathogen infection for some wildlife. However, it is unknown whether ARs also increase infection risk for target rodents, which are common hosts for zoonotic (animal-to-human transmitted) pathogens. In this study, we tested whether rats exposed to ARs were more likely to be infected with zoonotic pathogens, specifically *Leptospira* spp. or *Escherichia coli*, after controlling for known predictors of infection (i.e. sex, age, body condition). We collected biological samples from 99 rats trapped in Chicago alleys and tested these for *Leptospira* infection, *E. coli* shedding and AR exposure. We found that rats that had been exposed to ARs and survived until the time of trapping, as well as older rats, were significantly more likely to be infected with *Leptospira* spp. than other rats. We found no significant association between *E. coli* shedding and any predictors. Our results show that human actions to manage rats can affect rat disease ecology and public health risks in unintended ways, and more broadly, contribute to a growing awareness of bidirectional relationships between humans and natural systems in cities.

1. Introduction

Anticoagulant rodenticides (ARs) are one of the most common types of substance used to control rodent pest populations; however, little is known about potential unintended, *sublethal* AR effects on rodents. In other species, AR exposure has been associated with numerous sublethal effects (in addition to acute toxicity). For example, sublethal AR exposure can increase infection risk in urban predators (e.g. bobcats, *Lynx rufus*; mountain lions, *Puma concolor*; coyotes, *Canis latrans*; [1–3]) and has been linked to higher parasite and pathogen burdens in birds (e.g. great bustards, *Otis tarda*; [4]). Wildlife exposed to ARs may be more susceptible to infection because ARs have been shown to disrupt immune function [5]. Like the species above, rodents might also experience greater infection owing to AR exposure; in turn, this is relevant to human health as rodents are common hosts for zoonotic pathogens [6–8], especially in human-dominated areas [9]. ARs do not kill immediately; first-generation ARs require multiple feedings to provide a lethal dose, and second-generation ARs—more potent compounds that can kill after a single dose—typically lead to death in 5–10 days [10]. If infection risk is heightened during the period between AR exposure and death, widespread AR use might increase population transmission of pathogens among rodents. Additionally, this could pose a risk of zoonotic pathogen transmission.

Understanding any unintended effects of rodent control on rodent disease dynamics is important because commensal rats carry dozens of zoonotic pathogens [11,12], come in close proximity to people [13], and have a near-global distribution [14]. Brown rats (*Rattus norvegicus*) and black rats (*R. rattus*) can

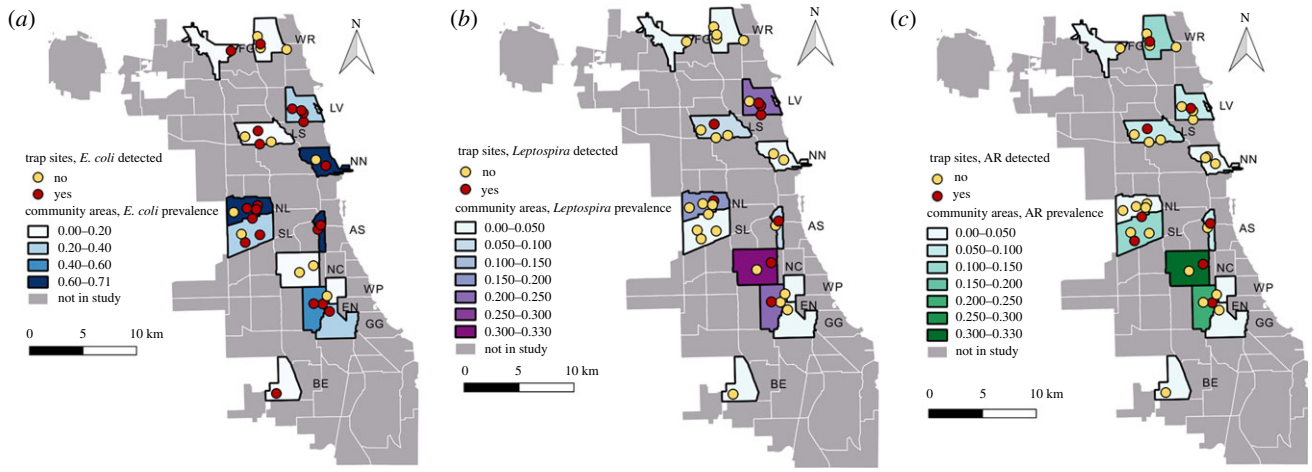

Figure 1. Maps of study community areas (polygons) and trap sites (circles) in Chicago. Colours show the prevalence (shading) or the presence (darker circles) of rats with (*a*) *E. coli* shedding, (*b*) *Leptospira* spp. infection, and (*c*) anticoagulant rodenticide (AR) exposure. Abbreviations correspond to table 1.

