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At-risk individuals in Feline Immunodeficiency Virus epidemiology: evidence from a multivariate approach in a natural population of domestic cats (*Felis catus*)

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SUMMARY

Prevalence of Feline Immunodeficiency Virus (FIV) infection was measured during 6 consecutive years in a natural rural population of domestic cats. Sex, age, weight, origin, group size and presence of antibodies to FIV were recorded for each sampled cat. Logistic regressions were used to estimate the influence of the recorded parameters on infection. FIV prevalence rates are as high as 19.6% in the total population, and do not statistically change between years, after controlling for changes in samples' age structure. FIV infection is characterized by risk factors linked to aggressive behaviour: old mature male adults having dispersed are more likely to be infected. A study of the cats group size and of the spatial distribution of infected individuals indicates the absence of infection clusters in males, and suggests the importance of roaming in the spreading of FIV. In conclusion, FIV infection spreads, with low contagiousness, mainly between particularly aggressive individuals, and the virus is endemic in this population.

INTRODUCTION

Feline Immunodeficiency Virus (FIV) is a worldwide feline lentivirus [1] which is genetically homologous and functionally analogous to HIV, the cause of human AIDS; its infection leads to fatal disease in cats [2]. Due to strong similarities between these viruses, the cat-FIV pair is considered as a suitable biological model for HIV studies in many fields [3, 4].

FIV antibodies have already been found in 16 non-domestic felid species (reviewed in [1]), with very high prevalence rates in some populations, e.g. more than 90% in several natural African lion populations (*Panthera leo* [5, 6]). Even though it has not yet been proven that the strains infecting the different species

are all pathogenic, FIV may be a substantial threat, given that all 37 species of Felidae, except the domestic cat, are considered threatened or endangered [7, 8]. For example, one third of an endangered population of less than 50 Florida panthers, *Felis concolor coryi*, is infected [9]. Further risk is that some threatened populations of wild felids are in close contact with infected domestic cats (e.g. *Felis silvestris* in Europe [10, 11] and *Felis iriomotensis* in Japan [12]). Unfortunately, due to the difficulty of studying wild felid species, epidemiological data on FIV within natural populations are scarce. Domestic cats are a much more suitable animal model to study, both in laboratories and in natural conditions. Domestic cat populations vary widely, from solitary cats to large social groups [13]. Such population differences in social organization can affect the spread patterns of parasites [14, 15]. In addition, some domestic cat populations may be compared, for given aspects, with

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non-domestic felid populations. In this context, as well as for domestic cat health considerations, and as a relevant biological model for HIV studies, FIV epidemiological studies of domestic cat populations are of major interest.

A large number of FIV serological surveys have been published for domestic cats, indicating relatively high prevalence rates all over the world (reviewed in [16]). Unfortunately, these studies were based on unrelated cats from veterinary facilities, without population reference. Further, the factors analysed were not considered simultaneously, which prevented identification of potential interactions between them on FIV infection. To our knowledge, no longitudinal epidemiological study of representative samples of FIV in natural populations of domestic cats has been published. Avoiding these shortcomings, we present an epidemiological study of a natural population of domestic cats living in a rural habitat in France. The temporal variation of FIV prevalence during the 6 years allows us to analyse whether FIV infection is endemic or epidemic in this population. We discuss the factors suspected to affect disease transmission, such as sex, age, weight and origin of the cats. Finally, the spatial distribution of infected cats and the effect of cats group size (number of conspecifics living in the same household) are also analysed in order to study the level of contagiousness of FIV.

MATERIALS AND METHODS

Population

The cat population of Saint-Just-Chaleyssin has been monitored yearly since 1982 [17]. It is located in south-east France, in a rural village (1500 inhabitants) 30 km from Lyons. We define the natural population as a group of cats that are able to meet and interact at any time (for example for reproduction, or social interactions). Three hundred to 340 cats belong to the population, two thirds of which are females. Approximately half of the cats are less than 2 years old. Most of them are owned but roam freely.

