Are insecticide-impregnated dog collars a feasible alternative to dog culling as a strategy for controlling canine visceral leishmaniasis in Brazil?

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Abstract

In a zoonotic visceral leishmaniasis (ZVL)-endemic area in Brazil, deltamethrin-impregnated collars (DMC) were fitted to 136 dogs for 5 months and significantly reduced the odds of increasing their anti-\textit{Leishmania} antibody titer during this period by 50% (95% confidence interval 29–87%, \(P = 0.01\)), as compared with a population of 97 uncollared dogs with pre-intervention prevalence within the same town. Mathematical modeling suggests that under typical Brazilian ZVL-endemic conditions, the epidemiological impact of community-wide DMC application should be greater than the currently practiced dog culling strategy, but that its impact will be dependent on collar coverage and loss rate. Both interventions should have a higher proportional impact in regions of lower endemicity, but the relative advantage of DMC over culling increases with transmission rate. Sensitivity analyses indicate that the impact of either intervention is not significantly affected by variation in the biology of the sandfly vector, but is greatly influenced by variation in dog mortality and serorecovery rates.

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1. Introduction

Domestic dogs (\textit{Canis familiaris}) are reservoir hosts of zoonotic visceral leishmaniasis (ZVL), a childhood disease caused by \textit{Leishmania infantum} and transmitted by phlebotomine sandflies. One of the approaches to reduce the incidence of human ZVL is to cull infected dogs. Notably, in Brazil 850,000 dogs are screened annually with 20,000 animals culled upon positive diagnosis (Vieira and Coelho, 1998). The impact of this culling program on ZVL incidence has been doubted both on theoretical (Dye, 1996) and practical grounds (Braga et al., 1998; Paranhos-Silva et al., 1998), and results of controlled culling trials are equivocal (Dietze et al., 1997; Ashford et al., 1998). The treatment of \textit{L. infantum}-infected dogs is an unfeasible control strategy, not only because of affordability but also because treated and clinically cured dogs often relapse and remain infectious to the sandfly vector (Gradoni et al., 1987; Alvar et al., 1994), increasing the risk of drug-resistant parasite strains developing. Whilst waiting for an effective canine (Gradoni, 2001) or human (Handman, 2001) vaccine, alternative control strategies are being actively sought.

Experimental trials have demonstrated that topical insecticides (Guanghua et al., 1994; Killick-Kendrick et al., 1997; Lucientes 1999; Halbig et al., 2000; David et al., 2001; Reithinger et al., 2001; Molina et al., 2002), and deltamethrin-impregnated dog collars (DMC) in particular (Reithinger et al., 2001), can protect dogs from >85% of sandfly bites for up to 6 months (Killick-Kendrick et al., 1997). Field trials in ZVL-endemic areas in Italy (Maroli et al., 2001) and Iran (Mazloumi Gavgani et al., 2002) have further demonstrated that dogs wearing DMC throughout...
a transmission season are at significantly less risk of being infected with *L. infantum*; and the trial in Iran (Mazloumi Gavagni et al., 2002) provided the first evidence that village-wide provision of DMC to domestic dogs can lead to a significant reduction in *L. infantum* incidence rate in children from the same villages. This epidemiological effect is presumably mediated not only by the collar-induced reduction in the sandfly biting rate on dogs, but also due to the enhanced mortality rate of sandflies attempting to feed on collared dogs (Killick-Kendrick et al., 1997; Reithinger et al., 2001). These results provide a firm basis for supposing that the provision of DMC to dogs could be an effective alternative to the controversial dog culling program in Brazil. Recent studies have confirmed the anti-feeding effects of DMC against *Lutzomyia longipalpis*, the ZVL vector throughout Brazil and most of Latin America, reducing the biting rate on dogs by 81–100% for up to 35 weeks (David et al., 2001).