carry several environmentally transmitted pathogens that cause human disease (e.g. *Leptospira interrogans*, pathogenic *Escherichia coli*; [15]). Leptospirosis in particular poses a large public health burden, causing an estimated 434 000–1 750 000 cases and 23 800–95 900 deaths in humans annually [16]. Among major cities in the USA, *Leptospira* seroprevalence in rats ranges from 44.1 to 65.3% [17]. Environmental features and management practices can modulate *Leptospira* prevalence. For example, in Chicago, IL, rats trapped in high-income areas with more standing water complaints were more likely to be infected with *Leptospira* spp. [18], while in Vancouver, Canada, rodent control via rat trapping was associated with higher *Leptospira* prevalence [19]. Importantly, low-income urban residents can be disproportionately exposed to rat-associated zoonoses [20] and lower-income countries are often reliant on ARs for rodent control [21]. It is thus crucial to understand how other widespread management practices such as use of ARs could also influence infection dynamics in rats.

In this study, we tested if rats exposed to ARs were more likely to be infected with zoonotic pathogens, specifically *Leptospira* spp. or *E. coli*, after controlling for known physiological predictors of infection. We focused on these pathogens because they are zoonotic, transmitted through the environment, and present in our study population [18]. Based on previous work in urban carnivores, we predicted the probability of *Leptospira* spp. infection and *E. coli* shedding would be higher for rats with detectable concentrations of common ARs in liver tissue relative to other rats. We also predicted the probability of *Leptospira* spp. infection and *E. coli* shedding would be higher for rats that were female, older, and in poorer body condition because these biological factors are known predictors of infection [18,22–24]. Our results will help design best practices for rodent management to protect public health and advance our understanding of how pest management affects urban wildlife ecology.

2. Methods

As part of a previous study [18], 254 rats were trapped in 13 community areas in Chicago, a city with numerous rat complaints (figure 1). Trapped rats were measured, examined for injuries, weighed, and sexed. Rats were considered to be brown rats based on ear and tail morphology, but this assumption was not verified with genetic analyses. A subset of 202 rats were necropsied and screened for environmentally-transmitted bacterial pathogens [18]. Rat kidney tissue was tested for *Leptospira* spp. using polymerase chain reaction (PCR) and rat colon contents (i.e. faeces) were tested for *E. coli* using aerobic culture [18] at Wyoming State Veterinary Laboratory. From these rats, we selected 99 (table 1) to be screened for seven commonly used ARs (first-generation: chlorophacinone, coumachlor, diphacinone, warfarin; second-generation: brodifacoum, bromadiolone, difethialone). Rats were chosen for screening such that sample sizes would be roughly balanced by capture location, sex, age and infection status. Liver screening was performed by the Animal Disease Diagnostic Laboratory at Purdue University (West Lafayette, IN) using high performance liquid chromatography. Method detection limits (lowest concentration that can be confidently identified) for each AR in liver tissue were as follows: chlorophacinone and diphacinone: 0.25 ppm; coumachlor and warfarin: 0.5 ppm; brodifacoum, bromadiolone and difethialone: 1.00 ppm. Animal use was deemed exempt from Lincoln Park Zoological Society IACUC approval because rat samples were procured through pest management professionals (protocol number 2019–005).