Sampling

Cats were first censused yearly (since 1982) by interviewing the village inhabitants. In 1991, the first year of the epidemiological study, a group of about 50 cats was sampled from owners who allowed a blood sample on their cats. These cat owners were randomly selected from the total number of cat owners of the village. This sample was representative of the structure

of the whole population (see results). In order to study long-term incidence rates, these cats were followed throughout the whole study period. Deceased or missing individuals were replaced by randomly selected ones to maintain a sufficient sample size. Cats were caught directly in their house. A few cats, known to be untamed, were trapped in baited cages. The cats were anaesthetized with a mixture of ketamin chlorhydrate (Imalgène 1000, Rhône Mérieux, 15 mg/kg) and acepromazin (Vétranquil 5.5%, Sanofi, 0.5 mg/kg) by intramuscular injection. For each cat, we recorded four individual parameters as potential risk factors: sex, age, weight and origin, as well as the number of cats living in the same household. As castrated males and neutered females were few (8 males, of which 2 were infected and 19 females, of which none was infected), neutering was not taken into account. Cat age classes were: less than 2 years old, 2–3 years old, 3–4 years old and more than 4 years old [18]. The weight classes, which divide individuals into three groups of approximately equal size, were ‘light’ (less than 3 kg), ‘medium’ (3–4 kg) and ‘heavy’ (more than 4 kg). Origin was: cats born in the village (‘local’), cats actively acquired from elsewhere by the owner (‘acquired’) and cats that ‘appeared one day’, from an unknown origin, probably dispersers (‘dispersed’). Finally, cats were divided into three groups size classes: cats living alone, groups of two cats, groups of more than two cats. In addition, through blood samples, we recorded the presence of antibodies to FIV (kittens under 6 months were not taken into account as they were not sampled for blood). Roaming habits is a classic risk factor discussed in the literature, with outdoor cats being more exposed to bites than indoor cats. We do not present results for this factor, as the roaming effect was not striking here, which may be explained by the homogeneity of cats roaming habits in our population (more than 90% of cats roam freely).

Because cats were monitored through time, and because each year missing cats were replaced by new randomly selected cats, the age structure of the sample changed with time. The age structure of the whole population however remained stable with time. Thus the estimation of the prevalence of FIV in the population was model-based (see below).

Serological tests

A large range of methods is available for the detection of either Feline Immunodeficiency Virus or associated antibodies (reviewed in [4]). Despite a possibility of a

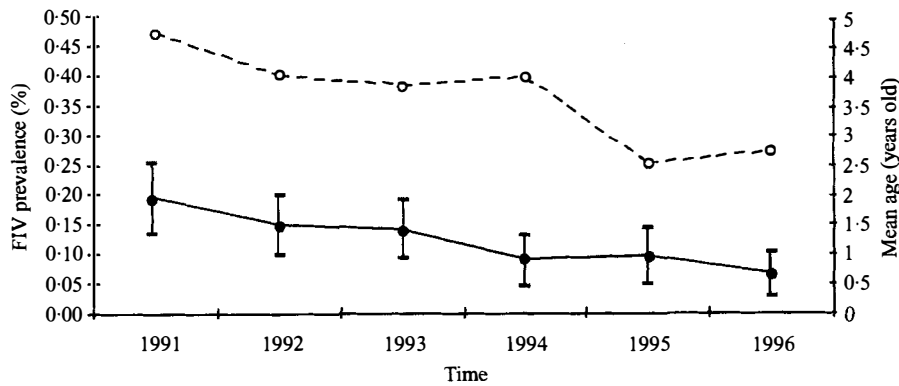


Fig. 1. FIV prevalence rates with time (●), and associated confidence intervals. The observed slight decrease is not statistically significant. Because we showed this decrease is due to a bias in the age structure of the sample, the average age of the 6 samples is shown (○).

few false seropositives and false seronegatives, the ELISA method we used is considered ‘the most sensitive and desirable’ for screening tests [4]: 98.3% sensitivity and 100% overall specificity [19]. To avoid false positives, all positive sera were confirmed by Western Blot [20].

