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IMPORTÂNCIA EPIDEMIOLÓGICA DE COBRAS-CORAIS (ELAPIDAE: *Micrurus*) NA AMAZÔNIA BRASILEIRA

PEDRO FERREIRA BISNETO

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UNIVERSIDADE FEDERAL DO AMAZONAS – UFAM

INSTITUTO DE CIÊNCIAS BIOLÓGICAS – ICB

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Tese apresentada ao Programa de Pós-Graduação em Zoologia, da Universidade Federal do Amazonas/Instituto Nacional de Pesquisas da Amazônia, como parte dos requisitos para obtenção do título de Doutor em Zoologia.

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Resumo

Na Amazônia Brasileira, o conhecimento dos envenenamentos de humanos por cobras-corais é restrito a poucos relatos de casos, alguns deles pouco detalhados. A maior parte das informações disponíveis para o Brasil vem das regiões Nordeste e Sudeste, mais populosas e com maior número de centros de pesquisa e de registros de acidentes. Nesse contexto, esta tese investigou a importância epidemiológica das cobras-corais (*Micrurus* spp.) na região amazônica, explorando ao longo de quatro capítulos aspectos relacionados à frequência dos acidentes, às principais espécies causadoras, os principais sintomas reportados nos casos, e quais áreas são mais propícias ao aparecimento deste grupo e aos acidentes causados por ele. No **primeiro capítulo** observamos uma baixa frequência e incidência nos acidentes elapídicos. Dor, edema e parestesia foram os sintomas mais comuns. Sintomas sistêmicos geralmente não associados a envenenamentos por cobras corais, como coagulopatia e trombocitopenia, têm sido relatados na Amazônia. O soro tem sido usado de maneira incorreta, e recomendamos a execução de programas educativos para evitar tais acidentes e ensinar tanto o público em geral quanto os profissionais de saúde o tratamento correto para as picadas. Sugerimos também melhoria na cobertura das Unidades de Terapia Intensiva na região. No **segundo capítulo**, descobrimos que cinco espécies foram envolvidas nos acidentes na região de Manaus, sendo *Micrurus lemniscatus* a responsável pelo maior número de casos. Não houve diferença entre os sexos das cobras que causaram as picadas, e os pacientes eram em sua maioria do sexo masculino. A maioria dos casos foi relatada em áreas urbanas e na estação seca, e houve uma clara segregação geográfica entre as espécies. Descrevemos sete casos de envenenamento. Parestesia, dor e edema foram os sintomas locais mais comuns. Características sistêmicas mais comuns foram dispneia, ptose palpebral, visão turva, disartria e dificuldade para andar. Os envenenamentos por cobras corais na região de Manaus são clinicamente graves, porém raros e esparsamente distribuídos ao longo do tempo, tornando a detecção de padrões epidemiológicos e clínicos um desafio para a saúde pública. No **terceiro capítulo** foram relatados dois casos de acidentes por *M. hemprichii* envolvendo duas pacientes, nos quais devido à confusão na identificação da serpente e risco de agravamento de caso, discutimos a importância de se identificar corretamente serpentes de acidentes ofídicos no contexto de atendimento hospitalar. No **quarto capítulo**, utilizamos modelagem de distribuição de espécies de cobras-corais na Amazônia, em conjunto com dados de acidentes elapídicos, para avaliar possíveis áreas de risco na região. Concluímos que todo o bioma apresenta alta adequação ambiental para a ocorrência de cobras-corais, e que tal adequabilidade explica pouco sobre a incidência de acidentes na região. Isso provavelmente se deve à baixa densidade humana na Amazônia, mas também às características da cobra coral como hábitos crípticos. Diferentemente de outras espécies de serpentes de importância médica, o cenário ecológico e epidemiológico das picadas de cobras-corais impede a detecção de áreas geográficas importantes de preocupação e exige uma disponibilidade ampla e equitativa de centros de saúde em toda a Amazônia.

Palavras-chave: Acidente ofídico; Animais peçonhentos; Doenças tropicais negligenciadas; Serpentes

Abstract

In the Brazilian Amazonia, knowledge of human envenomation by coral snakes is restricted to a few case reports, some of which are poorly detailed. Most of the information available for Brazil comes from the Northeast and Southeast regions, which are more populous and have the largest number of research centers and accident records. In this context, this thesis investigated the epidemiological importance of coral snakes (*Micrurus* spp.) in the Amazonian region, exploring over four chapters aspects related to the frequency of accidents, the main involved species, the main symptoms reported in the cases, and which areas are more prone to the emergence of this group and the its bites. In the **first chapter** we observed a low frequency and incidence in elapidic bites. Pain, edema and paresthesia were the most common symptoms. Systemic symptoms not generally associated with coral snake envenomation, such as coagulopathy and thrombocytopenia, have been reported in Amazonia. Antivenom has been misused, and we recommend carrying out educational programs to prevent such bites and teach both the general public and healthcare professionals the correct treatment for the cases. We also suggest improvement in the coverage of Intensive Care Units in the region. In the **second chapter**, we found that five species were involved in accidents in the region of Manaus, with *Micrurus lemniscatus* being responsible for the largest number of cases. There was no difference between the sexes of the snakes that caused the bites, and the patients were mostly male. Most cases were reported in urban areas and in the dry season, and there was a clear geographic segregation between the species. We describe seven cases of envenomation. Paresthesia, pain and edema were the most common local symptoms. The most common systemic manifestations were dyspnea, palpebral ptosis, blurred vision, dysarthria, and difficulty in walking. Envenomations by coral snakes in the Manaus region are clinically serious, but rare and sparsely distributed over time,

making the detection of epidemiological and clinical patterns a challenge for public health. In the **third chapter**, two cases of bites by *M. hemprichii* involving two patients were reported, in which, due to the confusion in the identification of the snake and risk of aggravation of the case, we discussed the importance of correctly identifying snakes of snakebites in the context of hospital care. In the **fourth chapter**, we used distribution modeling of coral snake species in Amazonia, together with data from *Micrurus* cases, to assess possible risk areas in the region. We concluded that the entire biome shows high environmental suitability for the occurrence of coral snakes, and that such suitability explains little about the incidence of bites in the region. This is likely due to the low human density in Amazonia, but also to coral snake characteristics such as cryptic habits. Unlike other medically important snake species, the ecological and epidemiological scenario of coral snake bites precludes detection of important geographic areas of concern and requires a broad and equitable availability of health centers across Amazonia.

Keywords: Neglected tropical diseases; Serpentes; Snakebite; Venomous animals

Glossário

Cephaloplegia (Cefaloplegia): paralisia dos músculos da cabeça e/ou pescoço.

Coagulopathy (Coagulopatia): distúrbios da coagulação sanguínea.

Cyanosis (Cianose): coloração azulada na pele, nos lábios e nas unhas causada por uma escassez de oxigênio no sangue.

Diplopia: visão dupla.

Dysarthria (Disartria): dificuldade de fala.

Dysphagia (Disfagia): dificuldade para engolir alimentos ou líquidos que ocorre na garganta ou no esôfago.

Dyspnea (Dispnéia): respiração difícil ou ofegante.

Edema: inchaço causado pelo acúmulo de líquidos entre os diversos tecidos e cavidades que compõem o corpo humano.

Equimose (Ecchymosis): extravasamento de sangue dos vasos sanguíneos da pele que se rompem formando uma área de cor roxa.

Eritema: vermelhidão da pele.

Erythema: ver Eritema.

Fasciculação: contração breve e espontânea ou espasmo em um músculo.

Forrageamento: busca e a exploração de recursos alimentares.

Fossorial: animal que está adaptado a cavar e a viver debaixo do solo.

Hyperaemia (Hiperemia): aumento do fluxo sanguíneo para uma parte do corpo.

Leukocytosis (Leucocitose): nível elevado de glóbulos brancos no sangue.

Mialgia (Myalgia): dores e desconforto nos músculos variando de leve a intenso.

Necrosis (Necrose): morte celular ou de tecidos no organismo.

Neglected tropical diseases (Doenças tropicais negligenciadas): grupo doenças tropicais infecciosas causadas por patógenos como vírus, bactérias, protozoários e helmintos, e que são comuns em populações de baixa renda em regiões em desenvolvimento da África, Ásia e Américas. Recebem menos fundos para tratamentos e pesquisas.

Ophthalmoplegia (Oftalmoplegia): paralisia de um ou mais músculos oculares.

Palpebral ptosis: ver Ptose palpebral.

Parestesia: sensação de formigamento, geralmente temporária, ocorrendo muitas vezes nos braços, nas mãos, nas pernas ou nos pés.

Paresthesia: ver Parestesia.

Ptose palpebral: caimento ou fechamento anormal da pálpebra superior.

Rhabdomyolysis (Rabdomiólise): degradação do tecido muscular que libera uma proteína prejudicial no sangue.

Thrombocytopenia (Trombocitopenia): número reduzido de plaquetas no sangue.

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Introdução Geral

Acidentes ofídicos estão entre os maiores problemas de saúde pública em áreas tropicais ao redor do mundo, especialmente em regiões subdesenvolvidas na Ásia, África e América Latina, devido à frequência dos casos e da morbidade e mortalidade que ocasionam (Chippaux 1998, Harrison et al. 2009). A Organização Mundial de Saúde (OMS) estima que, em nível global, ocorram anualmente aproximadamente 2.500.000 de acidentes por serpentes peçonhentas, com cerca de 125.000 mortes (Chippaux 1998). Parte desse índice de mortalidade e morbidade pode ser explicado pela demora no atendimento ao acidentado, a qual é normalmente ocasionada pela distância até unidades de saúde adequadas (Borges et al. 1999, Suchithra et al 2008, Waldez & Vogt 2009, Habib & Abubakar 2011, Feitosa et al. 2015). No mundo todo, acidentes ofídicos possuem relação com atividades agropecuárias, atingindo principalmente homens na faixa etária relacionada a esse tipo de atividade, sendo assim classificados como de risco ocupacional (Harrison et al. 2009).