Presented here are the results of the first of three trials testing DMC under field conditions in Brazil. The objective of this study was to test whether DMC can reduce canine visceral leishmaniasis (CVL) incidence in a Brazilian field setting, and – on finding positive evidence – to develop a mathematical model for investigating whether the widespread provision of DMC in Brazil is likely to lead to greater ZVL control than the current dog culling program.

### 2. Materials and methods

#### 2.1. Field trial

In September 1999, a cohort of 441 dogs was surveyed clinically, parasitologically and immunologically in two different neighborhoods (D1 and D2, respectively) of Capitão Eneas (16°30’S, 44°00’W), a *L. infantum*-endemic area in Minas Gerais State, Brazil; D1 and D2 were 500 m apart and selected at random. *L. longipalpis* occurs throughout the year and there is no documented *Leishmania braziliensis* or *Trypanosoma cruzi* transmission in the area. After blood samples (2–10 ml) had been taken from all dogs, 40 mg/g DMC (Scalibor, Intervet International) were attached to all dogs above 3 months of age in D1; D2 dogs remained uncollared. All dog owners that participated in the study (319/332 [96%] of dog owners surveyed) were informed about the objective of the study and possible side-effects due to collar use; participation was voluntary. Collar loss and side-effects were also recorded at 2-weeks intervals. After 5 months, i.e. February 2000, dogs in both areas were re-surveyed and a second blood sample was taken to estimate the effectiveness of DMC in reducing CVL incidence.

All blood samples were screened as described previously (Reithinger et al., 2002). Briefly, for parasitological diagnosis, we used a *Leishmania donovani* complex-specific PCR-hybridisation protocol with AJS31 (5′-GGGGTGGTGTTAAAATAGGGCC-3′) and DBY (5′-CCAGTTTCCGCCGCCCGAG-3′) primers and a [γ32P]-ATP-labelled B4RsaB (5′-GACCTGAAAAACCC-TGGGTCTGGGCGG-3′) probe. Samples were screened by ELISA for immunological diagnosis, with log-phased *L. donovani* promastigotes (MHOM/ET/67/L82) as antigen (107 promastigotes/microtitre plate well concentration) and peroxidase-conjugated, affinity-purified rabbit anti-dog IgG as antibody (1/1500 concentration). Using these protocols PCR and ELISA have a 100% specificity and 53–64 and 74–88% sensitivity, respectively, in detecting dogs with confirmed CVL infection; the combined sensitivity and specificity by using PCR and ELISA is 80–100 and 100%, respectively (Reithinger et al., 2002).

To measure the epidemiological impact of DMC, a logistic regression was used to estimate the odds of dogs from D1 and D2 becoming infected after controlling for pre-intervention prevalence in each locality (i.e. the proportion of dogs positive by ELISA or PCR, or both) and dog gender. Neither dog age nor collar loss during the trial were shown to significantly affect the odds of infection in dogs after analyses and so these factors were excluded in the final model. The outcome variables in the two models were: (i) positive by ELISA or PCR, or both; and (ii) increase in anti-*Leishmania* log antibody units/ml. All analyses were done in STATA 7 (Stata Corporation, TX, USA).

#### 2.2. Mathematical model

We simulated the potential effectiveness of DMC as compared to dog culling programs by using a compartmental epidemiological model. Total dog (*D*) and sandfly (*F*) populations are divided into epidemiological compartments that comprise uninfected and susceptible (*D* and *F*), latent (i.e. infected but not infectious) (*D* and *F*) or infectious (*D* and *F*) sub-populations. In the absence of any control intervention, changes in these sub-populations through time are given by the following equations:

\[
\frac{dD_s}{dt} = D_s \alpha - D_s \delta - D_s \rho
\]

\[
\frac{dD_l}{dt} = D_l \alpha - D_l \rho - D_l (\delta + \delta_t)
\]

\[
\frac{dD_i}{dt} = (D_N \delta + D_N \left( \alpha \frac{K - D_N}{K} \right) - D_i \delta + D_i \rho
\]