Statistical analysis

Population structure

The structure of the population with respect to year, age and sex ratio was analysed using log-linear models with observed numbers in each category as the response variable and year, sex and age as factors [21]. The tests used were likelihood-ratio tests (G-test). Note that observations between years are not independent (the same cats contribute to more than one year), and that the tests may be too liberal.

Risk factors

The risk factors (sex, age, weight, origin, group size) as well as year effects were analysed using logistic regression models [21]. We performed an analysis limited to one randomly selected observation per cat. We also analysed the whole data set, as well as random permutations of the observation chosen for each individual to assess the robustness of the results. The original variables were categorical, but we aimed also at simplifying the statistical model when the relationship for ordinal variables (e.g. weight, age) was apparently linear, by using continuous variables. We used the Akaike Information Criterion ($AIC = Deviance + 2p$, where p is the number of estimable parameters in the model) to select an appropriate model for inference [22]. Due to the low overall prevalence, some complicated models could not be

fitted due to boundary problems of fitting probabilities close to 0 (see [23]). We therefore restricted the possible models to the ones giving an appropriate convergence criterion (in particular, adequate parameter estimates and standard errors). The problem that complicated models were not estimable precluded any simple backward procedure starting with a full model. We therefore used a combination of forward (adding terms in the model) and backward (deleting terms) procedures, with manual checking of the estimability of the parameters [23]. The goodness of fit of the resulting model may be assessed using the residual deviance, but the fact that observations are binary precludes use of the χ^2 asymptotic distribution for the deviance [23]. On the other hand, the differences between the deviance of nested models could be used and were compared with χ^2 distributions with the appropriate number of degrees of freedom. Interpreting the selected model was done using the parameter estimates, which are logarithms of the odds ratio [21, 24]. We provide the actual odds ratio, back transforming confidence intervals calculated on the original logit scale.

The squared Pearson correlation, R^2 , between observed values and values predicted by the model provides one recommended measure of the variation explained by covariants [25]. This corresponds to the degree with which the model provides a good prediction of the probability that an individual of a given modality for each of the studied risk factors is FIV infected. Observed values are to be considered as binary [25, 26], i.e. for each individual, the observed value is 1 if the cat is infected, and 0 otherwise (the observed values are not to be considered by modality groups, e.g. 2 infected cats out of 7 among the light adult local males). Due to the specific nature (binary) of the dependent variable, observed R^2 are expected to

be rather low (see [27], for a discussion): a model predicting a probability of infection varying between 0 and 1 cannot predict precisely the absence (0) or presence (1) of the virus in a given cat.

FIV contagiousness

FIV contagiousness was assessed by two different and complementary analyses: an analysis of the spatial pattern of infected individuals, and an analysis of group size effect on FIV infection probability, using the logistic regression models described above, in order to determine whether this microparasite spreads easily or not within social groups. Since the spatial distribution of cats may influence FIV dissemination, each cat's home or shelter position was recorded on the village map, with the serological status of the cats: infected or not. In order to highlight potential clustering of infected cats, we analysed spatial distribution of infected cats compared to susceptible ones, through a distance matrix. As the spatial distribution of cats was highly non-homogeneous due in particular to the structure of their habitat (houses, shelter), we used permutation tests on the observed spatial distribution of cats [24, 28]. The calculated test statistic was the sum of the distance of each infected cat to all other infected cats, and we considered 10000 permutations of the infection status of the cats [28]. We used the empirical distribution of the test statistic to derive the *P*-value for the null hypothesis of no spatial aggregation. We did this analysis for the data set with one randomly selected observation per individual.

Software

Statistical analyses were performed with SPlus 3.3 (Statistical Sciences 1995, S-plus guide to statistical and mathematical analysis, StatSci, MathSoft Inc., Seattle, USA).

