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Assessing the impact of breeding strategies on inherited disorders and genetic diversity in dogs

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ABSTRACT

In the context of management of genetic diversity and control of genetic disorders within dog breeds, a method is proposed for assessing the impact of different breeding strategies that takes into account the genealogical information specific to a given breed. Two types of strategies were investigated: (1) eradication of an identified monogenic recessive disorder, taking into account three different mating limitations and various initial allele frequencies; and (2) control of the population sire effect by limiting the number of offspring per reproducer. The method was tested on four dog breeds: Braque Saint Germain, Berger des Pyrénées, Coton de Tulear and Epagneul Breton. Breeding policies, such as the removal of all carriers from the reproduction pool, may have a range of effects on genetic diversity, depending on the breed and the frequency of deleterious alleles. Limiting the number of offspring per reproducer may also have a positive impact on genetic diversity.

Introduction

Management of inherited diseases and genetic diversity in different breeds of dogs is a growing concern for breeders, owners and the general public (Nicholas, 2011). According to Online Mendelian Inheritance in Animals (OMIA)[1] more than 575 disorders/traits have been reported in dogs and at least 200 have monogenic determinism (Nicholas et al., 2011). The prevalence of a genetic disorder can be >50% within a given population (Collins et al., 2011) and the consequences for canine health may vary substantially, depending on the severity of the disorder and its frequency.

Increases in inbreeding and widespread dissemination of genetic disorders may have a deleterious impact on welfare of purebred dogs, as shown with hip dysplasia in German shepherd dogs and Golden retrievers (Mäki et al., 2001) or fertility in Irish wolfhounds (Urfer, 2009). Founder effects and extensive use of popular sires are considered to be the main reasons for the dissemination of genetic disorders and are linked to a reduction in genetic diversity within a breed (Leroy and Baumung, 2011). It has been suggested that the prevalence of genetic diseases could be reduced through careful selection and better management of genetic drift and inbreeding (Lewis et al., 2010).

The Federation Cynologique Internationale (FCI) recommends that the number of offspring per dog should not be >5% of the number of puppies registered in the breed population during a 5 year period.[2] In parallel, about 20% of disorders/traits reported in OMIA have been characterised at the molecular level (Nicholas et al., 2011). However, even when a genetic test is available, members of breed societies often do not know which is the best strategy to adopt to reduce the prevalence of genetic disorders. This is especially important when considering the use of valuable stud animals that may be disease carriers. There is also a need for members of breed societies to be aware of the impact of different policies on genetic diversity. Windig et al. (2004) modelled the consequences of a policy for eradication of genetic disorders in sheep using simulated populations. There is a need to extend such studies to take into account the level of complexity existing in real breeds, including non-random mating, importations and bottleneck events.

In this paper, we propose a method to assess the impact of breeding strategies on the frequency of deleterious alleles and genetic diversity, taking into consideration the genealogical information available for a given breed. Two strategies were investigated: (1) eradication of an identified monogenic recessive disorder using three different mating limitations and various initial allele frequencies; and (2) control of the popular sire effect through limitation of the number of offspring per reproducer.

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[1] See: omia.angis.org.au/.

[2] See: http://www.fci.be/uploaded_files/29-2010-annex-en.pdf.

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Materials and methods

To investigate the evolution of the frequency of a deleterious allele, we considered a single gene with two alleles (*A* and *a*), homozygous individuals *aa* being regarded as affected by the genetic defect. The initial allele frequencies of *a* were set at 20% and 50%, respectively. Carriers were randomly distributed among founders (i.e. individuals without known parents) of a given pedigree, with alleles being transmitted according to Mendelian segregation rules. It was assumed that there was no selection of the allele before the beginning of the breeding strategy.

Breeds selected for analysis

Four French breeds of dogs with different population sizes were selected for analysis: Braque Saint Germain (BSG), Berger des Pyrénées (BRP), Coton de Tulear (COT) and Epagneul Breton (EPB) (Table 1). The numbers of dogs registered in France for each breed from 2006 to 2010 ranged from 283 (BSG) to 27,326 (EPB). Generation intervals (*T*) were computed for each breed for dogs born from 2001 to 2010.