\[
\frac{dF}{dt} = apcF_3D_i - F_{L_1} \exp^{-\mu t} - F_L \mu
\]

\[
\frac{dF}{dt} = F_{L_1} \exp^{-\mu t} - F_{L_2} \mu
\]

\[
F_s = F_N - F_L - F_I
\]

where the parameters are as follows. The underlying dog and sandfly mortality rates are \(\delta\) and \(\mu\), respectively. These
mortality rates are age-independent, but we allow dog mortality rates to vary with infection status with an additional mortality of $d_l$ incurred by infectious dogs (i.e. due to CVL, (Courtenay et al., 1994)). The model assumes that the total sandfly population ($F_N$) is constant, but that dog recruitment rates are density dependent, described by

$$ (D_N \delta) + D_N \left( \frac{K - D_N}{K} \right) $$

(7)

where the average mortality rate is defined as

$$ \delta = \frac{(D_N \delta) + (D_L \delta) + D_T (\delta + \bar{\delta})}{D_N} $$

(8)

Hence, when dog population size ($D_N$) approaches zero the growth rate approaches $\alpha$, and when the population size approaches the carry capacity, $K$, the growth rate approaches zero, i.e. the birth rate of susceptible dogs is equal to the average mortality rate of the whole population. The value of $\alpha$ was set so that dog population size returned to the carrying capacity within 6 months of culling.

In the absence of definitive evidence for a bimodal distribution of innate susceptibility to $L. \text{infantum}$ amongst dogs (Dye, 1996), we assume a continuous distribution of susceptibility amongst the dog population, with latent dogs becoming infectious at rate $\sigma$ and infectious dogs recovering at rate $\rho$. Sandflies take bloodmeals at rate $p$, which is the proportion of feeds taken on dogs. Infectious sandflies have a probability $b$ of transmitting $\text{Leishmania}$ parasites when feeding on a susceptible host, while $c$ is the probability that a sandfly becomes infected when feeding on an infectious dog. The ratio of vectors to dogs is $m$; and $\tau$ is the extrinsic incubation period (i.e. the time required for the development of infective metacyclics in infected sandflies). Using the differential equations described by Eqs. (1)–(6) and using baseline parameters outlined in Fig. 2, simulations were run in EXCEL at 1 day intervals until an equilibrium prevalence of infected dogs (i.e. the percentage of dogs either latent or infectious) was obtained. All parameter values used were taken from published sources, except $b$ and $m$, which are hard to measure. The value of $m$ was selected so as to generate an equilibrium prevalence of 60%. The baseline value of $b$ was arbitrarily selected as three times $c$, but, as with all parameters, univariate sensitivity analyses were run to investigate the impact of varying this value on the model outputs. Finally, we tested the impact of varying the baseline prevalence of infected dogs by using the baseline values for all parameters except $m$ which we allowed to vary. The rationale for this decision is that geographic variation in CVL transmission rate within Brazil is likely to be most influenced by variation in $L. \text{longipalpis}$ density (Camargo-Neves et al., 2001). Thus, the parameter values were as follows: $\delta = 0.0012$/day (from this study), $\delta_l = 0.0012$/day (Courtenay et al., 1994), $\alpha = 25\delta$, $\sigma = 0.333$/day (Dye et al., 1991), $p = 0.25$ (Quinnell et al., 1992; Morrison et al., 1993; Agrela et al., 2002), $c = 0.107$ (Courtenay et al., 1994), $b = 3c$, $m = 79.65$, $\sigma = 0.005$/day (Courtenay et al., 1994), $\rho = 0$/day (Quinnell et al., 1997; Courtenay et al., 2002), $\mu = -a[\ln(\text{proportion parous})]$ where proportion parous = 0.4 (Dye et al., 1987; Ferro et al., 1993), $\tau = 7$ days (Lainson et al., 1977; Walters et al., 1989; Montoya-Lerma et al., 2003).