RESULTS

Population structure and sample representativeness

During the 6 years of the epidemiological study, as well as the 10 preceding years, the population size remained remarkably stable [17]. The analysis based on log-linear models of the relation between year, sex and age showed that the two interactions year \times age ($G = 13.07$, D.F. = 15, $P = 0.597$) and year \times sex ($G = 1.98$, D.F. = 3, $P = 0.577$), as well as the third-order

Table 1. *Description of the cat sample structure according to the studied parameters*

	Males*	Female*
Age		
< 2	24	19
2-3	15	23
3-4	14	9
> 4	42	17
Origin		
Dispersed	6	6
Acquired	19	13
Local	43	76
Weight†		
< 3	10	43
3-4	34	41
> 4	24	11

* Only one random observation per individual.

† In kilograms.

interaction ($G = 8.06$, D.F. = 15, $P = 0.922$) were not significant. The age and sex structures could therefore be assumed to be constant through time in the whole population, while sexes had different age structures. Size of the samples were 46, 53, 48, 44, 41 and 45 individuals for 1991, 1992, 1993, 1994, 1995 and 1996, respectively, which corresponds to 15–20% of the population size. The six samples were representative of population structures for sex distributions ($0.404 \leq \chi^2 \leq 5.797$, D.F. = 1, $0.9394 \geq P \geq 0.1219$). However, the age structure of the 6 samples changed with time, mean age becoming lower (Fig. 1). The first sample (1991) was, however, representative of the whole population for both sex and age structure (sex: $\chi^2 = 0.285$, D.F. = 1, $P = 0.594$; age: $\chi^2 = 5.797$, D.F. = 3, $P = 0.122$). In total, 169 different cats were sampled, 62.1% of which 1 year only, whereas 19.5, 12.4, 3.0, 2.4 and 0.6% were sampled 2, 3, 4, 5 and 6 years, respectively. Distribution of sampled individuals according to sex and other parameters is given Table 1.

FIV prevalence

The rate of FIV infection in the 6-yearly samples was 19.6 (± 5.8 , 95% C.I.)%, 15.1 (± 4.9)%, 14.3 (± 5.1)%, 9.1 (± 4.3)%, 9.8 (± 4.6)% and 6.7 (± 3.7)% for 1991, 1992, 1993, 1994, 1995 and 1996, respectively (Fig. 1). Considering a model with only year as a factor in a logistic regression model, we concluded that there was no significant heterogeneity with year ($\chi^2 = 7.09$, D.F. = 5, $P = 0.210$). However, there was a significant trend (decrease) in the sample

Table 2. Logs of the odds ratio for the different studied factors

Category‡	Only one observation per individual*		All observations (total sample)†	
	Odds ratio (log)	Standard error	Odds ratio (log)	Standard error
Age (continuous)	0.035	0.145	0.003	0.123
Weight (continuous)	-0.647	0.353	-0.631	0.288
Origin (acquired)	-1.887	0.851	-1.891	0.734
Origin (local)	-2.876	0.775	-2.306	0.626
Sex (male)	-0.704	1.009	0.055	0.761
Sex-age (male)	0.722	0.239	0.520	0.157

* Logs of the odds ratio (and standard error) for the different factors, and for the models including one observation per individual.

† Same but for the total sample.

‡ The reference category is '0' for weight and age, 'dispersed' for origin and 'female' for sex. As there is an interaction between sex and age, we provide for age (continuous) the odds-ratio for males vs. females.