No Brasil, dados epidemiológicos sobre acidentes por animais peçonhentos em humanos tinham como base estudos pontuais e baseados em exames de casos particulares, principalmente da região sudeste. Entretanto, durante a década de 80, após uma crise na produção de soros no Brasil, implantou-se o Programa Nacional de Ofidismo, passando o Ministério da Saúde a adquirir integralmente a produção nacional de soros para tratamento de acidentes por animais peçonhentos e a sua distribuição, por meio da antiga Secretaria Nacional de Ações Básicas (Oliveira et al. 2009). Com isso, os acidentes passaram a ser de notificação obrigatória no Brasil, com o estabelecimento de um sistema de troca de soros por informações epidemiológicas, método que racionalizou a distribuição dos soros de acordo com a demanda estimada para cada estado (CNZCAP 1991). Com o advento desse sistema, houve uma diminuição considerável na taxa anual de letalidade dos acidentes ofídicos (Cardoso & Wen 2009). Com a inclusão de dados de casos de escorpionismo e aracnidismo, a partir de 1988 o programa passou a se chamar Programa Nacional de Controle de Acidentes por Animais Peçonhentos (Cardoso 1993).

A partir de 1997, as informações epidemiológicas têm sido repassadas ao Ministério da Saúde (MS) e à Secretaria de Vigilância de Saúde de maneira informatizada, por meio do Sistema de Informação de Agravos de Notificação (SINAN) (Carvalho 1997). O SINAN foi criado com o objetivo de racionalizar o processo de coleta e transferência de dados relacionados às doenças e agravos de notificação compulsória, especialmente doenças crônicas e agudas, transmissíveis e não transmissíveis, incluindo os acidentes por animais peçonhentos (Bochner & Struchiner 2002). Atualmente a coleta de dados dos agravos é feita por meio de um sistema eletrônico (SINAN NET), que permite coletar, transmitir e disseminar dados gerados rotineiramente pelo Sistema de Vigilância Epidemiológica (SINAN 2022). Apesar dos problemas e limitações enfrentados por esse tipo de sistema, tais como a subnotificação, o SINAN tem permitido abordagens mais amplas, direcionando ações para reduzir o número de acidentes, e oferecendo tratamentos mais adequado. Assim, o sistema tem o potencial de reduzir a incidência de casos fatais, além da facilidade de acesso às informações epidemiológicas, por meio de consulta *online* (Oliveira et al. 2009).

As cobras-corais são as únicas representantes terrestres da família Elapidae no Novo Mundo. Existem mais de 80 espécies descritas nas Américas, divididas em três gêneros (Silva Jr. et al. 2021a, Uetz et al., 2022). O gênero *Micruroides* Schmidt, 1928, é encontrado somente em áreas abertas e desérticas do sudoeste dos Estados Unidos e norte do México, e contém apenas uma espécie; o gênero *Leptomicrurus* Schmidt, 1937, é distribuído pela floresta amazônica na Bolívia, Peru, Equador, Colômbia, sul da Venezuela, sul das Guianas, e Brasil, nos estados do Acre, Amazonas, Roraima, Amapá e Pará, contendo quatro espécies; o gênero *Micrurus* Wagler, 1824, ocorre desde o sudeste dos Estados Unidos até o sul da América do Sul. É o maior gênero do grupo, contendo 80 das 85 espécies de cobras-corais do Novo Mundo (Roze 1996, Campbell & Lamar 2004, Silva Jr. et al. 2021a). Não existe consenso sobre as relações filogenéticas dentro do gênero *Micrurus*, mesmo o gênero em sim sendo considerado monofilético (quando inclui *Leptomicrurus*) (Zaher et al. 2021). Tradicionalmente, quatro linhagens de *Micrurus* são reconhecidas: (1) grupo *Micrurus mipartitus* (bicolor, sulamericano); (2) *Micrurus* triadais das Américas Central e do Sul; (3) *Micrurus* monadais e (4) *Micrurus* triadais do México (Fig. 1A) (Roze & Bernal-Carlo 1987). Entretanto, alguns trabalhos de filogenia separam *Micrurus* em diferentes linhagens, baseadas na coloração e distribuição geográfica (Fig. 1B) (Gutberlet & Harvey 2004, Zaher et al. 2021). No Brasil, são conhecidas 38 espécies de cobras-corais, distribuídas em todo o território nacional, representadas pelos gêneros *Leptomicrurus* e *Micrurus* (a maioria com distribuição amazônica), mas com números passíveis de variação devido à instabilidade taxonômica do grupo (Costa et al. 2021, Silva Jr. et al. 2021a).

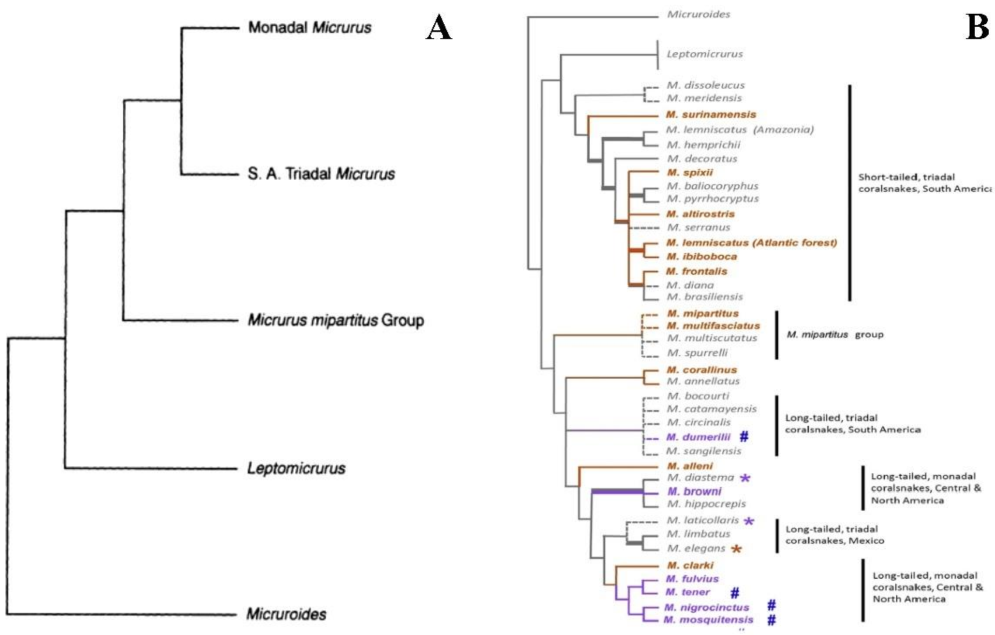


Figura 1: Hipóteses de relações filogenéticas das cobras-corais do Novo Mundo. A: relações filogenéticas tradicionais segundo Roze & Bernal-Carlo (1987), separando *Micrurus* em quatro linhagens distintas (retirada de Slowinski 1991). B: relações filogenéticas de *Micrurus*, segundo Gutberlet & Harvey (2004) (retirada de Lomonte et al. 2016). S. A.: América do Sul.

No Brasil, o número de acidentes ofídicos notificados entre 2000 e 2007 foi de 192.703 (média anual de 24.069), dos quais 1% foram causados por picadas de cobras-corais, tendo o ofidismo a segunda maior média anual de causas de agravos por acidentes por animais peçonhentos (Melgarejo 2009). A mesma porcentagem de acidentes causados por corais foi encontrada no ano de 2014 (Bucaretchi et al. 2016a).

Em parte, a baixa incidência destes acidentes pode ser explicada pelo comportamento tímido, hábitos fossoriais e baixa cinética craniana, reduzindo as chances de encontros, mordidas e envenenamentos (Melgarejo 2009). Entretanto, as proporções de cada tipo de acidente ofídico variam dentro das macrorregiões, em decorrência das variações na fauna, condições ambientais e atividades humanas dentro de cada uma dessas regiões (Borges et al. 1999, Nascimento 2000, Pinho et al. 2004, Rojas et al. 2007, Melgarejo 2009). No Brasil, o gênero *Leptomicrurus* é considerado como sem importância médica, não havendo registros de acidentes ofídicos por esse gênero, e das 30 espécies brasileiras de *Micrurus*, são conhecidos na literatura registros de acidentes apenas por *M. altirostris*, *M. corallinus*, *M. decoratus*, *M. filiformis*, *M. frontalis*, *M. hemprichii*, *M. ibiboboca*, *M. lemniscatus*, *M. spixii* e *M. surinamensis* (Bucaretchi et al. 2016a, Bucaretchi et al. 2016b). Recentemente, foi relatado um acidente causado por *M. averyi* no município de Presidente Figueiredo, Amazonas (Mendonça-da-Silva et al. 2018). Entretanto, o número de acidentes por corais pode ser superestimado, uma vez que parte desses acidentes pode ter sido causada por falsas-corais erroneamente identificadas como corais-verdadeiras (Bucaretchi et al. 2016a). Em um estudo de uma série de casos atendidos no Hospital Vital Brazil (HVB) entre 1945 e 2013, os quais tiveram identidade confirmada da serpente envolvida, foi mostrado que acidentes por corais representam 0,7% dos casos atendidos pelo hospital naquele período de tempo (Risk et al. 2016).

