Revista da Sociedade Brasileira de Medicina Tropical
Journal of the Brazilian Society of Tropical Medicine
Vol.:52:e20190156: 2019
doi: 10.1590/0037-8682-0156-2019

Short Communication

Brazilian Spotted Fever Prevention through a Nonlethal Capybara Population Control Strategy

***Derek Andrew Rosenfield*[1]*, Gina Polo*[2] *and Cristiane Schilbach Pizzutto*[1]**

[1]. Universidade de São Paulo, Faculdade de Medicina Veterinária e Zootecnia,
Programa de Pós-Graduação em Reprodução Animal, São Paulo, SP, Brasil.
[2]. Universidade de São Paulo, Faculdade de Medicina Veterinária e Zootecnia,
Departamento de Medicina Veterinária Preventiva e Saúde Animal, São Paulo, SP, Brasil.

Abstract

Introduction: Brazilian spotted fever (BSF), a lethal tick-borne Rickettsioses (2000 - 2018 >600 human deaths) involving synanthropic capybara as host. **Methods:** We introduced an alternative to mitigate human-capybara conflicts and epidemiologic concerns of BSF. Complex aspects like transmission dynamics, risk areas, host mobility, and birth rate control, were considered to develop a prevention strategy using an anti-GnRH vaccine. **Results:** The propositioned immunocontraceptive potentially remove and prevent the spread of BSF from endemic areas. **Conclusions:** We propose the anti-GnRH vaccine as a BSF prevention strategy based on these favorable results.

Keywords: Immunocontraception. Anti-GnRH. GonaCon. *Hydrochoerus hydrochaeris*. Rickettsia. *Amblyomma sculptum*.

In this study, we addressed the fundamental issue pertaining to the prevention of BSF in humans, while considering the dynamics between the vertebrate hosts and ticks, and the environmental and anthropogenic conditions[1,2].

In São Paulo, one of the primary tick vectors for BSF is *Amblyomma sculptum*, a species of three-host parasite. During any growth stage, ticks can either become infected or infect the host via three different routes (**Figure 1**): by horizontal transmission, where the pathogen is transmitted to the tick by feeding on an infected host's blood containing sufficient bacteremia; by vertical transmission, where the pathogen is transmitted from an adult female tick to her eggs; and through transstadial transmission, where the pathogen is maintained during the molting passages (egg to larva); however, some routes are much less effective in sustaining the pathogens. Humans, if infected by a pathogen-carrying tick, are considered accidental, dead-end hosts and do not play a role in maintaining the bacterium in the ecosystem[3]. Due to anthropogenic activities and subsequently diminishing natural habitats, wildlife species will either become extinct or be driven into human habitats, where various species are capable of quick adaptation to the urban and agricultural areas. Currently, as synanthropic pests, they provoke numerous human-wildlife conflicts by devastating crops and cause epidemiological threats, such as the aforementioned BSF[4].

Capybaras (*Hydrochoerus hydrochaeris*), the world's largest rodent, are considered as potentially amplifying hosts for *R. rickettsii*, as they fulfill all the following necessary criteria: *i*) the potential host species must be abundant in the endemic area; *ii*) be a good host for ticks; *iii*) be susceptible to Rickettsia infection; *iv*) be highly proliferative, ensuring the introduction of susceptible animals; and *v*) have enough bacteremia to infect feeding ticks[5,6]. In Brazil, reduction in the natural predators, mainly in areas of anthropological impacts, and abundant water and food sources, largely due to agricultural activities, provide favorable conditions for this highly proliferative species to turn into superpopulations[4,5].

Thus, to plan an effective BSF control strategy, several complex aspects should be emphasized: *i*) the modeling and understanding of the effects and contributions of capybaras and ticks in maintaining BSF transmission, including the associated effects of inter- and intra-species transmissions, births, and deaths; *ii*) defining the important reproductive parameters

---

Corresponding Author: Dr. Derek A. Rosenfield.
e-mail: dro@usp.br
Orcid: 0000-0001-5546-8872
Received 4 April 2019
Accepted 13 August 2019