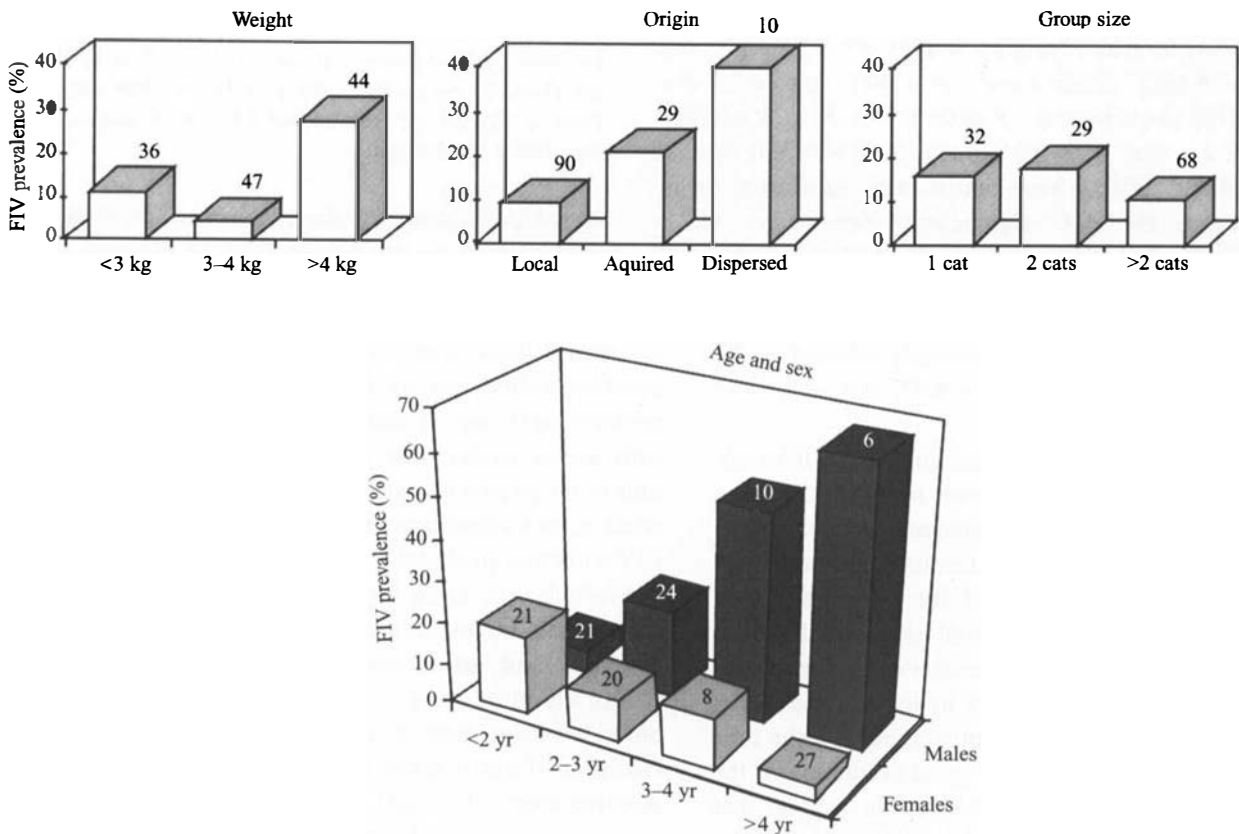


Fig. 2. FIV prevalence (%) according to the different categories of the studied risk factors: weight, origin, sex and age classes and to group size. The number of individuals involved is indicated above each bar. The sex and age chart highlights the link between sex and age on the probability of being FIV infected: the prevalence increases significantly with age in males while it is rather constant with age in females.

prevalence rates, as judged from the logistic regression model with year being fitted as a continuous variable (slope = -1.59, s.e. = 0.74, $t = -2.15$, $P = 0.016$). We

show that FIV prevalence is however stable in the population, after controlling for shift in age structure (see below).