The number of equivalent complete generations (*EqG*), inbreeding coefficient (*F*) and kinship coefficient (Φ; also known as 'co-ancestry', which corresponds to the degree of inbreeding of a potential offspring of a pair of individuals) were averaged for the 2006–2010 period (Leroy et al., 2006). Kinship was averaged over 10,000 pairs of dogs born during a given period. When considering simulated sub-scenarios, kinship was averaged over 100 pairs sampled over 100 iterations. The evolution of genetic diversity was assessed considering the evolution of yearly average Φ. For each scenario, kinship rate was computed per generation $\Delta\Phi$ using the formula $\Delta\Phi_t = (\Phi_{t+1} - \Phi_t)/(1 - \Phi_t)$, considering Φ_t and Φ_{t+1} as average kinship in 2000 (year before implementation of the breeding strategy) and 2010 (end of the period investigated) and correcting it by period considered and generation intervals.

Simulation process: 'what if'

Given the genealogical file of a breed, the '*what if*' simulation process investigated '*what*' would have happened '*if*' a given breeding strategy had been applied over a 10 year period (2001–2010). Evolution of genetic diversity and allele frequencies were compared between the original and the modified pedigree files. Pedigrees were modified using the rule that, for a litter born during the 2001–2010 period, if its sire (or dam) was affected by the mating restriction corresponding to the breeding policy (see below), the parent was replaced by the sire (or dam) of another dog randomly sampled from dogs born in the same year and not affected by the mating restriction. If all potential parents were affected by the mating restriction, then the sampling was made among dogs born in the preceding year. Mating restrictions were modelled according to two different breeding scenarios:

Scenario 'er'

In this scenario, we analysed strategies aiming to eradicate a monogenic recessive disorder, assuming that carriers may be identified early (e.g. through a genetic test). We compared three sub-scenarios of breeding strategies with an increasing severity of selection against the disorder. For each sub-scenario, the two initial allele frequencies were considered (20% and 50%): (1) sub-scenario *erA*, in which, from the first year of the programme, dogs *affected* by the disease (i.e. homozygote *aa*) were removed from the reproductive pool; (2) sub-scenario *erI*, an '*intermediate*' policy in which, from the first year of the programme, dogs *affected* by the disease (i.e. homozygote *aa*) were also removed from the reproductive pool; heterozygote dogs (*Aa*) were allowed to reproduce, but their carrier offspring (i.e. heterozygote *Aa* or homozygote *aa*) were removed from the reproductive pool; and (3) sub-scenario *erC*, in which, from the first year of the programme, *carriers* (i.e. heterozygote *Aa* or homozygote *aa*) were removed from the reproductive pool.

Scenario 'ps'

The aim of this scenario was to control the popular sire effect through a limitation on the number of offspring allowed per sire. When a reproducer had exceeded the maximum number of offspring, it was not allowed to reproduce any more; this mating restriction was applied from the first year of the programme. Three different thresholds for the number of offspring were considered for all breeds: 50 (*ps50*), 100 (*ps100*) and 200 (*ps200*). A limitation of 25 offspring per reproducer (*ps25*) was also considered for BSG and BRP, but could not be applied to COT or EPB, since sires of these breeds produce, on average, a number of offspring close to or >25 (Table 1).

In the two scenarios, we supposed a random replacement of reproducers. To test what would happen if new sires or dams were more or less related to those replaced, we studied the possibility that, among the simulations, 50% of the replacement sires (or dams) were sampled among the 10th percentile of the most (or least) related sire (or dam) of individuals born in the same year. This procedure was tested for one breed (COT) considering two of the sub-scenarios (*ps50* and *erC* for an initial frequency of 50%). Each scenario was programmed in Fortran 90, repeated and averaged over 100 iterations (see Appendix A: Supplementary file 1).

Results

The four breeds had a high level of pedigree completeness, *EqG* values for the period 2006–2010 ranging from 6.98 (COT) to 9.33 (EPB) (Table 1). In the same period, *F* ranged from 0.056 (EPB) to 0.091 (BRP) and Φ ranged from 0.036 (EPB) to 0.103 (BSG). As illustrated in Fig. 1, there was a global increase in kinship for each breed over the whole period.