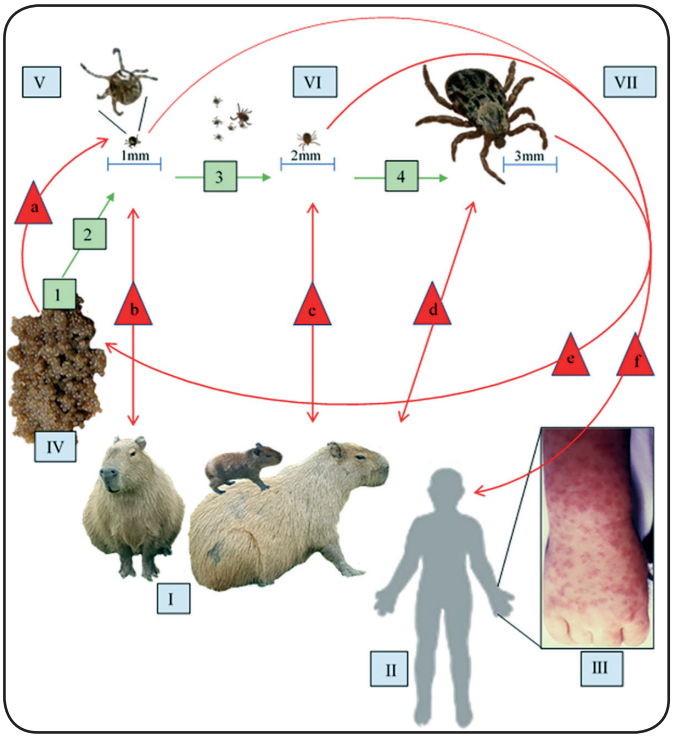

FIGURE 1: The Three-Host Life Cycle and the Dynamics of Pathogen Transmission. I) Amplifying hosts; II) incidental (dead-end) hosts; III) characteristic symptom: petechial rash; IV) tick eggs; V) larvae; VI) Nymph; VII) adult tick; Amblyomma life-cycle stages, 1) eggs; 2) molt to larvae; 3) molt to nymph; 4) molt to adult; *Rickettsia rickettsii*, transmission dynamics: a) transstadial; b) larvae-host; c) nymph-host; d) adult-host; e) transovarial transmission.

(e.g., basic reproduction number R_0)[1,4], and calculating the speed of dissemination; *iii*) describing the spatial relationships between BSF in human cases, environmental/anthropogenic conditions, and host mobility effects on BSF transmission and therefore, comprehending/predicting risk zones of BSF; and *iv*) determining an adequate and species-specific population control strategy, focusing on the most important species in the maintenance and propagation of BSF.

Population control methods must be strategically employed to act as an effective BSF transmission management tool. As suggested by a transmission dynamic model of *R. rickettsii* involving *H. hydrochaeris* hosts and *A. sculptum* vectors[6], to eliminate the etiological agent from an endemic area, a sustained reduction of 80% of the capybara's birth rate is necessary, which can result in the disappearance of the infected individuals by the 4th year. Moreover, if a 90% birth rate decrease could be achieved, infected capybaras and ticks would also cease to exist by the 2nd year[6]. Furthermore, based on the next-generation matrix approach, elements corresponding to the number of infected attached nymphs and adult ticks produced by an infected capybara and vice versa have been identified as critical contributors to changes in the basic reproduction number ($R_0 \approx 1.7$)[7]. Additionally, high-risk seasons correspond to the nymph (July to October) and adult (October to March) stages of the tick, indicating that preventive strategies must be planned accordingly, namely, from April to July or during the larvae season.

As described, the capybara's migration plays an important role in BSF dissemination. Thus, to prevent migration, the chosen population control must achieve a minimum of 58% birth rate reduction. Although this would not eliminate the disease, it would prevent *R. rickettsii* from spreading outside an endemic area. Using hyperspectral moderate-resolution satellite imagery, capybara's migration has been shown to be associated with the widespread sugarcane plantations[1], and these areas, in turn, have been associated with high-risk areas for BSF. Accordingly, capybara's migration can be predicted, while risk areas for human BSF can be identified. Correlating this pattern with the reported distribution of BSF in humans , the host mobility model confirmed that regions with high density of sugarcane has a higher BSF dissemination velocity[2], and consequently efforts on population control should be focused on these high-risk (sugar cane) areas.

In this context, to eliminate capybara conflicts including their influence on disease propagation, their migration and birth rate must be controlled. However, any intervention involving direct manipulation of the target animal is influenced by ethical, economic, logistical, and legal concerns. Specifically, environmental laws protect native fauna from being hunted (Federal Law, Brazilian Fauna Protection Act, 1967), and any population control efforts are limited in Brazil. For this reason, several wildlife population control concepts are being evaluated, such as strategies that indirectly influence their birth rate and migration by affecting an area's carrying capacity. For example, sugar cane plantations, one of São Paulo's principal crop production areas close to water bodies, are likely to be raided by animals. Knowing that capybaras are usually found a few hundred meters away from the water bodies[8], one approach could be the delimitation of movement through riparian reforestation, a natural barrier, respecting a perimeter far enough from water resources, to hinder their access to the food supply. However, a reported mean dispersal distance of 3366 m for capybara[9] might make this strategy less feasible.