The effect of collaring or culling dogs at 1 year or half-year pulses was then simulated. In the baseline collar model, we assumed that at the each annual pulse 80% of dogs are collared, that each collar initially provides 90% protection from sandfly bites, and that 25% of collars are ineffective within 8 months (i.e. the rate of loss of effectiveness = 0.001/day), either as they are lost (and not replaced) or because the insecticide effect has worn off (Table 3). We then investigated the impact of varying coverage at each pulse, frequency of collaring pulses, protection of collars against sandflies, and rate of loss of effectiveness. In the baseline culling model we assumed that 50% of all infectious dogs were culled at each annual pulse. Only 43% of the latently infected dogs are patent, i.e. detectable by the diagnostic test (Courtenay et al., 2002). Hence, the percentage of latent dogs culled was assumed to be 43% of that for the infectious dogs. We then investigated the impact of varying the percentage of patently infected dogs (i.e. all infectious plus 43% of latently infected dogs) culled, and the frequency of culling.

In all simulations, impact is defined as the reduction in the average prevalence of infected dogs over a 5-year period after the intervention is introduced in comparison with no intervention (i.e. stable equilibrium at a baseline prevalence of 60%). Finally, we tested how the effectiveness of both culling and collaring varies according to the baseline prevalence of infected dogs.

3. Results

Of the 441 surveyed dogs, 267 were male (mean age ± standard error: 30.6 ± 1.7 months, range: 3–180 months) and 174 female (28.2 ± 2.1 months, range: 2–168 months). Results for both pre- and post-intervention surveys are represented in Table 1. The local Ministry of Health (MOH) had reportedly killed all IFAT-seropositive dogs 1 month prior to our survey as part of their leishmaniasis control program, but baseline prevalence was very high: 18.7% (47/251) in D1 and 12.6% (24/190) in D2; 17.1% (43/251) and 12.7% (32/251) of surveyed dogs were positive by ELISA and PCR in D1, 12.1% (23/190) and 7.9% (15/190) of surveyed dogs were positive by ELISA and PCR in D2, respectively (Table 1). Although the baseline prevalence (i.e. dogs positive by ELISA or PCR, or both) was higher in the intervention population, the difference was not significant (Yates-corrected $\chi^2 = 2.54$, $P = 0.11$).

After 5 months, 136/251 (54%) and 97/190 (51%) dogs were re-surveyed in D1 and D2, respectively; 44/251 (18%) and 40/190 (21%) dogs had died and 40/251 (16%) and
21/190 (11%) dogs had emigrated from D1 and D2, respectively. In D1, 56/136 (41%) dogs lost their collar during the study; the collar loss rate was 0.006 collars/day. According to the dog owners, collars came off: (i) due to dogs being able to loosen the collar buckle shortly after application \(n = 14\); (ii) due to wear and tear \(n = 32\), possibly because most dogs had had no previous experience of being collared; or (iii) due to side-effects (skin irritation \(n = 5\), loss of appetite and epitaxis \(n = 4\) and trembling \(n = 1\)), so that collars ‘had to be’ removed. It should be noted that the causal link between the collars and these symptoms was suggested by the owners and not confirmed.