Eradication of recessive disorder

As illustrated in Fig. 2, the three breeding strategies had different impacts on the frequency of the deleterious allele. Removing all carriers from reproduction (sub-scenario *erC*) directly decreased the frequency to a value close to 0, whatever the initial frequency. Due to importations of some dogs (without known parents and considered here as founders), allele frequency was not exactly equal to 0 during the period. When heterozygotes were allowed to reproduce (sub-scenario *erA*), the consequences were limited; for COT, the allele frequency decreased over 10 years to 22% when the initial frequency was 50% and to 13% when the initial frequency was 20%.

When heterozygote offspring of carriers were not allowed to reproduce (sub-scenario *erI*), the decrease in allele frequency was amplified and reached values close to 0 after 10 years. These results were similar for all four breeds (see Appendix A: Supplementary Fig. 1).

When considering the impact of the different strategies on genetic diversity, more reproducers were removed from the reproductive pool and the kinship increase was larger with increased severity of selection against disorders and larger initial frequencies of the deleterious allele (see Appendix A: Supplementary Table 1). Breeds with small populations were affected more than breeds with larger populations (Fig. 1). When the initial allele frequency was set to 20%, kinship increase was, in general, limited. For example, when all carriers were removed from the reproductive pool (sub-scenario *erC*) in 2010, Φ for BSG increased from 0.135 to 0.154 (+14%, $P < 0.0001$), while there was no change for EPB (0.037 in each case, $P > 0.05$).

Table 1
Demographic and genealogical characteristics of the four breeds studied.

Breed name	Number of dogs in pedigree file	*T*	2006–2010 period				*EqG*	*F*	Φ
			Number of dogs	FCI threshold	Average number of offspring per reproducer (maximal number observed)				
					Sires	Dams			
Braque Saint Germain	1999	4.69	283	14	14.8 (62)	7.6 (30)	7.73	0.073	0.103
Berger des Pyrénées	28,834	4.77	3630	182	13.2 (82)	7.4 (40)	7.22	0.091	0.054
Coton de Tulear	40,563	4.37	10,784	539	27.4 (233)	9.8 (39)	6.98	0.061	0.039
Epagneul Breton	183,181	4.88	27,325	1366	18.6 (297)	9.6 (54)	9.33	0.056	0.036

T, generation interval; FCI threshold: 5% of the number of dogs produced during the 2006–2010 period; *EqG*, number of equivalent generations; *F*, mean inbreeding coefficient; Φ, mean kinship coefficient.