Another strategy involves the relocation or translocation of capybaras to an area of less potential conflict. This is a valuable technique for conservation efforts of threatened taxa; yet, when it comes to synanthropic capybaras, this practice is less recommended, as it brings more problems than solutions, especially epidemiologically, considering that one single infected individual, with a minimum of one attached tick, is enough to trigger BSF in a non-endemic area[1]. In addition, susceptible animals may be introduced into an infected area, thus, aiding the maintenance of an etiological agent within a population, given the long-term survival of unfed ticks[9]. An alternative concept is based on a direct control strategy, which manipulates the animal's reproduction capacities (sterilization). A myriad of wildlife contraceptive methods are available and is categorized into three methods: invasive, gonadectomy; less invasive, vasectomy in males or tubal ligation in females; and minimally invasive, chemical contraceptives. Within this approach, either hormone-based or employed immunocontraception is the most common antifertility method[10].

The majority of contraceptive concepts are applied to captive wildlife; however, the options are limited in free-ranging wildlife. Moreover, its "adequacy" is determined by the overall objective, species, and environment. Controlling capybara populations should consider making these hosts infertile for a longer duration and the impact of such interventions on the capybara's polygynous (harem-like) society. Group stability and procreation are driven by the dominant male's alpha attributes, such as secondary sexual characteristics that include a prominent nasal gland and perianal glands for territorial marking, and agonistic conduct (vigilance, fighting), as well as courtship behavior[11]. Contraceptive methods that maintain the alpha male's dominant behavioral and phenotypical characteristics while rendering the animal infertile, are imperative to successfully managing the population growth[11]. Therefore, procedures that preserve the gonad quality to maintain any steroid-dependent characteristics of the male should be chosen. This makes vasectomy the most commonly employed male contraceptive for controlling the capybara population in Brazil. Reproductive control in capybaras through vasectomy and tubal ligation are highly effective techniques in rendering males or females infertile; nevertheless, the logistics (in-the-field execution, competence, and high costs) make these procedures less attractive, especially when required to be performed for larger numbers[12]. Additionally, an injured or sick capybara may potentially distance itself from the group until recuperated[11]. This temporary absence of the alpha male (5-20 days) allows opportunistic solitary males to take over the group, undoing any population control efforts[11].

As mentioned, capybaras quickly escape into the water when threatened; therefore, prior to intervention, capture and chemical restraint are imperative to avoid death due to drowning. These capture-recovery-release events are cumbersome and time-consuming. Taking all these undesirable factors into consideration, seeking better and more appropriate alternatives become necessary, while respecting the animals' well-being and logistics. Ongoing research for alternative methods led to the concept of an anti-GnRH vaccine, believed to offer most of the desired contraceptive characteristics. This immunocontraceptive, given in a single-dose, is a long-term antifertility vaccine, which has been studied successfully, worldwide, in many species over the last decade [10].

Briefly, after immunization, the body produces anti-GnRH antibodies, which eventually bind to endogenous GnRH molecules forming a large immunocomplex. This ceases its bioactivity and consequently inhibits the synthesis and liberation of the gonadotropin luteinizing hormone and follicle-stimulating hormone, necessary for gonadal activities[13] (**Figure 2**). The overall reported high success rate in several species[13-15] initiated the very first study using an anti-GnRH vaccine (GonaCon™, APHIS, USDA, Fort Collins, CO, USA) in male and female capybaras. The proposed population control method using a single-dose immunocontraception has been successfully employed in male capybaras, providing a antifertility effect over a 24-month trial[16]. Besides rendering the capybara males infertile, it also preserves their alpha traits such as secondary sexual characteristics and agonistic behavior, attributes that are absolutely imperative for the success of any population strategy for this species. No remarkable adverse effects were reported, except for an abscess formation at the injection site, which is common. The results are corroborated by similar studies conducted in several other species, although a number of conflicting conclusions were observed regarding its impact on the male's agonistic behavior and secondary sexual characteristics[17]. This invites the hypothetical question: Is this a species-specific response?