Risk factors

The selected model on the basis of the AIC included the effects of age (*A*), sex (as a factor, *S*), weight (*W*) and origin (as a factor, *O*), and the interaction between sex and age:

$$\text{Logit}(P) = A + S + W + O + A \times S,$$

where *P* is the probability of being FIV positive. Age and weight could be considered as continuous (model with age and weight continuous: deviance = 88.49, AIC = 102.49, age categorical and weight continuous: AIC = 106.24, age continuous and weight categorical: AIC = 105.73). The resulting model provided a fit to the data which, based on the deviance, indicated some degree of under-dispersion (deviance = 88.49, D.F. = 156). However, as observations were binary, this under-dispersion should be interpreted cautiously [23], and would in any case result in too conservative tests. No other interaction had to be included in the statistical model (origin \times weight: $\chi^2 = 3.64$, D.F. = 2, $P = 0.160$; origin \times sex: $\chi^2 = 0.43$, D.F. = 2, $P = 0.810$; sex \times weight: $\chi^2 = 0.01$, D.F. = 1, $P = 0.920$; age \times origin: $\chi^2 = 0.55$, D.F. = 2, $P = 0.760$), but all included effects were statistically significant or increased the AIC significantly (sex \times age: AIC = 113.29, $\chi^2 = 12.80$, D.F. = 1, $P = 0.0003$; weight: AIC = 104.09, $\chi^2 = 3.60$, D.F. = 1, $P = 0.058$; origin: AIC = 111.92, $\chi^2 = 13.43$, D.F. = 2, $P = 0.001$). Note that adding the year effect to the previously selected model did not improve the fit ($\chi^2 = 4.57$, D.F. = 5, $P = 0.470$).

The odds ratio and associated confidence intervals of the selected model are shown in Table 2. These values do not depend on the particular value selected for each cat, as shown by the results obtained on the basis of 1000 permutations of the individual value selected (data not shown), as well as the total sample (see Table 2). The logistic regression equivalent of the per cent of explained variability by the selected model (R^2) is 0.314, indicating that information on the four studied factors allows a rather good prediction of the probability of being FIV infected. Table 2 shows that there is no effect of age for females (age), but an important effect of age in males (sex-age). Weight has a marginally significant negative effect (weight). Cats that are not dispersers (origin) are less likely to be infected ('local' < 'acquired' < 'dispersed'). Figure 2 shows FIV prevalence versus the four studied parameters (and group size, see below), showing the interaction between age and sex. We give the model-

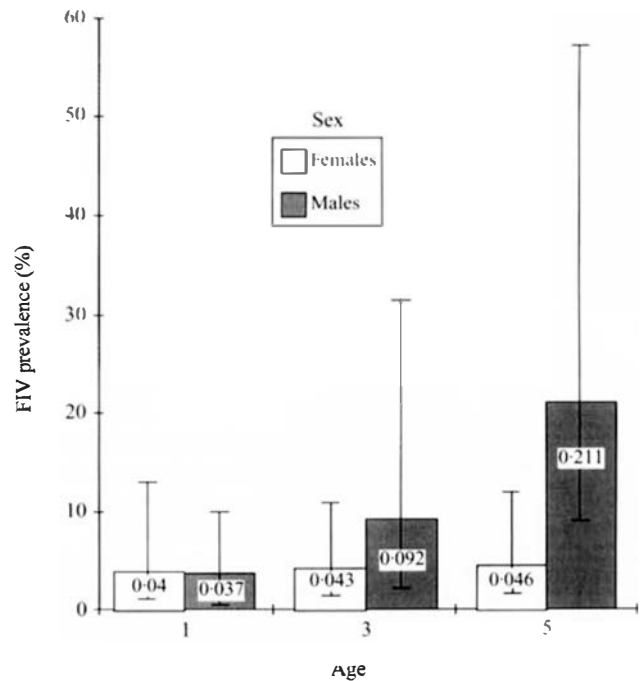


Fig. 3. Model-based predicted values for the FIV prevalence for some given categories of age (1, 3 and 5 years old) and sex (female and male) in the population. The weight was fixed at 3 kg for the females and 4 kg for the males, and we assumed a local origin.

based predictions for the prevalence for some given categories in the population (Fig. 3). We used age 1, 3 and 5, and sex female and male. The weight was fixed at 3 kg for the females and 4 kg for the males. We assumed a local origin. The predicted values for the prevalence show that the FIV prevalence rate is nearly constant with age in females, and increases sharply with age in males. The prevalence is constant with time in the population, as we have shown that the year effect is not significant. Our results thus show that FIV infection probability is influenced by age (older individuals are more likely to be infected), origin (individuals having dispersed are more likely to be infected), and the interaction between sex and age (males are more likely to get infected when they get older, whereas there is no such effect for females). However, if age is taken into account, the significant positive effect of weight alone ($P = 0.038$) becomes negative or non-significant ($P = 0.854$).