Estudos experimentais têm demonstrado atividade neurotóxica (Brazil 1987, Francis et al. 1997, Cecchini et al. 2005), miotóxica (Cecchini et al. 2005, 2012), hemolítica (Arce-Bejarano et al. 2014), nefrotóxica (Cecchini et al. 2012, Arce-Bejarano et al. 2014); hemorrágica (Francis et al. 1997) e edematogênica (Barros et al. 1994, Cecchini et al. 2005) do veneno dessas serpentes. Entretanto, em humanos, apenas atividades neurotóxicas e miotóxicas foram relatadas (Bucaretchi et al. 2016a, Bucaretchi et al. 2016b, Risk et al. 2016). Apesar de experimentos *in vitro* e *in vivo* demonstrarem alta toxicidade dos venenos de cobras-corais, estudos com envenenamento desses animais demonstram que casos graves com paralisia e óbitos são raros (Bochner & Struchiner 2003, Bucaretchi et al. 2006, Bucaretchi et al. 2016b).

A descrição a seguir dos principais sintomas de picadas de corais é baseada em Silva Jr. & Bucaretchi (2009), Bernarde (2014), Bucaretchi et al. (2016a) e Oliveira et al. (2016). O quadro local é discreto: o edema, quando presente, é leve, e geralmente associado ao uso de torniquetes. Não se observa equimose ou sangramento. Há presença de eritema e dor de intensidade variável, podendo se estender pelo membro afetado. O quadro sistêmico envolve a atuação neurotóxica do veneno, com a presença de ptose palpebral; parestesia, visão turva, fraqueza muscular, sonolência, mialgia, fasciculação muscular, diplopia; vômitos, tonturas, dificuldade de deglutição, de fala e de se manter em pé. Em casos graves, porém raros, ocorrem paralisia, insuficiência respiratória, e óbito.

Mesmo sendo consideradas de importância médica e com potencial de causarem acidentes graves em humanos, cobras-corais são muito pouco estudadas. A dificuldade de estudos em campo se deve principalmente aos hábitos crípticos e ao fato de que esses animais normalmente não são comuns na natureza, e algumas espécies são conhecidas apenas por um punhado de exemplares (Silva Jr. et al. 2021a, Silva Jr. et al. 2021b). Cobras-corais são encontradas em uma diversidade de hábitats devido à ampla distribuição geográfica. Podem ser encontradas do nível do mar até altitudes próximas de 3000 metros, em áreas secas ou em florestas tropicais, podem ser tipicamente de vegetação nativa ou podem habitar perímetros urbanos em grandes metrópoles, como Manaus (Martins & Oliveira 1998, Campbell & Lamar 2004, Almeida-Corrêa et al. 2020, Frazão et al. 2020, Marques & Sazima 2021). A maioria das espécies é encontrada principalmente na camada de folhas na superfície do solo, mas podem usar tocas subterrâneas como abrigo, substrato de forrageamento ou simplesmente entrar em buracos em busca de presas. O período de atividade diário é variável entre espécies e populações, e aparentemente o clima é importante na modulação desse comportamento. Espécies de regiões desérticas tendem a ter maior atividade noturna, para evitar o calor diurno, enquanto espécies florestais tendem a ter atividade diurna, mas também evitando os horários mais quentes do dia (Marques & Sazima 2021). Algumas espécies podem ser encontradas em ambiente aquático, e *Micrurus surinamensis* é considerada uma espécie aquática, forrageando em áreas alagadas da Amazônia (Martins & Oliveira 1998, Santos-Costa et al. 2015, Marques & Sazima 2021). Em algumas regiões da Amazônia, diversas espécies coexistem na mesma área, embora algumas sejam mais comuns do que outras (Dixon & Soini 1977, 1986, Martins & Oliveira 1998, Santos-Costa et al. 2015, Masseli et al. 2019, Almeida-Corrêa et al. 2020, Frazão et al. 2020).

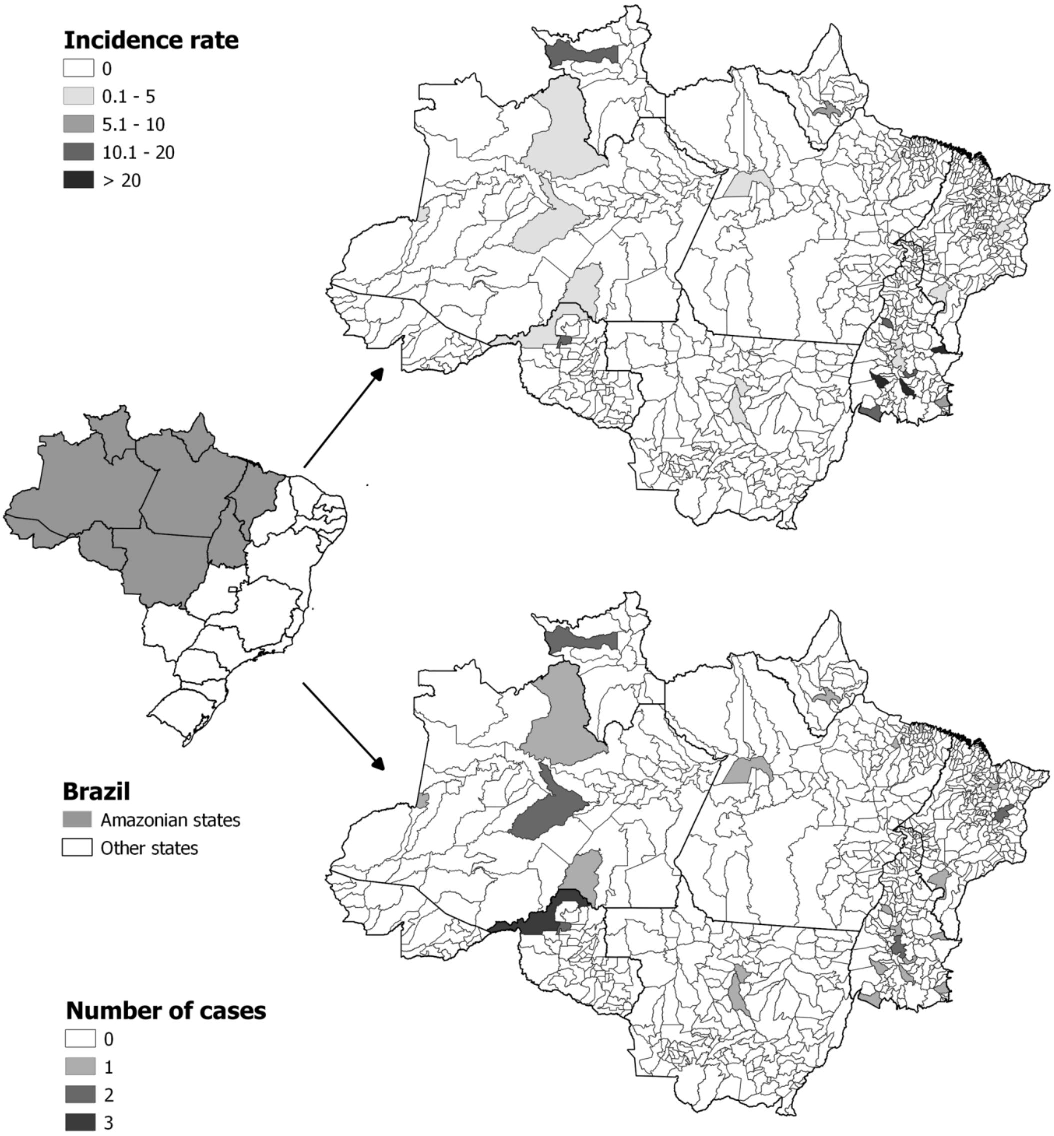
Uma vez que estudos de campo e estudos epidemiológicos amplos com cobras-corais são difíceis, são necessárias ferramentas para se conseguir entender e prever os acidentes elapídicos. Uma das ferramentas recentemente usadas para mapear áreas de potencial interesse relacionado ao ofidismo é a Modelagem de Distribuição de Espécies (MDE). Esse método relaciona dados de distribuição de uma espécie com informações sobre características ambientais e espaciais destas distribuições, através de algoritmos computacionais, com o objetivo de se entender e/ou prever distribuições de espécies ao longo do espaço e tempo (Elith & Leathwick 2009, Peterson et al. 2011). Modelagem de Distribuição de Espécies pode ser utilizada com animais de interesse médico para se prever regiões de importância epidemiológica, tanto no contexto das mudanças climáticas, que certamente irão alterar a distribuição de muitas dessas espécies, quanto de espécies pouco estudadas (Needleman et al. 2018). Com relação às serpentes peçonhentas, estimar a potencial distribuição desses animais pode ajudar na preparação de uma política adequada relacionada ao tratamento de picada de cobra (Yañez-Arenas et al. 2018, Citeli et al. 2020).

Mesmo com as ferramentas atualmente disponíveis, a dificuldade em se estudar biologia de cobras-corais se reflete no estudo dos envenenamentos, uma vez que, além da pouca frequência de casos impedir que padrões epidemiológicos sejam obtidos, também se impossibilita que questões ecológicas relacionadas aos acidentes elapídicos sejam abordadas, tais como: (a) quais as principais espécies de importância médica na Amazônia?; (b) quais fatores ambientais estão associados com os envenenamentos elapídicos?; (c) existem diferenças entre sexo e estágio de vida das serpentes causadoras de acidentes e se isso se reflete na clínica dos pacientes?; (d) existe alguma tendência espacial na distribuição dos acidentes elapídicos?; (e) quais áreas na Amazônia Brasileira têm maior potencial de distribuição para cobras-corais?; (f) essas áreas de potencial distribuição coincidem com os acidentes reportados na região e com (g) a distribuição dos centros médicos para atendimento de acidentes ofídicos?