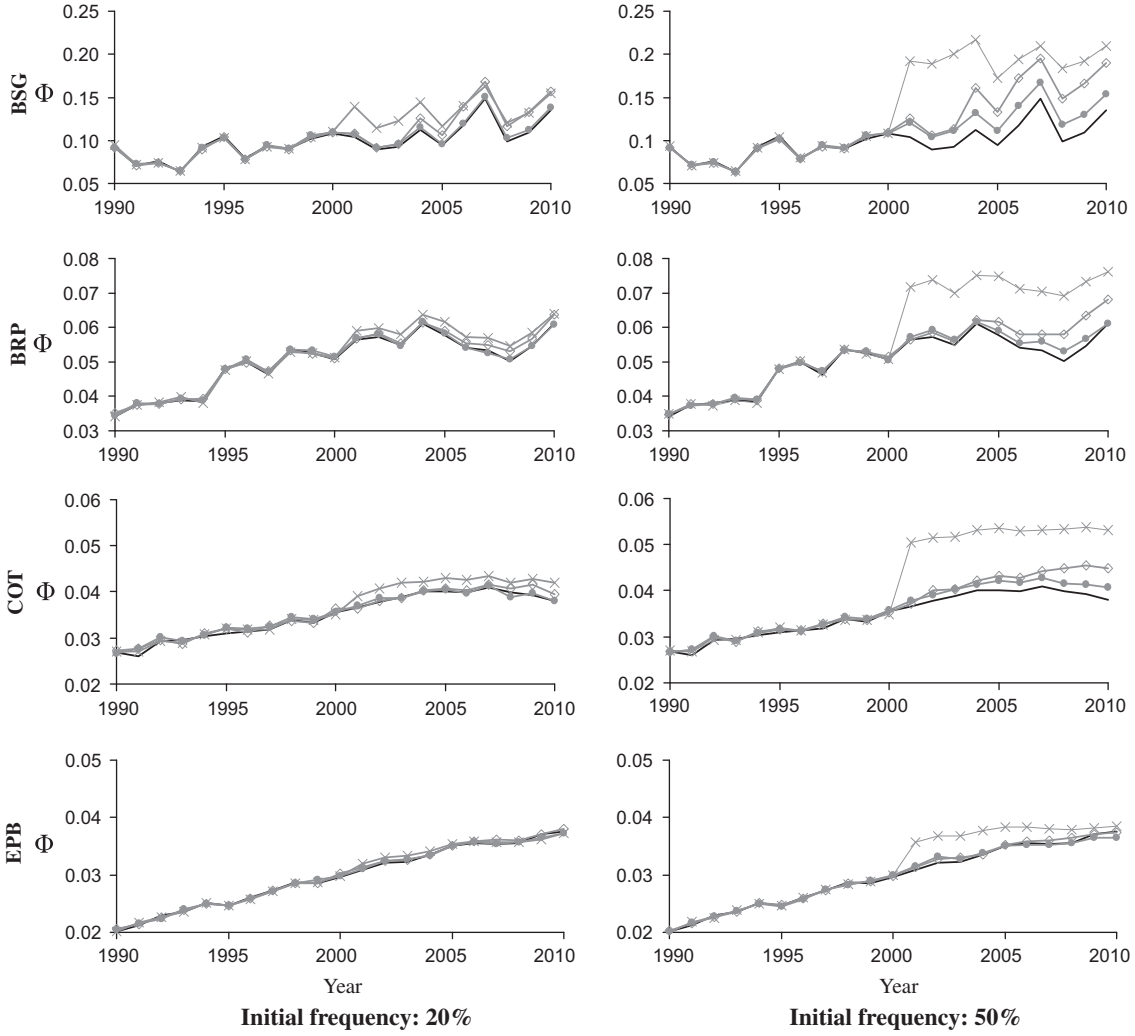

Fig. 1. Evolution of average kinship (Φ) over 10 years according to scenarios related to the eradication of a monogenic recessive disorder. BSG, Braque Saint Germain; BRP, Berger des Pyrénées; COT, Coton de Tulear; EPB, Epagneul Breton. — Observed evolution; ● scenario *erA*; ◊ scenario *erI*; ╳ scenario *erC*.

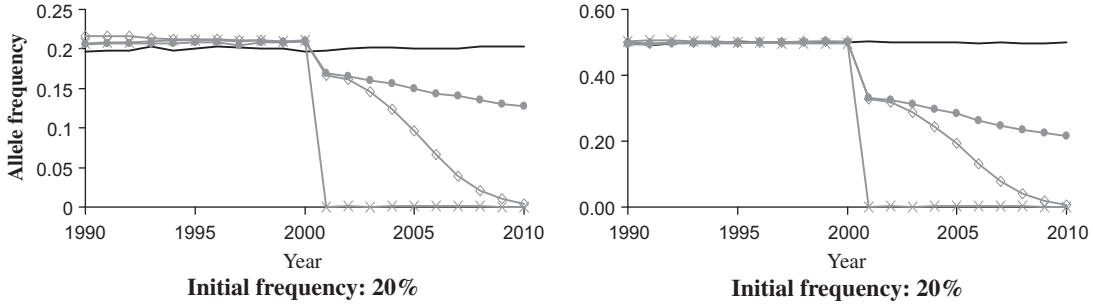

Fig. 2. Evolution of the frequency of a deleterious allele over 10 years according to scenarios related to the eradication of a monogenic recessive disorder in the Coton de Tulear. — Observed evolution; ● scenario *erA*; ◊ scenario *erI*; ╳ scenario *erC*.