We used generalized linear mixed models (GLMMs; binomial distribution, logit link) to test whether infection status varied by rodenticide exposure status (binary; we considered a rat exposed to poison if at least one AR was detected in the liver) as well as other biological predictors previously found to influence rat infection status. We constructed two GLMMs, one with a response variable of *Leptospira* infection status (positive or negative) and the other with a response variable of *E. coli* shedding status (positive or negative). Explanatory variables for each model included AR exposure status, sex, age class and body condition. We estimated rat age in days based on their mass using growth curve equations, following the methods of [25], and binned rats as younger (30–65 days) or older (greater than 65 days; electronic supplementary material, dataset). We quantified body condition using the scaled mass index [26] using tip-to-tip length (i.e. tip of nose to tip of tail) because it was most highly correlated with mass (see the electronic supplementary material for more detail). While injuries have also been found to be associated with infection [15], we did not include this as a variable because we observed only a few, mild wounds in the study population. Given the low sample size, only main effects of the explanatory variables were considered. We also included capture location (i.e. community area) as a random effect to account for non-independence among samples from the same neighbourhood. Analyses were performed using the glmmTMB package [27] in the R statistical environment v. 4.0.3 [28].

Table 1. Sex, age class and anticoagulant rodenticide poisoning status of rats, separated by trapping location (community area).

	sex		age class		poisoning status	
community area	F	M	younger (30–65 days)	older (>65 days)	AR detected	AR not detected
Armour Square (AS)	5	10	14	1	1	14
Beverly (BE)	1	0	1	0	0	1
Edge Water (ED)	1	1	1	1	1	1
Englewood (EN)	0	4	3	1	1	3
Forest Glen (FG)	1	0	1	0	0	1
Greater Grand Crossing (GG)	2	2	2	2	0	4
Lake View (LV)	14	6	16	4	2	18
Logan Square (LS)	11	5	14	2	1	15
Near North Side (NN)	5	2	7	0	0	7
New City (NC)	2	1	1	2	1	2
North Lawndale (NL)	4	1	4	1	0	5
South Lawndale (SL)	11	2	8	5	2	11
Washington Park (WP)	0	1	1	0	0	1
West Ridge (WR)	7	0	6	1	1	6

3. Results and discussion

We analysed infection status as a function of AR exposure, sex and age class for 99 rats that were trapped in 14 community areas (table 1). Ten liver samples were positive for AR residues (6 females, 4 males; 2 older, 8 younger). Specifically, seven were positive for second-generation ARs (brodifacoum: $n = 3$, bromadiolone: $n = 3$, difethialone: $n = 1$) and three were positive for first-generation ARs (diphacinone: $n = 3$). *Leptospira* prevalence was higher for AR-exposed rats (30%, 3/10) than for unexposed rats (7.9%, 7/89), and *E. coli* prevalence was higher for AR-exposed rats (50%, 5/10) than for unexposed rats (42%, 37/89; figure 2).

GLMMs indicated that AR exposure status was a significant predictor of *Leptospira* infection status (odds ratio = 7.02, 95% CI = 1.10–45.0, $p = 0.04$), as was age class (figure 2 and electronic supplementary material, table S1). Older rats (greater than 65 days) were significantly more likely to be infected with *Leptospira* spp. than younger rats (30–65 days; odds ratio = 5.88, 95% CI = 1.20–28.9, $p = 0.03$). Neither sex nor SMI was a significant predictor in the model. The marginal R^2 (i.e. proportion of variance explained by fixed effects) for the *Leptospira* infection model was 0.21, while the conditional R^2 (i.e. proportion of variance explained by both fixed and random effects) was 0.33. No explanatory variables were significant predictors of *E. coli* shedding status. The marginal R^2 for this model was 0.01, while the conditional R^2 was 0.12.

We found that rats exposed to ARs that survived until the time of trapping were significantly more likely to be infected with *Leptospira* spp. than other rats. Though it is known that ARs can promote infection risk in non-target wildlife, our results demonstrate increased zoonotic infection risk in target rodents. This result is significant for public health and urban ecology because commensal rodents are abundant reservoirs of zoonotic pathogens in cities. More generally, this relationship between rodenticide exposure and infection risk demonstrates an unintended effect of wildlife management on a target species that can feed back to human health.