Of re-surveyed dogs, 17.6% (24/136) and 20.6% (28/136) of surveyed dogs were positive by ELISA and PCR in D1, 17.5% (17/97) and 18.6% (18/97) of surveyed dogs were positive by ELISA and PCR in D2, respectively (Table 1). In contrast to pre-intervention CVL prevalence which was greater in D1, CVL incidence (i.e. proportion of dogs converting by ELISA, PCR, or both) in the intervention dog population (D1) was considerably (but not significantly, \(P = 0.24\)) less, 11.9% (13/109), than in the control population (D2), 17.6% (15/85). Using multiple regression analysis adjusting for dog sex and pre-intervention ZVL prevalence, it was shown that the proportion of dogs whose anti-\textit{Leishmania} antibody titer had increased after 5 months was significantly less in D1 (55/136) than in D2 (55/97), i.e. the collars reduced the odds of dogs increasing their antibody titer by 50% (95% confidence interval 29–87%, \(P = 0.01\)) (Fig. 1).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>1999 ELISA+/PCR+</th>
<th>1999 ELISA+/-PCR+</th>
<th>1999 ELISA-/PCR+</th>
<th>2000 ELISA-/PCR+</th>
<th>NR*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment area (D1)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA+/PCR+</td>
<td>10</td>
<td>–</td>
<td>2</td>
<td>4</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>ELISA+/PCR−</td>
<td>5</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>ELISA-/PCR+</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>ELISA-/PCR−</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>96</td>
<td>95</td>
<td>204</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>20</td>
<td>4</td>
<td>8</td>
<td>104</td>
<td>115</td>
<td>251</td>
</tr>
<tr>
<td><strong>Control area (D2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA+/PCR+</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>ELISA+/PCR−</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>ELISA-/PCR+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>ELISA-/PCR−</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>70</td>
<td>81</td>
<td>166</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
<td>4</td>
<td>5</td>
<td>75</td>
<td>93</td>
<td>190</td>
</tr>
</tbody>
</table>

* NR, not re-surveyed.

21/190 (11%) dogs had emigrated from D1 and D2, respectively. In D1, 56/136 (41%) dogs lost their collar during the study; the collar loss rate was 0.006 collars/day. According to the dog owners, collars came off: (i) due to dogs being able to loosen the collar buckle shortly after application \(n = 14\); (ii) due to wear and tear \(n = 32\), possibly because most dogs had had no previous experience of being collared; or (iii) due to side-effects (skin irritation \(n = 5\), loss of appetite and epitaxis \(n = 4\) and trembling \(n = 1\)), so that collars ‘had to be’ removed. It should be noted that the causal link between the collars and these symptoms was suggested by the owners and not confirmed.

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In contrast to pre-intervention CVL prevalence which was greater in D1, CVL incidence (i.e. proportion of dogs converting by ELISA, PCR, or both) in the intervention dog population (D1) was considerably (but not significantly, \(P = 0.24\)) less, 11.9% (13/109), than in the control population (D2), 17.6% (15/85). Using multiple regression analysis adjusting for dog sex and pre-intervention ZVL prevalence, it was shown that the proportion of dogs whose anti-\textit{Leishmania} antibody titer had increased after 5 months was significantly less in D1 (55/136) than in D2 (55/97), i.e. the collars reduced the odds of dogs increasing their antibody titer by 50% (95% confidence interval 29–87%, \(P = 0.01\)) (Fig. 1).
Having demonstrated empirically the effectiveness of DMC in a Brazilian setting, the potential epidemiological impact of collars and culling was then compared by model simulation. Fig. 2 shows how the model predicts dog seroprevalence to change during the first 5 years after either culling or DMC are introduced (using baseline parameter values). It also demonstrates how the dog recruitment rates are density-dependent, with the dog population size reverting to carrying capacity within 6 months after each culling pulse. Undoubtedly, there is uncertainty in some of the parameter values we selected, but the model results were remarkably robust to variation in most of the entomological parameters, i.e. the variation in the proportion of feeds taken on dogs (from 0.1 to 0.33); the intervals between feeds (3–4 days); the percentage of sandflies infected when feeding on an infectious dog (5–25%); the percentage of dogs infected when bitten by an infectious sandfly (5–50%); and sandfly mortality rate (parous rate: 0.2–0.6). Within each of these parameter value ranges, and using the baseline values of the other parameters in the model (Fig. 2), collars provided 60% protection compared to only 50% protection from culling in each of the simulations.