FIV contagiousness

The spatial analysis reveals that aggregation between infected individuals is significant (test statistic = 1310, $P = 0.01$). We conducted the same test on males and females separately. This shows that infected females

are significantly aggregated (test = 104, $P = 0.03$), whereas infected males are not at the 0.05 level (test = 595, $P = 0.09$). The difference in P -values is however small, and should be interpreted cautiously.

Taking the selected model as the reference model, the effect of the group size was not significant (group size as a categorical variable: $\chi^2 = 7.98$, D.F. = 8, $P = 0.435$; as a continuous variable: $\chi^2 = 1.31$, D.F. = 1, $P = 0.250$). An increase of the group size does not induce an increase in the probability of being FIV infected.

DISCUSSION

FIV prevalence rate

Since cats become on average younger in the samples, and as age is a risk factor for infection (see below), the decrease in the prevalence rate observed in the sample was expected. As the different yearly samples are not all representative of the population (in the sense of being random samples), the overall prevalence in the population could, however, be based on the model used for analysing risk factors and on the overall population structure. It is interesting to notice that the statistically significant decrease of the prevalence in the sample is totally explained by the change in the age structure of the samples. However, the first sample was randomly selected and is representative of the population structure, and the corresponding prevalence rate was 19.6% (± 5.8 , 95% C.I.). As there was no evidence for a year effect, we could assume that this prevalence was constant along the 6 years of the study. This is a high value for a lethal disease, which however is endemic.

Risk factors

The main mode of FIV transmission is thought to be through bites [29]. The mating system of our cat population is suspected to be polygynous [30]. Such a mating system is based on fights between male competitors for monopolizing one or several females [18] and of females against males to prevent potential infanticides [31, 32]. Moreover, cats also fight in territorial defence. Even if males have a higher immunological susceptibility to parasites [33], their more aggressive behaviour [13] is sufficient to explain the male predisposition to FIV infection. Castrated males are no longer involved in reproduction-linked fights, but they seem, however, to be infected at the

same level as non-castrated males (unpublished data, and [16]). This may indicate that territorial-linked fights, which are still present in castrated male behaviour, are a main cause of FIV infection in males. This hypothesis is also supported by our spatial analysis (see below). In a previous study [16], we hypothesized that females could be infected mainly by males through neck biting during the coital mount. In this population, none of the 19 neutered females was FIV infected, whereas 6 of the 49 reproductive females (12.3%) were FIV infected. This supports our previous hypothesis: females could be predominantly infected during mating.

The heavier cats are overall more likely to be infected, which may be explained by the fact that they consist mainly of the older cats. In addition, heavier cats are more aggressive and fight more often than lighter ones. This is in agreement with Liberg [18], who showed in farm cats that the heaviest males were the most dominant and aggressive ones, and with Yamane and colleagues [34], who highlighted the importance of body weight on the favourable outcome of agonistic encounters.

There is no evidence of natural vertical FIV transmission [29, 35], and maternal antibodies prevent or limit infection in neonates [36]. Moreover, kittens and juveniles do not fight before they become a threat to sexually mature cats (at more than 1 year old). We thus hypothesize that a high infection rate arises when the young cats have reached sexual maturity, followed by a lower but quite constant rate. As FIV infection has a very long duration, an accumulation of infected cases develops with age. This may explain why, although young adult are more likely to get infected, oldest cats are also often found infected: most of them may have got infected several years younger. This is especially true for males, which are increasingly likely to fight as they get more mature (see Figs. 2 and 3), as shown by the interaction between sex and age in the selected model.