AR-exposed rats may be more susceptible to infection in the period between exposure and death because of immunomodulatory effects of ARs. Rats exposed to warfarin for 30 days exhibit increased lymphocytes, basophils and monocytes [29,30], suggesting immune dysfunction. In carnivores, AR exposure has been associated with immune dysfunction consistent with cytokine-mediated inflammatory processes, including the suppression of neutrophils [31]. These phenotypic changes might interfere with rodents' ability to mount an effective defence when exposed to infectious leptospires in the environment. Although we quantified rat exposure to rat poison as a binary status, the detection limit in our study exceeded concentrations deemed indicative of acute AR poisoning in other species (200 ng g^{-1} or 0.2 ppm; [4]), suggesting they were high enough to interfere with physiological processes. If rats are more likely to become infected with *Leptospira* spp. after consuming ARs, infection would have to occur before the poison kills the rat (approx. 1 week). Experimental work has demonstrated successful *Leptospira* infection 7 days post-infection [32,33], yet further work is needed to examine *Leptospira* spp. infection dynamics at a shorter timescale and determine how long rats can survive following AR exposure.

Alternatively, infected rats might be more likely to consume poisoned bait. For instance, infected rats could be more attracted to bait stations if they have less energy to actively forage for other food. However, rats are considered asymptomatic, chronic carriers of *Leptospira* ([17]; though see [34]), suggesting it is unlikely that infected rats are more likely to consume AR bait. Future work could also investigate behavioural and physiological changes in poisoned and infected rats to clarify causal mechanisms.

Interestingly, the only other study, to our knowledge, to examine AR poisoning and infection risk in target rodents found that common voles (*Microtus arvalis*) infected with