É neste contexto que esta tese foi desenvolvida. Com o objetivo de abordar estas perguntas, nós investigamos, através de dados de um hospital de referência na Amazônia Brasileira, do banco de dados do Ministério da Saúde, e de mapas de distribuição potencial das espécies amazônicas de *Micrurus*, os aspectos clínicos, epidemiológicos e ecológicos dos acidentes elapídicos e a distribuição desse grupo de serpentes na região. Os resultados se dividem em quatro capítulos:

- **Capítulo 1:** trata de uma revisão do conhecimento sobre acidentes elapídicos na Amazônia, com enfoque na Amazônia Brasileira, com uso de novos dados epidemiológicos adquiridos do Ministério da Saúde do Brasil.
- **Capítulo 2:** apresenta um estudo sobre acidentes elapídicos atendidos na Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, em Manaus (FMT-HVD), com uso dos dados clínicos dos prontuários médicos, e de dados epidemiológicos e ecológicos dos dados da coleção científica mantida pela instituição.

- **Capítulo 3:** apresenta o relato de dois casos de envenenamento por *Micrurus hemprichii* recentemente atendidos pela FMT-HVD.
- **Capítulo 4:** analisa as áreas de risco de acidentes elapídicos na Amazônia, avaliando a distribuição potencial de várias espécies amazônicas de *Micrurus* e relacionando essa distribuição com os acidentes ocorridos e com a distribuição de centros de atendimento médico da região.



CAPÍTULO 1

Bisneto P. F., Alcântara J. A., Silva I. M., Sachett J. A. G., Bernarde P. S., Monteiro W. M., Kaefer I. L. **Coral snake bites in Brazilian Amazonia: Perpetrating species, epidemiology and clinical aspects**. Artigo publicado na revista Toxicon em fevereiro de 2020. **DOI 10.1016/j.toxicon.2019.11.011**

Coral snake bites in Brazilian Amazonia: Perpetrating species, epidemiology and clinical aspects

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Abstract: Coral snakes constitute a relatively diverse and little known group of venomous snakes. So far, data for this kind of snakebite in the Amazon region are based only on case reports. This study takes advantage of novel data from the Brazilian Health Ministry database from 2010 to 2015 and presents a review of the cases reported in the literature regarding the Amazonian biome both from Brazil and nearby countries. Thirty-four cases reported in the database were used in the study, representing 0.05% of the snakebites in Brazilian Amazonia for that period. The incidence rate was 0.123 cases/100,000 inhabitants/year. The most affected group is that of working age men, suggesting occupational risk. Most of bites were on lower limbs. Pain, edema and paresthesia were the most common symptoms. Systemic symptoms not usually associated with coral snakes envenomings, such as coagulopathy and thrombocytopenia, have been reported in Amazonia. Five patients received less antivenom than indicated by the Health Ministry. Based on these results, we recommend the execution of educational programs to avoid such accidents and to teach both the general public and health professionals the correct treatment for the bites. We also suggest that the covering of Intensive Care Units in the region needs to be improved to avoid deaths.

1. Introduction

Worldwide, snakebites represent a serious burden, especially in the poorest and most underdeveloped regions around the globe, where both many people work in the rural area, in contact with these animals, and the access to healthcare is the most difficult due to economic and social aspects (Harrison et al., 2009). It is estimated that each year between 1.8 and 2.7 million people are envenomed by snakes, 81,000 to 138,000 of these die as a result of such envenomings, and many more become permanently disabled (Gutiérrez et al., 2017). In Brazil, snakebites are the third most common cause of envenoming by animals, being scorpions and spiders the first and second most common, respectively (SINAN 2016). Snakebites have the highest incidence in the North region (52.6 cases/100,000 inhabitants), with many areas in northern Roraima, Eastern Pará, and Amapá states with incidence higher than 100 cases/100,000 inhabitants (Wen et al., 2015). However, these values may be underestimated due to underreporting, and in remote areas they could be much higher (Wen et al., 2015).

Most of the information about snakebites in the Brazilian Amazonia is based on surveillance data, hospital medical records or case reports (eg. Borges et al., 1999; Moreno et al., 2005; Pardal et al., 2010; Pierini et al., 1996; Waldez and Vogt, 2009), but studies with information from notification systems are also available, allowing the observation of patterns and tendencies in snakebites, both locally and in the wider areas (e.g., Alcântara et al., 2018; Feitosa et al., 2015; Nascimento, 2000; Paula Neto et al., 2005; Wen et al., 2015). Since 1986, in Brazil the health providers are required to notify authorities about envenomations by snakes. Later, in 1997, it was created the current system of notification used by the Ministry of Health, the *Sistema Nacional de Agravos de Notificação* – SINAN (Brazilian Information System of Notifiable Diseases), that is the main source of epidemiological data for envenomations by venomous animals in the country.

The data from Brazilian Amazonia shows a pattern much similar to that found in many other places about the epidemiology of snakebites in the region: the main groups affected are adult males, suggesting occupational risk, inhabitants of the rural area and/or workers involved in forestry activities, like farming, hunting, and logging. Most of the bites occur in the lower limbs and during the rainy season (Feitosa et al. 2015a, 2015b; Wen et al., 2015; Alcântara et al., 2018). The time from the bite to medical care was usually more than 6 h, and the fatality rates varied from 0.4% to 3.9% (Wen et al., 2015). In the region, there are only a few roads, and most of the transportation is made on rivers, so the most isolated settlements can be hours apart from the nearest hospital with the antivenom (AV). The time for reaching medical care can contribute to a higher risk of severity and death in Amazonia (Feitosa et al., 2015b; Souza et al., 2018).

2. Coral snakes from Amazonia

Coral snakes are the only terrestrial representatives of the family Elapidae in the New World. Traditionally, there are 3 genera recognized: *Micruroides*, *Leptomicrurus* and *Micrurus*, but only the two latter are found in Brazil (Campbell and Lamar 2004, Silva Jr. et al., 2016a). These taxa compose one of the groups of medically important snakes in Brazil. They are called coral snakes because of their combination of colorful red/orange, black and yellow/white rings (Bernarde, 2014), although that combination is not always present (for instance, in *Leptomicrurus* and in *Micrurus albicinctus*). These differences are even harder to deal with due to the presence of the so-called false coral snakes, a group of snakes of many genera (e.g.: *Anilius*, *Apostolepis*, *Atractus*, *Erythrolamprus*, *Oxyrhopus*, *Phalotris*, *Phimophis*, *Pseudoboa*) that mimic the colorful bands and even the behavior of these animals (Almeida et al., 2016). Because of that, it is recommended that only experts manipulate these snakes (but see Strauch et al., 2018) and that the general public treat all the red snakes as "possible true coral snakes", avoiding bites with them (Oliveira et al., 2016).

Coral snakes live mainly in tropical forests, but also on open areas (Campbell and Lamar 2004). Although some are typical of undisturbed areas, some may also be found in disturbed crops and pastures (Bernarde, 2014; Martins and Oliveira, 1998). Some species (e.g.: *Micrurus corallinus*, *M. filiformis*, *M. lemniscatus*, *M. paraensis* and *M. surinamensis*) can also be found around or in cities in Brazil, such as Manaus, Belém and São Paulo (Marques et al., 2009; Almeida et al., 2016). They are mostly fossorial and semifossorial in their habits, but three species (*M. lemniscatus*, *M. nattereri* and *M. surinamensis*) have semiaquatic or aquatic habits (Almeida et al., 2016; Martins and Oliveira, 1998). Coral snakes feed mainly on elongated vertebrates, like caecilians, amphisbaenians and snakes (including other coral snakes), while the aquatic species feed on fish like *Callichthys*, *Gymnotus* and *Symbranchus*, and there are records of velvet worms ingested by *M. hemprichii* (Almeida et al., 2016; Bernarde, 2014; Martins and Oliveira, 1998; Masseli et al., 2018). These snakes are oviparous, with records of one to 14 eggs, which vary between species and the size of the snake (Almeida et al., 2016; Martins and Oliveira, 1998; Roze, 1996; Solórzano and Cerdas, 1998).

Fig. 1: Coral snake species from Brazilian Amazonia with records of envenomings in humans. A: *Micrurus annellatus;* B: *Micrurus averyi*. C: *Micrurus filiformis*. D*: Micrurus hemprichii*. E: *Micrurus lemniscatus*. F: *Micrurus spixii*. G: *Micrurus surinamensis*. Credits: A, D, F and G: Paulo Sérgio Bernarde B: Gabriel Masseli; C: Sérgio Marques de Souza; E: Pedro Bisneto.

In Brazilian Amazonia, 24 species of coral snakes are recorded (Silva Jr. et al., 2016b; Bernarde et al., 2018), but only seven of them known to have bitten humans (Fig. 1): *Micrurus annellatus, M. averyi, M. filiformis, M. hemprichii, M. lemniscatus, M. spixii* and *M. surinamensis* (Bucaretchi et al., 2016a; Bucaretchi et al., 2016b; Mendonça-da-Silva et al., 2018; da Silva et al., 2019). Of those, *M. hemprichii, M. lemniscatus, M. spixii* and *M. surinamensis* seem to be the main causes of bites. Bucaretchi et al. (2016b) made a review of coral snake bites in Brazil, but from their literature, only four references were about cases in the Amazonian biome, with five cases of bites in the total. One of these cases (Santos et al., 1995) was only quickly described and other two were personal communications.

Recommendations:

1. Study differences in biology of species and populations of elapid snakes both in native and in anthropomorphized habitats.
2. Assess which factors play a role in the probability of encounter be- tween people and coral snakes.
3. Establish partnerships for captive breeding of *Micrurus* species in the region, led by specialists in their habits in nature and maintenance in captivity, with the goal of collecting venom both for research and for future production of more specific AV.
4. Stimulate biological studies about little known species to assess their life habits.