When the initial allele frequency was set to 50%, kinship increase was much higher. In 2010 for BSG, Φ increased from 0.135 to 0.154 for *erA* (+14%, $P < 0.0001$), 0.19 for *erI* (+41%, $P < 0.0001$) and 0.21 for *erC* (+56%, $P < 0.0001$). However, the impacts were limited for EPB when considering the last year of simulation. Proportionally to absolute kinship increase, $\Delta\Phi$ computed from 2000 to 2010 was also affected (see Appendix A: Supplementary Table 2), e.g. for BSG, $\Delta\Phi$ increased from 1.3% to 5.3% per generation when the *erC* scenario was applied with an initial allele frequency of 50%.

Limitation of popular sire effect

Application of sub-scenarios involving increasing constraints on the number of offspring had an impact on the proportion of replaced parents (Table 2), as well as the average kinship (Fig. 3). When limiting the number of offspring to 200 per reproducer (*ps200*), only a small proportion of matings were affected. There was no impact on Φ for BSG and BRP, while there were small decreases in Φ from 0.038 to 0.036 (−6%, $P < 0.0001$) and from 0.038 to 0.037 (−4%, $P < 0.0001$) for COT and EPB, respectively, in 2010.

Table 2
Proportion of sires and dams changed over the 2001–2010 period depending on the maximum number of offspring allowed per reproducer (*ps* scenarios).

Breed name	Proportion of sires and dams changed (%)							
	Threshold: 25		Threshold: 50		Threshold: 100		Threshold: 200	
	Sire	Dam	Sire	Dam	Sire	Dam	Sire	Dam
Braque Saint Germain	22.8	5.8	2.9	0	0	0	0	0
Berger des Pyrénées	67.0	10.0	19.0	0.1	2.8	0	0.3	0
Coton de Tulear	–	–	76.9	0.3	35.7	0	6.8	0
Epagneul Breton	–	–	49.0	1.3	22.7	0	4.6	0

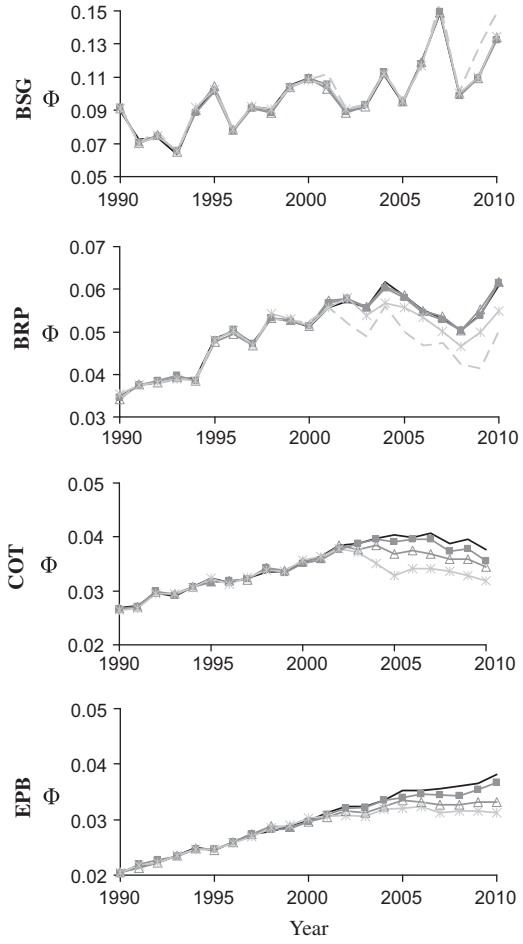

Fig. 3. Evolution of average kinship (Φ) over 10 years according to scenarios related to the limitation of the number of offspring allowed per reproducer. BSG, Braque Saint Germain; BRP, Berger des Pyrénées; COT, Coton de Tulear; EPB, Epagneul Breton. — Observed evolution; ■ scenario *ps200*; △ scenario *ps100*; ╳ scenario *ps50*; ╳ scenario *ps25* (only for BSG and BRP).

When a smaller number of offspring was allowed, the proportion of affected matings increased dramatically, modifying kinship evolution at the same time. When the number of permitted offspring was limited to 50, sires were replaced for 77% of COT individuals, leading to a decrease in Φ from 0.038 to 0.032 for this breed in 2010 (−15%, $P < 0.0001$), while sires were replaced for 19% of BRP individuals, resulting in a decrease in Φ from 0.061 to 0.055 (−10%, $P < 0.0001$). In BSG, there was little change in evolution of diversity in consecutive *ps* sub-scenarios. When the number of offspring per reproducer was limited to 25, there was an unexpected increase of Φ from 0.135 to 0.149 in 2010 (+10%, $P < 0.0001$).