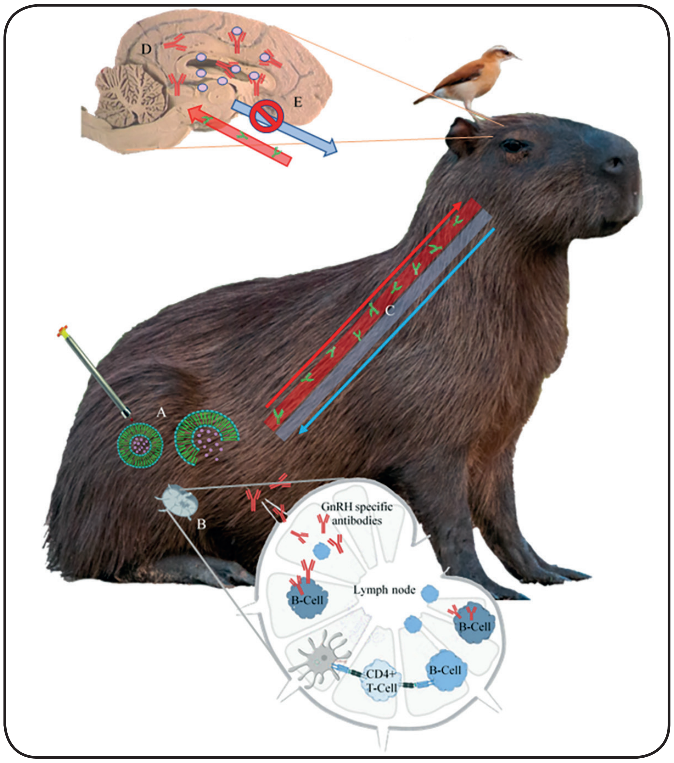

FIGURE 2: Illustrated Mechanism of Action of the Immunocontraceptive Anti-GnRH. A) Anti-GnRH Vaccine Dart mediated liberation of adjuvant and antigens. B) Immune response in the lymph node and formation of GnRH-specific antibodies. C) Hypothalamic-pituitary-gonadal axis, normal passage of gonadotropin hormones (LH, FSH) from the anterior pituitary gland to the gonads. After immunization, anti-GnRH antibodies are transported to the hypothalamic region. D) Anti-GnRH antibodies capture GnRH hormones, forming large immunocomplex molecules, inhibiting transfusion and ligation to GnRHR (receptors) in the pituitary region, ceasing LH and FSH synthesis and liberation. E) Impeding LH and FSH biological activities in the gonadal region (steroidogenesis and gametogenesis).

In conclusion, human-wildlife conflicts are inevitable as the human population continuously grows, expanding their living spaces and activities. Consequently, threats to human health, especially vector-borne zoonotic diseases, will also increase; thus, population control of wild, feral, and synanthropic animals must be addressed. Each circumstance, environment, and species require a specific plan to manage their populations.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Support

Sao Paulo Research Foundation, doctoral scholarship (grant number 2016/12549-5).