3. Coral snake bites in Brazilian Amazonia

In Brazil, this group is associated with about 1% of the yearly snakebites, with 191 cases notified in 2014 (SINAN 2015; Bucaretchi et al., 2016b). The low number of cases is associated with the fact these snakes are not aggressive, coupled with their little fangs, mouth with narrow gape and small amount of venom they can yield and inject. These traits make difficult for them to bite or envenom someone (Melgarejo, 2009; Gutiéerrez et al., 2016). However, this number could be overestimated due to misidentification of cases caused by false coral snakes. For instance, in a study conducted in Hospital Vital Brazil, in São Paulo, using snakes positively identified, coral snake bites represented only 0.7% of the cases (Risk et al., 2016). In Amazonia there is a lack of studies making a series of cases regarding coral snake bites. The only source of data comes from isolated case reports or personal communications (Santos et al., 1995; Pardal et al., 2010; Bucaretchi et al., 2016b; Mendonça-da-Silva et al., 2018; da Silva et al., 2019). Data coming from other countries in the region, like Colombia, suggests that the incidence could be even lower than the Brazilian average of 1% (Otero-Patiño, 2018; Gordo et al., 2016). In an undergoing research in Fundação de Medicina Tropical Heitor Vieira Dourado (FMT-HVD), a reference hospital in Manaus, Amazonas State, we used the book of records from the scientific collection to check the number of confirmed snakebite cases (with the snake brought by the patient for identification), since the records began in 1985. Coral snake bites represented about 2.6% of the total, a number closer to a proportion found for the state of Rondônia, Western Amazonia (Roriz et al., 2018).

We collected both the number of cases and the incidence rate per 100,000 inhabitants for each municipality to describe the spatial distribution of the snakebites. Data on the municipal population was obtained from the 2010 official census and the intercensus projections (IBGE, 2018). The period of study ranged between 2010 and 2015. All snakebites in Brazil are officially reported to the Ministry of Health. The department responsible for snakebites surveillance provided the data used in this work.

In Brazilian Amazonia (North Region of Brazil: states of Acre, Amapá, Amazonas, Pará, Rondônia, Roraima and Tocantins, plus the states of Mato Grosso and Maranhão), there were reported, from January 2010 to December 2015, 70,816 cases of snakebites (SINAN, 2016). Of these, 236 (0.33%) were reported as caused by coral snakes (elapidic snakebites). Since the snakes could not be positively identified, we classified the snakebites in two groups, following Casais-e-Silva and Brazil (2009): those who show the classic symptoms related to elapidic envenomation (especially related to palpebral ptosis, paresthesia, local pain, difficulty in walking or blurred vision), but did not bring the snake, were classified as probable. Those cases where the patient did not bring the snake neither showed the classic symptoms or were reported with symptoms unrelated to elapidic snakebites (such as necrosis, blistering, hemorrhage, acute kidney failure, for example) were classified as doubtful. The cases combined are briefly discussed, but only probable cases were used in the analysis. We also discarded doubled cases. This study was approved by the Ethics Review Board (ERB) of the Núcleo de Medicina Tropical of the University of Brasília (approval number 1.652.440/2016).

From the 236 notified cases, 202 (86%) were classified as doubtful and 34 (14%) as probable. There was little variance among the years regarding the number of probable cases reported, except for the year of 2012, when there was a peak in the number of snakebites reported. The annual incidence of probable coral snake bites was 0.123 case/100,000 inhabitants. When all cases were considered, this value was 0.85 case/ 100,000 inhabitants. There was also little variance in the incidence among the years, except for a peak in 2012 (Table 1).

The cases classified as probable represent 0.05% of the total of the snakebites reported during the period of study. Most of cases occurred in males, *pardos* (people with mixed ethnic ancestries), in ages between 11 and 40 years. The youngest patient was three, the oldest was 77 years old (mean 29.39). Over half of the patients were illiterate or did not finish Elementary School. Fifty-three % of the cases occurred in the urban area. The anatomical site of the bite was concentrated in the lower limbs (legs, feet and toes) (71%). The distribution within the years showed little variation, 21% of the cases were reported as resulted from occupational risk (Table 2).

Table 1: Annual distribution of the coral snake bites reported by the Brazilian Information System of Notifiable Diseases (SINAN), between 2010 and 2015. The data are restricted to probable cases (n = 34).

Probable cases	**Year**	**Number of cases**	**%**	**Incidence (cases/100,000 inhabitants)**
	2010	5	15%	**0.020**
	2011	5	15%	**0.019**
	2012	12	35%	**0.046**
	2013	5	15%	**0.019**

2014	3	9%	**0.011**
2015	4	12%	**0.014**
Total	**34**	**100%**	**0.123**

Table 2: Epidemiological data from the coral snake bites reported by the Brazilian Information System of Notifiable Diseases (SINAN), between 2010 and 2015. The data are restricted to probable cases (n = 34).

Epidemiological data	**Number of cases**	**%**
Sex		
Male	22	65%
Female	12	35%
Race		
White	1	3%
Black	3	8%
Asian	1	3%
Pardo	25	69%
Indigenous	3	8%
Ignored	1	3%
Age (years)		
0 – 10	1	3%
11 – 20	9	26%

21 – 30	9	26%
31 – 40	7	21%
41 – 50	3	9%
51 – 60	2	6%
> 60	3	9%
Minimum age (years)	3	
Maximum age (years)	77	
Mean age (years)	29.39	
Schooling		
Illiterate	4	12%
Elementary School incomplete	14	42%
Elementary School complete	2	6%
High school incomplete	2	6%
High school complete	2	6%
Higher education incomplete	0	0%
Higher education complete	1	3%
Ignored or unfilled	8	24%
State		
Acre	0	0%
Amapá	5	15%
Amazonas	1	3%
Maranhão	6	18%

Mato Grosso	2	6%
Pará	3	9%
Rondônia	5	15%
Roraima	2	6%
Tocantins	10	29%
Zone of the bite		
Urban	18	53%
Rural	14	41%
Periurban	1	3%
Ignored or unfilled	1	3%
Region of bite		
Head	0	0%
Arm	1	3%
Forearm	0	0%
Hand	4	12%
Finger	4	12%
Trunk	0	0%
Thigh	0	0%
Lower leg	2	6%
Foot	14	41%
Toe	8	24%
Ignored or unfilled	1	3%

Seasonal distribution		
1st trimester	9	26%
2nd trimester	8	24%
3rd trimester	8	24%
4th trimester	9	26%
Snakebite related to work		
Yes	7	21%
No	22	64%
Ignored or unfilled	5	15%

Although the database has reported only 21% of work-related bites, the profile of victims (working-age men) suggests that there is an occupational risk associated with this kind of snakebite. The same pattern was found in the area for snakebites in general (Wen et al., 2015), lanceheads (Alcântara et al., 2018) and rattlesnakes (Santos et al., 2019) bites. Studies with coral snakes in other areas also have associated occupational risk with these bites (Bucaretchi et al., 2016; Casais-e-Silva and Brazil, 2009; de Roodt et al., 2013; Kitchens and Van Mierop, 1987; Wood et al., 2013). Unlike most of snakebites that occur in the rural zone, over half of the bites were reported for the urban zone. Some species of coral snakes in the Amazonia, like *Micrurus surinamensis* and *M. lemniscatus*, are known to live near or inside urban perimeter, in fragments of vegetation, or even near house settlements (Marques et al., 2009; Almeida et al., 2016). They may be the main cause of bites, at least in that zone. The higher incidence of people living in cities or the migration of the snakes to the periphery of the urban area could explain why there are more bites there (Lima et al., 2009; Albuquerque et al., 2013). Another explanation could be an underreporting from the rural zone, once Brazilian Notification System bears problems regarding it (Fiszon and Bochner, 2008) and the fact that Amazonia is a vast biome, with many places far away and isolated from each other, hindering the access to health care units and reporting posts. Many studies (e.g. Bucaretchi et al., 2006; Casais-e-Silva and Brazil, 2009; Wood et al., 2013) reported the main site of the bite as the upper limbs. That is because these colorful snakes draw the attention of young people or people under effects of alcohol or other drugs. However, in some studies (e.g. de Roodt et al., 2013), like this one, the main site of the bites were the lower limbs, when people accidently step on them. The quarterly distribution of the snakebites was even. Eighteen bites (53%) occurred in the rainy season, sixteen (47%) occurred in the dry season. The average monthly precipitation for the municipalities with reported cases was 144.86 mm^3 (Chen et al., 2008).

The cases are unevenly distributed through the region (Fig. 2). From the nine states in the region, Acre did not report any case, while Tocantins reported 10 (29%). The highest number of the snakebites have been reported in the Maranhão and Tocantins states. One municipality (Porto Velho, Rondônia) recorded 3 bites; three municipalities (Alto Alegre dos Parecis, Rondônia; Coari, Amazonas and Porto Nacional, Tocantins) recorded two bites each; the remaining municipalities with records reported only one bite each. The highest incidence rates came from Tocantins and Amapá, and the lowest from Amazonas, Pará and Acre (Fig. 3). The municipalities of São Félix do Tocantins (68.35 cases/100,000 inhabitants), São Valério da Natividade (23.35 cases/100,000 inhabitants) and Dueré (21.75 cases/100,000 inhabitants), all in the state of Tocantins, showed the highest incidence rates. The distribution of both number of cases and incidence rates showed that most of the bites were reported in regions when Amazonia meets open areas of savannah. These are the areas where there are more intense human activities like logging, farming, and higher density of people, all of them positively associated with snake bites (Alcântara et al., 2018; Lima et al., 2009). Factors related with the life habits of the snakes, such as the higher probability of encounters with them in more open spaces (in contrast with a more forested habitat, with more places to hide) should not be ruled out.

Recommendations:

1. Perform multicenter studies with a larger series of confirmed cases to identify the socioeconomic, environmental and clinical aspects related to snakebites caused by coral snakes in Brazilian Amazonia.
2. Establish partnerships for creating a network of research among biological and health professionals in the countries of the region, with the goal of notify and study the cases.
3. Improve the Brazilian notification system to have a better view of the real problem that coral snakes represent in the region.