Non-random replacement of reproducers

Fig. 4 illustrates the evolution of kinship in COT when breeders tend to choose replacement sires and dams more related or less related to the replaced one under two scenarios (*erC* initial allele frequency = 50% and *ps50*). The replacement of reproducers by related animals tended to increase average kinship, while choosing unrelated reproducers tended to decrease kinship.

Discussion

Management of genetic diversity constitutes an important issue for controlling the dissemination of inherited diseases and hence the welfare of dogs. In the present study, we used kinship to investigate the evolution of genetic diversity, since it is a key component of breed conservation (Baumung and Sölkner, 2003) and is directly related to the number of founder genome equivalents, i.e., theoretical remaining alleles inherited from founders (Caballero and Toro, 2000). Therefore, the risk of spreading new inherited disorders is proportional to kinship increase. In an ideal closed population, average kinship increases steadily over time. However, in practice, fluctuations in its evolution may occur due to practices such as importation of dogs without known pedigree.

The *'what if'* procedure developed in this study was used to investigate the consequences of breeding practices based on real pedigree data. It takes into account parameters that are difficult to include together in classical population simulations, such as overlapping generations, non-random mating and bottleneck events. Using sub-scenario *erI*, in which heterozygotes were allowed to reproduce, but their carrier offspring were removed from reproduction, it was estimated that a deleterious allele could be eliminated after 10 years of selection.

In practice, the FCI recommendations concerning the number of offspring per reproducer are not applicable for the BRP, COT and EPB (Table 1), since the maximum number of puppies produced by all reproducers in the period from 2006 to 2010 was less than the recommended threshold specific to each breed. Furthermore, the FCI recommendation would be difficult to implement for the BSG breed, since sires currently produce more offspring on average than the recommended threshold. However, our simulation approach enables specific recommendations to be provided within the context of a given breed.

The approach used in this study relies on several hypotheses and simplifications. We assumed that the current genetic structure would be similar to that of 10 years previously, but this may lead to bias if the breed has undergone a large change in population size. We also assumed that there was random replacement of reproducers, which seldom happens in real populations. As illustrated in Fig. 4, a non-random choice of replacement sires or dams may have an effect on the evolution of diversity. It is difficult to estimate if, and at which level, breeders may choose reproducers more related or less related to the replaced ones; however, future

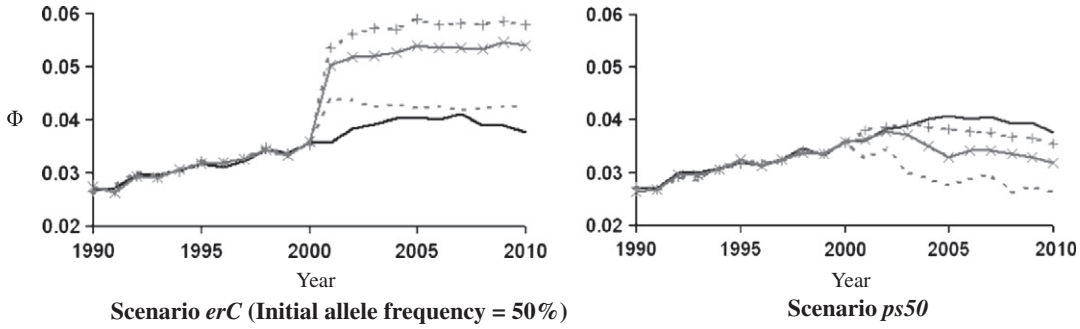

Fig. 4. Evolution of average kinship (Φ) over 10 years for scenarios *erC* (initial allele frequency = 50%) and *ps50* in the Coton de Tulear, according to the level of relatedness between replaced sires and dams and sires and dams chosen for replacement. Φ, Kinship; — observed evolution; X scenario with random replacement; –·–+–·–+–·– scenario with 50% of replacement sires (or dams) sampled among the 10th percentile of the most related sire (or dam); ------- scenario with 50% of replacement sires (or dams) sampled among the 10th percentile of the least related sire (or dam).

surveys could be implemented to give an indication about such choices.