REFERENCES

1. Polo G, Labruna MB, Ferreira F. Satellite Hyperspectral Imagery to Support Tick-Borne Infectious Diseases Surveillance. Plos One [Internet]. 2015 Nov 24 [cited 2019 Mar 29];10(11):e0143736. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0143736
2. Polo G, Labruna MB, Ferreira R, Brockmann D. Hosts mobility and spatial spread of *Rickettsia rickettsii*. PLoS Comput Biol [Internet]. 2018 [cited 2018 Dec 17]; Available from: https://www.researchgate.net/publication/329075227_Hosts_mobility_and_spatial_spread_of_Rickettsia_rickettsii
3. Guedes E, Leite RC, Prata MC, Pacheco RC, Walker DH, Labruna MB. Detection of *Rickettsia rickettsii* in the tick *Amblyomma cajennense* in a new Brazilian spotted fever-endemic area in the state of Minas Gerais. Mem Inst Oswaldo Cruz [Internet]. 2005 Dec [cited 2019 Jun 26];100(8):841-5. Available from: http://www.scielo.br/scielo.php?script=sci_abstract&pid=S0074-02762005000800004&lng=en&nrm=iso&tlng=en
4. Marchini S, Jr PGC. Human-Wildlife Conflicts in Brazil: A Fast-Growing Issue. Hum Dimens Wildl [Internet]. 2015 Jul 4 [cited 2017 Apr 9];20(4):323-8. Available from: http://dx.doi.org/10.1080/10871209.2015.1004145
5. Verdade LM, Ferraz KMPMB. Capybaras in an anthropogenic habitat in Southeastern Brazil. Braz J Biol [Internet]. 2006 Feb [cited 2018 May 13];66(1b):371-8. Available from: http://www.scielo.br/scielo.php?script=sci_abstract&pid=S1519-69842006000200019&lng=en&nrm=iso&tlng=en
6. Polo G, Acosta CM, Labruna MB, Ferreira F. Transmission dynamics and control of Rickettsia rickettsii in populations of Hydrochoerus hydrochaeris and Amblyomma sculptum. PLoS Negl Trop Dis [Internet]. 2017 Jun 5 [cited 2017 Nov 18];11(6):e0005613. Available from: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005613
7. Polo G, Labruna MB, Ferreira F. Basic reproduction number for the Brazilian Spotted Fever. J Theor Biol [Internet]. 2018 Dec 7 [cited 2019 Mar 29];458:119-24. Available from: http://www.sciencedirect.com/science/article/pii/S0022519318304405
8. Moreira JR, editor. Capybara: biology, use and conservation of an exceptional neotropical species. 1st ed. New York: Springer; 2013. 419 p.
9. Herrera EA, Salas V, Congdon ER, Corriale MJ, Tang-Martínez Z. Capybara social structure and dispersal patterns: variations on a theme. J Mammal [Internet]. 2011 Feb 16 [cited 2018 May 14];92(1):12-20. Available from: https://academic.oup.com/jmammal/article/92/1/12/938070
10. Rosenfield DA. Wildlife population control comprehensive and critical literature review on contraceptive methods in wildlife - mammals [Dissertation (MSc)]. [Sao Paulo, Brazil]: Department of Animal Reproduction/Wildlife, Faculty of Veterinary Medicine and Animal Science, University of São Paulo, 219 f.il.; 2016.
11. Rosenfield DA, Pizzutto CS. On the importance of alpha behavior integrity in male Capybara Hydrochoerus hydrochaeris (Mammalia: Rodentia: Caviidae) following immuno-contraceptive treatment. J Threat Taxa [Internet]. 2019 Jun 26 [cited 2019 Jun 26];11(8):13967-76. Available from: https://threatenedtaxa.org/index.php/JoTT/article/view/4747
12. Rodrigues MV, Paula TAR, Silva VHD, Ferreira LBC, Junior ACC, Araujo GR, et al. Manejo de população problema através de método contraceptivo cirúrgico em grupos de capivaras (*Hydrochoerus hydrochaeris*). Rev Bras Reprodução Anim [Internet]. 2017;41(4):710-5. Available from: http://cbra.org.br/br/
13. Cowan D, Massei G, Ward A, Miller LA. Field evaluation of the immunocontraceptive vaccine GonaConTM in free-living mammal populations. In: Julius-Kühn-Archiv [Internet]. 2011 [cited 2016 Feb 4]. p. 115. Available from: http://pub.jki.bund.de/index.php/JKA/article/view/1525
14. Bertschinger HJ, Sills ES. Chapter 6. Contraceptive Applications of GnRH-analogs and Vaccines for Wildlife Mammals of Southern Africa: Current Experience and Future Challenges. In: Gonadotropin-Releasing Hormone (GnRH): Production, Structure and Function. 1st ed. Nova Science Pup; 2013. p. 287. (Endocrinology Research and Clincial Developments).
15. Ferro VA, Khan MAH, McAdam D, Colston A, Aughey E, Mullen AB, et al. Efficacy of an anti-fertility vaccine based on mammalian gonadotrophin releasing hormone (GnRH-I)—a histological comparison in male animals. Vet Immunol Immunopathol [Internet]. 2004 Sep 1 [cited 2018 Jun 28];101(1):73-86. Available from: http://www.sciencedirect.com/science/article/pii/S0165242704001321
16. Rosenfield DA, Nichi M, Losano JDA, Kawai G, Leite RF, Acosta AJ, et al. Field-testing a single-dose immunocontraceptive in free-ranging male capybara (*Hydrochoerus hydrochaeris*): Evaluation of effects on reproductive physiology, secondary sexual characteristics, and agonistic behavior. Anim Reprod Sci. 2019; Available from: https://doi.org/10.1016/j.anireprosci.2019.106148
17. De Nys HM, Bertschinger HJ, Turkstra JA, Colenbrander B, Palme R, Human AM. Vaccination against GnRH may suppress aggressive behaviour and musth in African elephant (Loxodonta africana) bulls--a pilot study. J S Afr Vet Assoc. 2010 Mar;81(1):8-15.

OPEN ACCESS
https://creativecommons.org/licenses/by/4.0/