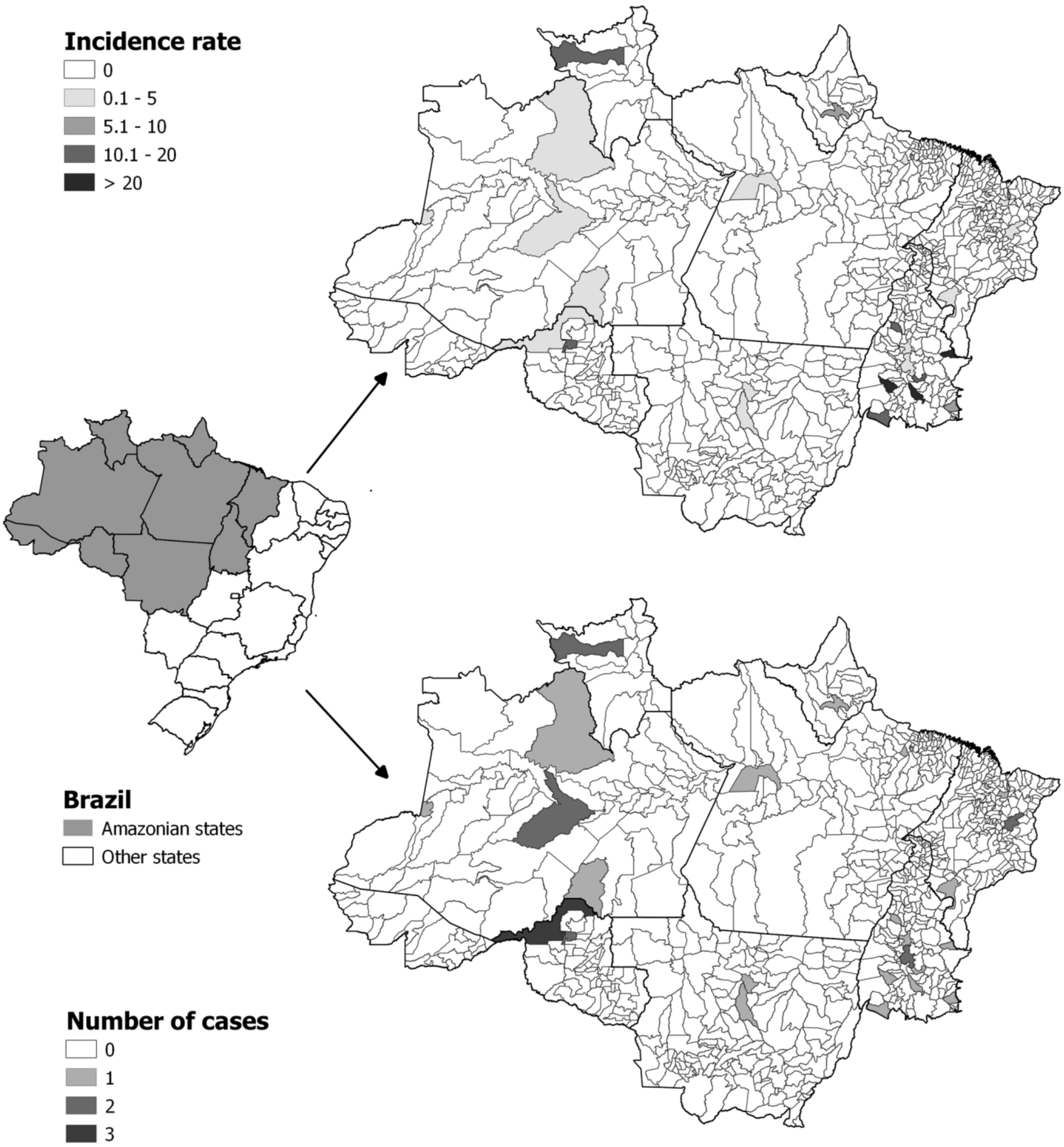

Fig. 2: Spatial distribution of coral snake bites in the Brazilian Amazonia from 2010 to 2015. Incidence rate is given in cases/100,000 inhabitants/year. The highest incidence rates are found in Maranhão, Roraima and Tocantins states, while the highest number of cases is found in Maranhão, Rondônia, Roraima and Tocantins states, in regions bordered by savannah areas. The data are restricted to probable cases (n = 34).

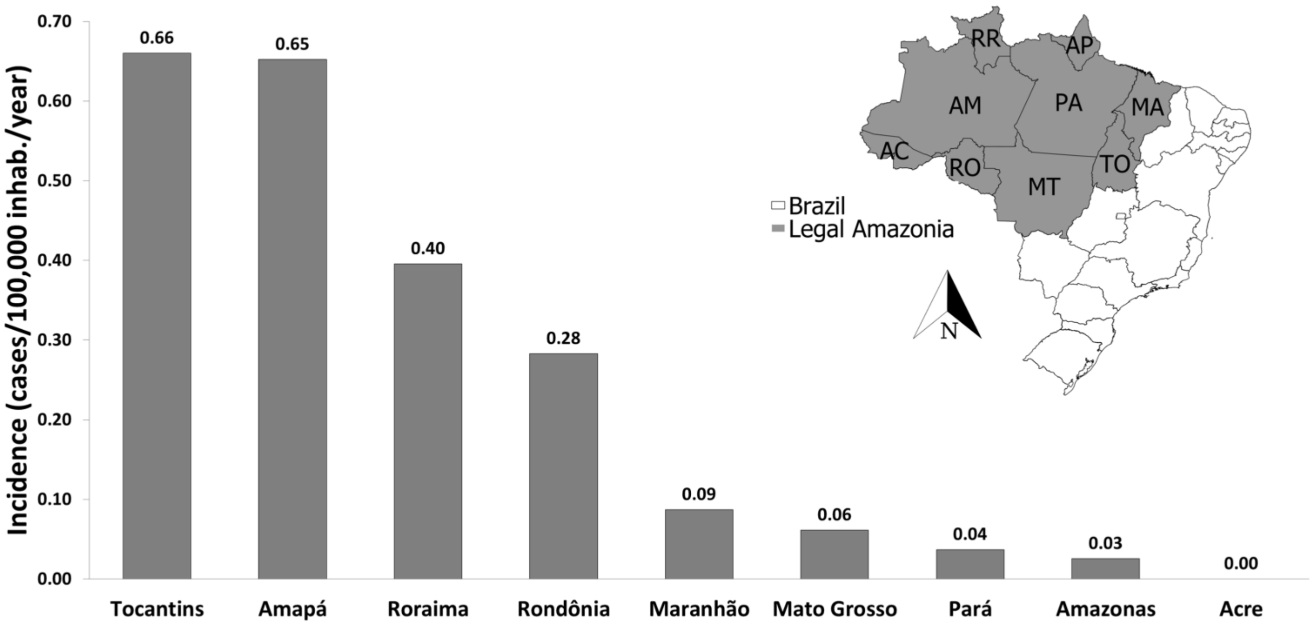

Fig. 3: Incidence rate of coral snake bites reported by Brazilian states. The highest incidence rates were reported in Tocantins (0.66 case/100,000 inhabitants/year) and Amapá (0.65 case/100,000 inhabitants/year). The lowest rates were reported in Acre (0 case/100,000 inhabitants/year), Amazonas (0.03 case/100,000 inhabitants/year) and Pará (0.04 case/100,000 inhabitants/year). The data are restricted to probable cases (n = 34). AC: Acre; AM: Amazonas; AP: Amapá; MA: Maranhão; MT: Mato Grosso; PA: Pará; RO: Rondônia; RR: Roraima; TO: Tocantins.

4. Toxinology and pathophysiology

Although *Micrurus* is a group composed by over 80 species with a wide geographical range, all their venoms are composed by up to 11 families of toxins, mainly by Phospholipases A2 (PLA2) and nonenzymatic three-finger toxins (3FTx) (Alape-Girón et al., 1996; Correa-Netto et al., 2011; Sanz et al., 2019). Beyond those already mentioned, Kunitz-type inhibitor (Kun), C-type lectin/lectin-like (C-lect), metalloproteinase (SVMP), L-amino acid oxidase (LAO), hyaluronidase (Hya), phospholipase B (PLB), serine proteinase (SP), phoshodiesterase (PDE), 50 -

nucleotidase (50 nuc) also have been reported in their venoms (Lomonte et al., 2016, Rey-Suárez et al., 2016). There is a geographical and phylogenetic distinctiveness between the expression phenotypes of the two main classes of toxins (PLA2 and 3TFx), possibly related to the evolutional history of the *Micrurus* clade. Northern South America seems to be an overlap zone between these two main groups (Lomonte et al., 2016). Most of South American species with protein families identified through proteomic studies showed 3TFx predominant venoms, with exception of *M. dumerilii*, which has a PLA2 predominant venom (Ciscotto et al., 2011; Corrêa-Neto et al., 2011; Rey-Suárez et al. 2011, 2016; Lomonte et al., 2016; Sanz et al., 2016). Differences in the composition of the venom of South American coral snakes can be attributed to prey-selectivity, geographical distribution, phylogenetic affinity and/or a combination of factors, including paedomorphosis in derived clades, and gene transfer through ancestral hybridization events (Olamendi-Portugal et al., 2008; Lomonte et al., 2016). *Micrurus* snake venoms are primarily neurotoxic, with the toxins being divided in pre and postsynaptic neurotoxins (Vital Brazil and Fontana, 1984; Vital Brazil, 1987). Presynaptic toxins have phospholipasic activity, being able to block the presynaptic release of acetylcholine (Ach) in the synapse, while the postsynaptic toxins act by competitively binding with Ach receptors in the neuromuscular joint (Silva Jr. and Bucaretchi 2009). These activities are responsible for most of the symptoms presented by bitten patients. Amazonian species with postsynaptic toxins include *Micrurus surinamensis* and *M. mipartitus* (Aird et al., 1993; Olamendi-Portugal et al., 2008; Rey-Suárez et al., 2012). However, most of the research regarding Brazilian species involves those from Southeastern, Southern and Mid-Westwern Brazil (Gutiérrez et al., 2016).