Cats that 'appeared one day' in the village are much more likely to be FIV infected than cats that have a known origin (born in the village, or acquired from elsewhere). Either the cats of unknown origin were infected during their dispersal, having crossed territories of infected individuals, or they were cats with strong roaming habits, and thus having probably experienced fights. Dispersing animals have a higher probability of contacting pathogens and a stress-induced increased susceptibility to diseases [37]. Cats brought from a neighbouring village are also more

likely to become infected than cats born in the village. A possible explanation is that these cats are often acquired when kittens [17], and may be allowed to roam only when they become adults. Thus, when they encounter other cats, they are perceived as adult strangers and are more frequently attacked. A higher prevalence rate in neighbouring populations is not a satisfying explanation, as these populations have the same characteristics [17].

The study of several parameters taken into account simultaneously allowed the identification of an interaction between age and sex (Table 2, Fig. 2): prevalence increases with age only in males, reflecting their increasing aggressiveness.

FIV contagiousness

The spatial analyses show that infected cats are aggregated but the separate treatment of males and females indicates that only infected females are aggregated. In a study of a group of farm cats, unlike peripheral females, all peripheral male cats were FIV infected [38]. This spatial pattern was expected under the hypothesis that females were principally infected by males during coital bites [16], and because males tend to monopolize a group of females during oestrus periods in this population [30]. Males that monopolize females generally are not resident in the neighbourhood of these monopolized females (Pontier, unpublished data). Cats living in the same household are often related in this population (Pontier, unpublished data) and hence more amicable and socially stable [39]. These results (spatial analysis and effect of group size) are in agreement with laboratory experiments which tend to show that bites are not very efficient in transmitting this microparasite [29]. The low contagiousness of FIV has also been predicted by a mathematical model of FIV dynamics [40]. Given the high prevalence rate and the endemic pattern of FIV epidemiology, a low infection rate was to be expected in a stable population.

An important and novel result of this study is that the FIV prevalence rate of a natural population of domestic cats, studied through samples of known structure, is as high as 20% (it is the first recorded prevalence, and comes from the random sample). A second important result is that FIV is endemic in our population, a result which was predicted by a previous theoretical study [39]. Thus this is a very high prevalence rate for a lethal endemic virus. A third

important result is that individuals do not have the same infection risk, and the factors influencing FIV infection are strongly linked to behavioural classes, defined by sex, age, weight and origin. Finally the spatial analysis and the study of the group size effect demonstrate that the virus is not very contagious, confirming previous laboratory [29] and theoretical [40] work, and the importance of behaviour for FIV epidemiology. Unlike environmentally transmitted diseases, this behaviourally transmitted microparasite follows a non-diffusive pattern. At-risk individuals, probably roaming dominant males, infect spatially distant males (competitors), probably for reproductive or territorial defence (hence the absence of infected males clusters) and groups of monopolized females, probably during mating (hence the clusters of infected females). Thus, a small number of individuals with an at-risk behaviour seems to be responsible for most infections in the population. Previous published FIV epidemiological studies did not consider the population structure in their analysis. In this work, by considering the ecological dimension, we were able to characterize the dynamic (endemic, high prevalence) and spatial (sex-specific clusters) patterns of FIV epidemiology. This approach also allows assessment of the influence of the spatial and social structure on the spread and impact of parasites, through comparisons of contrasting populations [14, 15, 41]. Finally, this will allow us to follow known individuals over several years, and to study the fate of infected cats and related individuals in natural conditions. The high variability of social structures of cat populations [13, 42] and their associated behaviours make these populations a relevant model for the study of parasitic transmission in wild felid populations, which are more difficult to study and may be threatened by disease outbreaks (e.g. feline infectious peritonitis in the cheetah, *Acinonyx jubatus*, in Oregon [7, 43], or more recently, canine distemper virus in Serengeti Park lions, [44]).

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