On the basis of these results, some recommendations can be made for each of the four breeds included in this study, considering either an absolute increase in kinship or evolution of $\Delta\Phi$ over the 10 year period according to scenario. To limit the extent of inbreeding depression, it is generally considered that acceptable values of inbreeding (or kinship) rate per generation should not be >0.5–1% (Bijma, 2000). This value could be somewhat larger or smaller than the threshold for the BRP and COT, depending on the various scenarios considered in this study. Note that in scenarios aiming to eradicate a monogenic recessive disorder, a brief increase of rate in kinship was followed by more stable kinship evolution once the disease had been removed.

Given its small population size, the situation with the BSG seems to be the most problematic. In order to remove a deleterious allele with a large frequency (50%) from the breed, the most efficient eradication policies (*erI* and *erC*) should be excluded, given their potential negative impact on genetic diversity. For a moderate frequency of the allele (20%), it is more conceivable to use such policies, even if the predicted impact on genetic diversity (a relative increase in kinship level of 14% in 2010) is not negligible. Otherwise, given the efforts already implemented for the management of genetic diversity within the breed, imposing a reasonable threshold of number of offspring will not improve the situation substantially. The two sires used the most in 2010 show a low level of kinship with the current population, explaining why kinship was increased when applying the *ps25* scenario. The recommendation could be made to increase the number of reproducers or to implement more binding breeding schemes, for example minimising kinship (Fernandez et al., 2005). Outcrossing may be an interesting option for the BSG and is periodically used by the breed society.

In the BRP and COT, the same recommendations could be given regarding eradication of a specific disease. For a large allele frequency (50%), directly removing all carriers (*erC*) is not desirable, since $\Delta\Phi$ computed over the period would increase from 0.5% to 1.2% and from 0.1% to 0.8%, respectively (see Appendix A: Supplementary Table 2), exceeding recommended thresholds. An intermediate policy (*erI*) would have a moderate impact on genetic diversity (a relative increase in kinship level of 11% and 18% for BRP and COT in 2010, respectively). For an allele frequency close to 20%, direct removal of carriers (*erC*) would have a limited effect on kinship (a relative increase of 5% and 8% in 2010, respectively).

A greater contrast may be observed between the BRP and COT when limits are imposed on popular sire effects given a more 'intensive' use of reproducers in the COT. In this breed, in order to have a relative decrease of kinship level of 15%, no reproducer should produce more than 50 offspring, which in turn would affect 77% of the matings with respect to sire replacement. It would be more reasonable to recommend a threshold around 100 (36% of mating affected regarding sire pathway), even if the impact on genetic diversity will be more limited (a relative decrease of Φ of 10%). In the BRP, a threshold of 50 would allow kinship rate to decrease from 0.5% to 0.2%.

In the EPB, even with a high frequency of a deleterious allele, direct removal of carriers would not affect genetic diversity substantially and *erC* policy can be recommended in any case. Given the large number of reproducers within the breed, even when a large number of individuals are removed from reproduction, the probability of a complete loss of genetically original families is small. Therefore, the risk of occurrence of a bottleneck in relation to breeding strategies is more limited within the EPB breed. An offspring threshold of 100 should be adequate for the breed, since changing only 23% of sires in 2010 would have led to a predicted relative decrease of kinship of 12%.

Conclusions

The simulation method developed here sought to assess the impact of different breeding strategies on the frequency of a deleterious allele and on genetic diversity for four French dog breeds. By simulating changes occurring within a pedigree file after implementation of a chosen breeding strategy, we have provided breed-specific recommendations relating to issues such as the removal of an inherited disease or limitation of number of offspring per reproducer. The choice of a given strategy is also highly dependent on the existence of other traits to be selected, such as those related to behaviour and to severity of the disease. For a same frequency, a disease with a dramatic impact on viability will likely require a stricter breeding policy than a mildly deleterious one. Adaptation of the procedure to more complex situations (more complex inheritance, segregation of several diseases) could be the subject of further studies.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tvjl.2012.06.025.

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