In contrast, the relative effectiveness of collars and culling was very sensitive to both variation in the additional mortality incurred by infectious dogs (as \( \delta_f \) increases, culling becomes less effective, but collars become more effective), and to variation in basic dog demography (as underlying dog mortality rates \( \delta \) increase, collars become more effective, but culling becomes less effective) (Table 2). Indeed, in circumstances where uninfected dogs typically live for over 8 years or where CVL causes no additional dog mortality, culling appears to be more effective than DMC. However, these estimates assume no recovery in dogs from infectious status to susceptible status, and so may underestimate the relative advantage of DMC over culling (which increases as recovery rates increase).

The above comparisons all assume a single culling pulse which culls 50% of patently infected dogs. This is probably a realistic target for the Brazilian control program (even though it may well not be currently achieved (Braga et al., 1998)), but our models demonstrate how culling effectiveness increases in accordance with percentage culled, or by culling twice per year (Table 3). The effectiveness of collaring is likewise sensitive to the percent of dogs covered, the degree of protection provided, and the rate of loss of insecticidal effectiveness (Table 3). But carrying out collar pulses biannually generally has relatively little advantage over an annual pulse (Table 3).

Finally, the effectiveness of collars and culling under conditions of varying endemicity was evaluated (Fig. 3). While effectiveness of both interventions drops with increasing endemicity, the impact of DMC is little affected by changes in infectious dog prevalence from 10 to 60%. The impact of culling is more sensitive to variation in endemicity, indicating that a control program which successfully culls 50% seropositive dogs once per year would be more effective than a DMC program (with baseline parameter values) where the prevalence of infected dogs is less than 30%.

### Table 2

Epidemiological impact of culling and collaring on the prevalence of infected dogs: parameter sensitivity. Except where stated, all parameters have baseline values (see Fig. 2 legend).

<table>
<thead>
<tr>
<th>Average % predicted reduction in prevalence over a 5-year period from the start of the interventiona</th>
<th>Culling (%)</th>
<th>Collaring (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline parameters</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Additional mortality due to ZVL (multiple of ( \delta ), ( x = 0 ))</td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td>Additional mortality due to ZVL (multiple of ( \delta ), ( x = 4 ))</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>Underlying death rate, ( \delta = 1/500 ) days (fixed additional mortality)</td>
<td>42</td>
<td>64</td>
</tr>
<tr>
<td>Underlying death rate, ( \delta = 1/3000 ) days (fixed additional mortality)</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Recovery ( \rho = 1/1 ) year</td>
<td>33</td>
<td>74</td>
</tr>
<tr>
<td>Recovery ( \rho = 1/5 ) years</td>
<td>45</td>
<td>64</td>
</tr>
</tbody>
</table>

a \( \delta \), dog mortality rate; and \( \rho \), recovery rate from *Leishmania* infection.
4. Discussion

Despite the low number of tested animals (a total of only 233 dogs were sequentially surveyed), the possibly high number of animals with pre-patent infections during the baseline survey, and the high rate of collar loss as compared to other published studies (8% in Italy (Maroli et al., 2001), and 10% in Iran (Mazloumi Gavgani et al., 2002)), we show that collar application over 5 months significantly reduces the probability of an increase in anti-\textit{Leishmania} antibody titer in collared dogs. Hence, we now have some evidence that DMC can reduce the risk of \textit{L. infantum} infection for dogs in Brazil. Preliminary results from ongoing field trials in Ceará and Bahia (recording seroconversion rates in over 1000 collared dogs between them) seem to provide further evidence that DMC can protect dogs from \textit{L. infantum} infections in Brazil (Bدارو, R., 2002. Preliminary results of a field trial in Bahia State, Brazil, to reduce the risk of human visceral leishmaniasis by controlling CanL with deltamethrin-impregnated collars. Proceedings of the Second International Canine Leishmaniasis Forum, Seville, Spain, 2002. Intervet, Boxmeer, p. 97; Oliveira-Lima, J.W., De Souza, R.N., Teixeira, M.J., Pompeu, M., Killick-Kendrick, R., David, J.R., 2002. Preliminary results of a field trial to evaluate deltamethrin-impregnated collars for the control of canine leishmaniasis in northeast Brazil. Canine Leishmaniasis: moving towards a solution. Proceedings of the Second International Canine Leishmaniasis Forum, Seville, Spain, 2002. Intervet, Bomeer, pp. 91–95.). Although we also observed a lower CVL incidence in collared dogs than in uncollared dogs, the effect was not significant. The discrepancy between the analyses of the two outcome measures in our trial may be because by taking into account all positive changes in antibody titer we are able to include new cases in the process of seroconverting (i.e. samples which otherwise are excluded from the relatively arbitrary ELISA + category in Table 1) (Reithinger et al., 2002). This approach may represent a more accurate estimate of the CVL transmission rate, because the duration of the trial was short (5 months) and the number of incident infections may have been significantly underestimated due to the long (about 2 months) CVL pre-patent period (Dye, 1996).