Myotoxic activity has been demonstrated for the venoms of many *Micrurus* species, including groups from Amazonia, like *M. spixii*, *M. hemprichii* and *M. lemniscatus* (Gutiérrez et al., 1992; de Roodt et al., 2012). The venom of *Micrurus surinamensis* has not showed toxic activity (Gutiérrez et al., 1992). The myotoxic activity of *Micrurus* venoms from Brazilian Amazonia is evidenced experimentally by both the increase in plasma levels of creatine kinase and acute muscle damage on the tissues (Gutiérrez et al., 1992; de Roodt et al., 2012; Terra et al., 2015). There is no coagulant activity in the venoms of *Micrurus averyi, M. hemprichii, M. lemniscatus, M. spixii* and *M. surinamensis* from Brazilian Amazonia (Oliveira et al., 2016). Except for that of *M. surinamensis*, the venoms of the other species have edematogenic and myotoxic activities, while *M. averyi* is the only species for the region with evidence for haemorrhagic activity (Barros et al., 1994). Nephrotoxicity by indirect glomerular damage was described for the venoms of *Micrurus fulvius* and *M. nigrocinctus*, which do not occur in the region (de Roodt et al., 2012).

Recommendations:

1. Perform additional experiments with venom of Amazonian species, both *in vitro* and *in vivo*, in order to elaborate a general background on their activities, including species less common and with no reported cases of bites.
2. Study the venom chemical composition of species in the region, in intra- and inter-population level to contextualize their relation to aspects of the natural history, phylogeny and biogeography of the group.
3. Perform transcriptomic studies in order to describe possible new modes of action by the venoms of coral snakes.

5. **Clinical aspects**

In this study, all cases showed local clinical manifestations. The most common were, in decreasing order: pain, edema and paresthesia. Ninety one percent of the cases showed systemic manifestations. The most common systemic symptoms marked in the notification forms were neuroparalytics (palpebral ptosis/blurred vision), vagals (vomiting/ diarrhea) and myolytics (myalgia). Other kinds of systemic manifestation also listed in the notification forms were disorientation, headache, dizziness, dyspnea, fainting and respiratory failure. Forty seven percent of the cases were classified as severe, and 79% evolved to cure. Only systemic complications were reported, in three cases (9%). Two of them were listed as respiratory failure, one was not specified. No deaths were reported in the period of study (Table 3). The high number of cases classified as severe is due the fact that Brazilian Health Ministry classified all the envenomings by *Micrurus* as severe, despite the symptoms the patient actually developed (BRASIL, 2001). This changed in 2014, when a new protocol was created and classified the envenomings by *Micrurus* as mild, moderate or severe (BRASIL, 2014). Bucaretchi et al. (2016b) additionally showed that in Brazil some symptoms related to severe cases (like blurred vision, dyspnea and diplopia) can be found in less than 30% of the cases. Moreover, the short time between the bite and medical care found in the vast majority of the cases (see section 5) can explain the general good outcome.

Table 3: Clinical data from the coral snake bites reported by the Brazilian Information System of Notifiable Diseases (SINAN), between 2010 and 2015. The data are restricted to probable cases (n = 34).

Clinical data	**Number of cases**	**%**
Local manifestations	**34**	**100%**
Pain	30	88%
Edema	16	47%
Paresthesia	8	22%
Systemic manifestations	**31**	**91%**
Neuroparalytics	24	71%
Vagals	9	26%
Myolytics	4	12%

Other manifestations	**9**	**26%**
Dyspnea	2	6%
Headache	2	6%
Disorientation	1	3%
Blurred vision	1	3%
Dizziness	1	3%
Vomiting	1	3%
Fainting	1	3%
Presence of systemic complications		
Yes	3	9%
No	23	68%
Ignored or unfilled	8	23%
Systemic complications		
Respiratory failure	2	6%
Not specified	1	3%
Severity of the case		
Mild	7	21%
Moderate	8	24%
Severe	16	47%
Ignored or unfilled	3	9%
Evolution of the case		
Cure	27	79%

Death by snakebite	0	0%
Death by another cause	0	0%
Ignored or unfilled	7	21%

A detailed clinical overview for *Micrurus* envenomings in the region is given in Table 4. They cause local, and more significantly, systemic manifestations that may depend on some factors involved: size of the snake, characteristics of the victim and amount of venom injected. Because of the similarity with false coral snakes and the difficulty of the health professionals and general population in differentiate them, the diagnostic should be made based mainly on clinical aspects, especially regarding the symptoms related to the neurotoxic activity of the venom. *Micrurus*, opposite to other venomous snakes in the region that bite and release, usually "chew" to inject as much venom as possible (Melgarejo, 2009). The frontal fangs (proteroglyphous) (Fig. 4) are the only way to positively identify coral snakes from false coral snakes, that are non-front-fanged (aglyphous or opisthoglyphous). However the fangs of *Micrurus* are tiny, difficult to see and seldom leave marks in the bite site.

Because of anatomical limitations, like small fangs, small mouth gape and small venom storage capacity, many bites are "dry" (without venom injection) or inject so little venom that the symptoms are mild or absent (Melgarejo, 2009; Bucaretchi et al., 2016b), and could be wrongly associated with bites by false coral snakes. Asymptomatic cases can make up to over half of the total (Wood et al., 2013). The correct identification of the perpetrator and the immediate analysis of the symptoms of the patient in the admission are of vital importance, because they could help to direct the management of the treatment and avoid the unnecessary use of antivenom (Wood et al., 2013).

Table 4: Summary of published cases of *Micrurus* bites in the Amazon region.

Species	Patient history	Local	Reported effects	Time from bite to first signals	Reference
M. annellatus bolivianus	47-year-old man; bitten on right hand while working in a shop; treated with 5 doses of antivenom ('soro antielapídico bivalente', Instituto Butantan, São Paulo, Brazil; F(ab')2); discharged after 5 days	Cruzeiro do Sul; Acre; Brazil	Local: *P; Pa* Systemic: *BluV; Coag; Ed; Na; Thro*	Local: 30 min Systemic: 30 min	da Silva et al. 2019
M. averyi	7-year-old girl;	Presidente	Local: *Ed; Ery; P; Pa*	Local: 15 min	Mendonça-

	bitten on foot; treated with 10 doses of antivenom (‘soro antielapídico bivalente’, Instituto Butantan, São Paulo, Brazil; F(ab')2); discharged after 48h	Figueiredo; Amazonas; Brazil	Systemic: *Dro; Na; Sal*	Systemic: 15 min	da-Silva et al. (2018)
M. hemprichii	Woman; bite site and use of antidote NR	Manaus; Amazonas; Brazil	Local: *Ed* Systemic: *AbP; Vom*	NR	Santos et al. (1995)
M. hemprichii ortoni	Individual bitten on the hand; complete recovery 6–8 h after bite; no use of antidote	Brazilian Amazonia Basin	Local: *Ed; P; Pa*	NR	Bucaretchi et al. (2016b)
M. filiformis	19-year-old man;	Village of	Local: *Ed; FgM; Pa*	Local: just	Pardal et

	bitten in the left hand finger while handling the snake; treated with 10 doses of antivenom ('soro antielapídico bivalente', Instituto Butantan, São Paulo, Brazil; F(ab')2); discharged after 24h	Boa Vista, Acará; Pará Brazil	Systemic: *AbP; Vom*	after Systemic: 1h	al. (2010)
M. lemniscatus helleri	27-year-old man; bitten in the right thumb while capturing the snake; treated with 10 doses of antivenom (Costa	Shell; Pastaza; Ecuador	Local: *Ble; FgM; P; Pa* Systemic: *Anx; BluV*; Coag; *Dro; Dysa; Dysp; FPa; PPt; Rha; ReF; Sw; Thro; UrI; We*	Local: 20 min Systemic: 20 min (Anx); 14h (the others)	Manock et al. (2008)

	Rican Instituto Clodomiro Picado ‘panamerican suero: anticoral Polyvalente’); needed to be intubated three times; made a bronchoscopy to remove mucus of the lungs; weakness and urinary incontinence persisted for 15 days				
M. psyches	15-year-old boy; bitten on the left thumb while trying to capture the snake; no	St. Laurent-du-Maroni; French Guiana	Local: *FgM; Nu; Pa* Systemic: *EleC*	Local: 30 min Systemic: 30 min	Heckmann et al. (2017)

	antidote was given; discharged after 24h; he showed hypersomnia and hypoesthesia four months after bite				
M. spixii	Man; bite site and use of antidote NR. Patient developed pain in joints, bones and teeth sockets	Manaus; Amazonas; Brazil	Systemic: *Pa*	NR	Bucaretchi et al. (2016b)
M. surinamensis	18 year-old man; bitten on the left thumb while trying to capture the snake; treated with 10 doses of antivenom ('soro antielapídico	Belém; Pará; Brazil	Local: *FgM; P* Systemic: *BluV; Dysa; Foa; InW; LC; PPt; ReF*	Local: few minutes Systemic: 20 min	Pardal et al. (2010)

bivalente', Instituto Butantan, São Paulo, Brazil; F(ab')2); he was put on a ventilator for 48h; discharged 3 days after bite

Abbreviations: *AbP*: abdominal pain; *Anx*: anxiety; *Ble*[a]: bleeding; *BluV*: blurred vision; *Coag*[b]: coagulopathy; *Cep*: cephaloplegia; *Cya*: cyanosis; *Dro*: drooling; *Dysa*: dysarthria; *Dysp*: dysphagia; *Ed*: edema; *EleC*[c]: electrocardiac changes; *Ery*: erythema; *FgM*: fang marks; *Foa*: foaming; *FPa*: facial paralysis; *InW*: inability to walk; *LC*: loss of consciousness; *MPa*: muscular paralysis; *Na*: nausea; NR: not reported; *Nu*: numbness; *P*: paresthesia; *Pa*: pain; *PPt*: palpebral ptosis; *Rha*[d]: rhabdomyolysis; *ReF*: respiratory failure; *Sal*: salivation; *Sw*: sweating; *Thro*[e]: thrombocytopenia; *UrI*: urinary incontinence; *Vom*: vomiting; *We*: weakness.