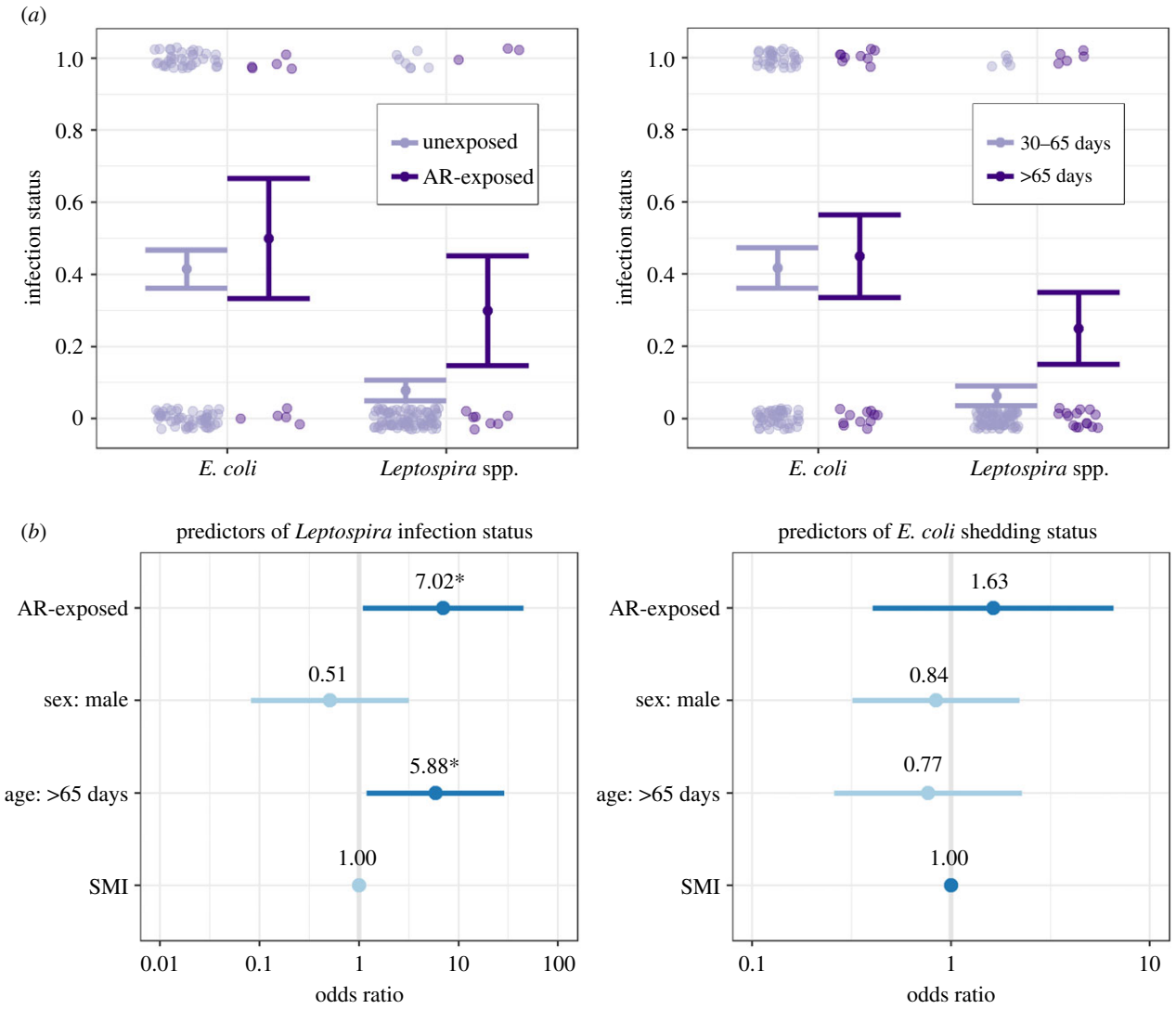

Figure 2. (*a*) Pale-shaded points display binary infection status and solid points and lines represent means and standard errors of infection prevalence. (*b*) Points and lines represent odds ratios and 95% confidence intervals for predictors of infection status from GLMMs. Darker blue lines indicate odds ratios greater than 1, while lighter blue lines indicate odds ratios less than 1. 95% confidence intervals that cross the vertical line at 1 indicate that a predictor is not significant. Asterisks indicate $p < 0.05$.

Francisella tularensis had lower concentrations of the AR chlorophacinone relative to uninfected voles [35]. These results likely differ from ours because all poisoned voles were found dead rather than trapped and *F. tularensis* infection is fatal in voles. However, these differences highlight the need to understand interactions among ARs, pathogens, and hosts with different ecologies. Future epidemiological surveys and experimental work could help identify which types of pathogenic infections are affected by AR exposure.

We also found that older rats were significantly more likely to be infected with *Leptospira* spp. than younger rats. This aligns with previous research and is likely attributable to a greater chance of exposure and infection over time [22]. We might not have found significant associations with other biological factors because of small sample size, which could also explain the relatively large confidence intervals around the odds ratios (figure 2). Contrary to our predictions, we found no association between AR exposure and *E. coli* infection. We may not have detected an increased risk of *E. coli* infection in poisoned rats because our methods could only detect active shedding of *E. coli* in faeces, rather than true infection. Although this is informative for public health, rats could have been infected with *E. coli* but not actively shedding, which might have confounded our results. In addition, while we accounted for non-independence among rats within the same community area using a random effect (under the assumption that community areas are statistically independent from one another, supported by the small home ranges of rats (less than 200 m) [36]), our results may have been confounded by spatial autocorrelation.

Our results add to a growing literature showing environmental hazards of managing rats using ARs, and highlight potential unintended and unpredicted effects of AR exposure on the ecology of rat-associated pathogens of public health importance. Apart from disease ecology, urban rats have exhibited genetic resistance to ARs for decades. Resistant rats carry genetic mutations in the *Vkorc1* gene that interfere with anticoagulant effects on blood clotting [37], rendering the rats less susceptible to anticoagulants. Rats have exhibited genetic resistance even as new generations of ARs are developed [38,39], demonstrating how lethal management can have evolutionary consequences for zoonotic hosts [40]. AR resistance may have important consequences for leptospiral shedding if ARs act as modulators of immune and inflammatory responses and resistant rats are less likely to die

following AR exposure. Instead of relying on ARs, integrated pest management might offer a more sustainable approach by improving urban sanitation and rodent exclusion [41]. Such an approach would align with One Health principles and prevent mortality of urban carnivores, which provide ecosystem services such as rodent population control. More broadly, our results contribute to a growing awareness of bidirectional relationships between humans and natural systems in cities: in our case, that human actions to manage rats can affect rat disease ecology and public health risks in unintended ways.

Ethics. Animal use was deemed exempt from Lincoln Park Zoological Society IACUC approval because rat samples were procured through pest management professionals (protocol no. 2019-005).

Data accessibility. The dataset used in our analysis is available on Zenodo at https://zenodo.org/badge/latestdoi/387547164 [42].

Authors' contributions. M.H.M. led the conceptualization of the study and the collection of biological samples. C.A.S. contributed to project design and led the statistical analysis. M.H.M. and C.A.S. wrote and edited the manuscript, approved the final version of the manuscript agree to be held accountable for the content therein.

Competing interests. The authors declare that they have no competing interests.

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