Although we used conservative estimates for the effect of collars (i.e. 80% coverage rate and 25% loss of effectiveness within 8 months) and relatively optimistic estimates for the effect of culling (i.e. 50% of infected and infectious dogs are culled), the model exposes – despite recent contrary claims (Palatnik de Sousa et al., 2001) – the problems associated with the culling strategy. In endemic transmission areas, the remaining non-culled, infected and infectious dogs are sufficient to drive transmission over time, with newly recruited susceptible dogs rapidly acquiring CVL infection (Dye, 1996; Braga et al., 1998; Paranhos-Silva et al., 1998). Unlike previous models (Dye, 1996; Courtenay et al., 2002), we do not overestimate this effect by assuming that dog populations revert to their carrying capacity instantaneously after each culling pulse (Palatnik de Sousa et al., 2001). Instead we permit dog populations to return to equilibrium levels within 6 months, consistent with field experience (Palatnik de Sousa et al., 2001).

Culling strategies are especially hampered by the long delay between dog sampling, CVL diagnosis and culling. This delay has been shown to be as high as 90-days.

<table>
<thead>
<tr>
<th>Simulation scenarios</th>
<th>Average % predicted reduction in prevalence over a 5-year period from the start of the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>One pulse per year (%)</td>
<td>Two pulses per year (%)</td>
</tr>
<tr>
<td>Variations in culling intensity (% of dogs culled)</td>
<td>50% [baseline] 75 50 75 75 75</td>
</tr>
<tr>
<td>25%</td>
<td>23 41 23 41 41 41</td>
</tr>
<tr>
<td>80%</td>
<td>81 93 81 93 93 93</td>
</tr>
<tr>
<td>Variations in collaring intensity (% of dogs initially collared, % initial protection from each collar, % of collars not effective after 8 months application)</td>
<td>80%, 90%, 25% [baseline] 60 69 60 69 69 69</td>
</tr>
<tr>
<td>50%, 90%, 25%</td>
<td>43 59 43 59 59 59</td>
</tr>
<tr>
<td>90%, 90%, 25%</td>
<td>64 71 64 71 71 71</td>
</tr>
<tr>
<td>80%, 50%, 25%</td>
<td>35 45 35 45 45 45</td>
</tr>
<tr>
<td>80%, 75%, 25%</td>
<td>52 63 52 63 63 63</td>
</tr>
<tr>
<td>80%, 95%, 25%</td>
<td>62 70 62 70 70 70</td>
</tr>
<tr>
<td>80%, 90%, 50%</td>
<td>47 63 47 63 63 63</td>
</tr>
<tr>
<td>80%, 90%, 5%</td>
<td>68 72 68 72 72 72</td>
</tr>
</tbody>
</table>

Table 3: Epidemiological impact of culling and collaring on the prevalence of infected dogs: variations in culling and collaring intensity

Fig. 3. The influence of pre-intervention prevalence on the average reduction in prevalence over 5 years through use of collars (baseline parameters of 80% coverage, 90% protection, 75% persistence of effectiveness after 8 months, annual pulses: continuous line) and culling (annual pulse of 25, 50 and 80% patently infected dogs culled; broken lines).
(Braga et al., 1998), with infected dogs remaining infectious to sandfly vectors and driving CVL transmission (Dye, 1996; Braga et al., 1998; Paranhos-Silva et al., 1998). Also, the diagnostic test used by the Brazilian control program (IFAT on filter paper eluate) to mass-screen dogs may not be 100% sensitive for infectious dogs: one study suggests that up to 65% of infected dogs are not detected by IFAT-based CVL diagnosis (Braga et al., 1998). The effect of culling programs will additionally be undermined by the immigration of infected dogs into culling areas (Braga et al., 1998; Paranhos-Silva et al., 1998). Hence, it is probable that far fewer patently infected dogs than the 50% in our model are culled because they are not detected or because owners refuse to have their dogs culled. This appears to be confirmed in our study site, as despite the culling of infected dogs by the local MOH 1 month prior to the intervention trial, mean pre-intervention prevalence in D1 and D2 was 16%.

Perhaps the most interesting finding of our sensitivity analyses is that while the predicted epidemiological impact of either intervention is relatively unaffected by variation in sandfly biology, the predictions are strongly dependent on the underlying demography of the dog population, and to an even greater extent – by the additional dog mortality resulting from CVL. This has rarely been measured in the field, and our analysis indicates that future field studies should aim to provide accurate measurements of this parameter. The predicted impact was also dependent on the serorecovery rate in dogs, another parameter whose value has rarely been reliably estimated in the field.

The other unexpected finding was the discovery that the relative advantage of collaring over culling should be greatest where transmission rates are high. In low endemic sites, culling could have a bigger epidemiological impact than DMC. Future trials to compare the relative effectiveness of DMC and culling should therefore embrace the range of transmission rates found in endemic ZVL sites. Unlike for culling, the predicted impact of DMC drops only marginally as transmission rate increases (within the range characteristic of ZVL endemic sites). Hence, our model predictions provide no support for the previous assertion (Maroli et al., 2001) that the apparent increase in impact of DMC in the Italian trial in the second year (86% protection compared to only 46% in the first year) was due to the higher incidence rate during the second year (26% per year versus only 5.4% during the first year). Rather, our model explains this observation by showing how sequential annual collar pulses are likely to have a cumulative effect (Fig. 2) irrespective of any change in underlying incidence. Future DMC trials should provide further measurements of this cumulative effect to investigate the likely consequences of a sustained DMC control programme.

There is now increasing evidence that DMC not only protect dogs from sandfly bites (Killick-Kendrick et al., 1997; Lucientes, 1999; Halbig et al., 2000; David et al., 2001; Reithinger et al., 2001) but also from CVL (Maroli et al., 2001; Mazloumi Gaviani et al., 2002). Because dogs are ZVL reservoirs, the findings suggest that DMC could be effective in controlling human disease in Brazil as well. Our simulations show that in order to achieve a significant epidemiological impact on CVL transmission, high dog collar coverage rates will be essential (Table 3). This will not only require the rapid replacement of lost collars, but also the collaring of new dogs recruited into the population. Where population turnover rates are high, as in Brazil and most tropical CVL-endemic countries, maintaining high coverage rates will be a logistic challenge. The effectiveness of collaring domestic dogs will also be diminished in those endemic areas where wild reservoirs (e.g. crab eating foxes, Cercdocyon thous, and opposums, Didelphis spp.) or stray dogs play a major role in maintaining ZVL transmission. Similarly, the effectiveness of collaring dogs would be reduced should sandflies become insecticide-resistant due to the mass use of DMC or change their feeding preferences to preferentially feed on hosts other than dogs.

Ultimately, the decision to replace the dog culling strategy in Brazil with community-wide application of DMC will depend on: (1) the practical applicability of DMC in the field (e.g. the willingness of the community to apply DMC and the efficiency with which they replace collars which have detached); and (2) the relative cost of the intervention (Akhavan, 1996).

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References