[a]Caused only by fang punctures.

[b;e]Evidenced by blood count with a marked leucocytosis with left shift.

[c]Evidenced by transient first-degree atrioventricular block and biphasic T waves showed in the electrocardiogram exam.

[d]Mild rhabdomyolysis evidenced by raised levels of creatine kinase.

Roriz et al. (2018) cited a bite caused by a *Micrurus lemniscatus* in Rondônia, Brazil, but gave no details about the history of the case or its outcome.

Fig. 4: Head and mouth of *Micrurus spixii*, with the frontal fangs (proteroglyphous) indicated by the arrow. *Micrurus* fangs are tiny, making them difficult to see in small individuals, even by specialists, but they are the only way to truly differentiate them from false coral snakes.

Less severe local manifestations are mild pain, numbness and paresthesia limited to the bite site, starting few minutes after the bite (Pardal et al., 2010; Heckman et al., 2017; Cañas et al., 2017; Mendonça-da-Silva et al., 2018; da Silva et al., 2019). Bleeding, when present, is caused only by the injury inflicted by the fangs, not being long lasting or significant. There is no local ecchymosis or necrosis. Edema, when present, is mild and usually associated with the use of tourniquets (Silva Jr. and Bucaretchi 2009; Bucaretchi et al., 2016a). Local manifestations may increase progressively and may affect the whole limb. Signals such as moderate pain and progressive paresthesia in the affected limb can appear only a few minutes after the bite (Manock et al., 2008; Pardal et al., 2010; Cañas et al., 2017; Heckman et al., 2017; Mendonça-da-Silva et al., 2018) or take hours to manifest. Pain can evolve to a very severe state, with need to use opioids to relieve it (Manock et al., 2008). Usually, there are no local complications in patients bitten by coral snakes. However, in some cases, local paresthesia/numbness has lasted for three weeks (Bucaretchi et al., 2016a).

Symptoms and signs of systemic envenoming are mainly due to the neurotoxic action of the venom. The most common neurotoxic systemic symptoms, in decreasing order are: palpebral ptosis, dizziness, blurred vision, weakness, dysphagia and dyspnea. Diplopia, salivation, somnolence, headache, inability to walk, vomiting, abdominal/thoracic pain and ophthalmoplegia may also occur (Bucaretchi et al., 2016b). The beginning of the systemic manifestations in *Micrurus* envenoming ranges from a few minutes to over 12 h (Kitchens and Van Mierop, 1987; Manock et al., 2008; Pardal et al., 2010; Ocampo-Trujillo, 2016; Cañas et al., 2017; Mendonça-da-Silva et al., 2018). Late manifestations (later than 12 h) may occur even if the patient has not experienced any local symptoms at all (Kitchens and Van Mierop, 1987). Other systemic manifestations are related to the myotoxic action of the venom. Human victims can experiment slight increase in the blood level of creatine kinase (Bucaretchi et al., 2016a). In Amazonia, the only case with such increasing of CK in the blood was described in a patient bitten by *M. lemniscatus helleri* in Ecuador (Manock et al., 2008). Local or generalized myalgia may occur, and is possibly associated with the myotoxic effect of the venom (Bucaretchi et al., 2016a). In Amazonia, thrombocytopenia, and mild coagulopathy were described in bites by *M. annellatus bolivianus* and *M. lemniscatus helleri* (Manock et al., 2008; da Silva et al., 2019), and electrocardiogram changes have been re- ported in an envenoming by *M. psyches* (Heckman et al., 2017).

Systemic complications are related to the severe paralysis, with respiratory failure and needing of tracheal intubation and mechanic ventilation. The respiratory symptoms can lead to pneumonia, bacterial infections, pneumothorax, bronchial obstruction or need for tracheostomy (Kitchens and Van Mierop, 1987; Pifano et al., 1986). Loss of muscle strength can last many weeks (Kitchens and Van Mierop, 1987; Manock et al., 2008). In some cases total recovering can take one to two months (Kitchens and Van Mierop, 1987).

Recommendations:

1. Create a research group for clinical studies of envenomations of coral snakes in the Amazonian biome, aiming to investigate the manifestations presented by the patients.
2. Pay attention to clinical manifestations other than neurotoxic ones, in order to describe their frequency, importance and how and in whom they manifest, and which species cause those manifestations.
3. Perform wider studies with clinical signals developed in the course of the envenoming, describe and analyze how they relate to patient pre-admission condition, and predict the outcomes based on patient and admission conditions.
4. Study the developed complications, the conditions related to them, how and how long they affect the patients.

6. Therapeutics

The specific treatment of *Micrurus* envenomations in the Brazilian Amazonia follows the protocol established by the Ministry of Health according to the severity of the envenomation (BRASIL, 2014). Formerly, the instructions said that all *Micrurus* envenomings should be treated as a severe case, with application of 10 doses of Micrurus antivenom (soro antielapídico [SAE]) (BRASIL, 2001; Bucaretchi et al., 2016a). Recently, aiming to avoid the waste of SAE, it was proposed the current classification of severity, following the signals and symptoms presented by the victims: mild (asymptomatic or only with local manifestations), moderate (acute myasthenia without paralysis) and severe (intense myasthenia followed by intense muscular weakness or paralysis) (BRASIL, 2014; Bucaretchi et al., 2016a).

In the cases with clinical suspect or with a confirmed accident, even asymptomatic, patients should be taken to a medical center that possess the SAE, as well the structure for ventilatory support, once the patients may need this kind of support (Bucaretchi et al., 2016a). With the possibility of systemic signals of early appearance, the patients should be kept calm and taken to the hospital as soon as possible. The application of tourniquets, although widely widespread by lay people, is not advisable (Jamieson and Pearn, 1989; Norris et al., 2005; Currie, 2006; Oliveira et al., 2016).

The antivenom should be administered as soon as the neuroparalytic signals appear. In Brazil, the antivenom used is an enriched solution of F (ab')2 immunoglobulins obtained from horses immunized with a mixture of two species that cause the highest number of accidents in the country: *Micrurus corallinus* and *M. frontalis* (Bucaretchi et al., 2006). Currently, the venom is produced by two manufacturers, Instituto Butantan, in São Paulo, and Fundação Ezequiel Dias, in Belo Horizonte. According to them, one vial contains 10 mL, and 1 mL of it neutralizes, at minimum, 1.5 mg of reference *M. frontalis* venom in mice. (Bucaretchi et al., 2006, BRASIL, 2014). The use of AV is indicated for *Micrurus* bites only in moderate and severe cases (five and 10 doses, respectively) (BRASIL, 2014). The use of anticholinesterase drugs has been useful in accidents caused by species with predominantly or exclusively post-synaptic action, but succeeded only in accidents by *M. frontalis* (Coelho et al., 1996, Vital Brazil and Vieira, 1996), which geographical range does not reach the Amazonian region. For local species, so far, this treatment is useless (Manock et al., 2008). In severe cases, the ventilatory assistance may be needed if respiratory failure settles in (BRASIL, 2014). Bronchoscopy may be needed in some cases to remove mucus (Manock et al., 2008).

Some studies with cross-reaction have shown that the polyvalent SAE manufactured in Brazil does have intermediate to low cross-reaction with the venom of some Amazonian species, like *Micrurus hemprichii, M. lemniscatus, M. spixii* and *M. surinamensis* (Tanaka et al., 2010; Oliveira et al., 2017). Also, fast diversification in both groups of *Micrurus* toxins could have an impact on the management of snakebites, including selection of specimens for antivenom producing and antivenom efficacy (Sanz et al., 2019). The differences in the composition of the venoms showed above (see section 3) also may affect the efficiency of the AV among different species, since species with the same predominant classes of toxins found in the venoms used for the production of the AV have better cross-reactivity, while those with different predominant classes have lower cross-reactivity (Rey-Suárez et al., 2011; Rey-Suárez et al., 2016). Further studies are necessary to assay the need to incorporate venoms from Amazonian species in the SAE pool (Tanaka et al., 2016). Adverse reaction against the AV for *Micrurus* has been described for the North American Coral Snake Antivenin® (NACSAV). Adverse reactions were observed in 18.3% of the patients treated with that AV in Florida. The reactions ranged from hives, rash, and/or welts to itching, shortness of breath, hypotension, and angioedema (Wood et al., 2013), while in Brazil 30% of the patients treated with the AV for coral snakes can develop early manifestations, like urticaria, itching and abdominal pain (Bucaretchi et al., 2006). This difference in the numbers may be due differences in the AV themselves. Factors depending on the manufacturing practices, physicochemical and immunochemical characteristics can be related to appearance of adverse reactions (León et al., 2013). Other factor can be the difference in the number of patients assessed in each study (256 in the US, 10 in Brazil). In Brazilian Amazonia, between 16.5% and 19% of patients treated with AV for *Bothrops* and *Lachesis* bites developed adverse reaction (Pardal et al., 2004; Mendonça-da-Silva et al., 2017; Alves et al., 2018). Only early adverse reactions were reported (the most common were urticaria, pruritus, facial flushing and vomiting, respectively). No patient developed late adverse reactions (Mendonça-da-Silva et al., 2017). The adverse reaction against the antivenom for *Micrurus*, combined with the fact that severe reactions can develop, including respiratory failure, hypotension and chock (Wen, 2009) should serve as alert for professionals using the antivenom therapy in Amazonia. Studies about adverse reactions against SAE in the region are also necessary.

In this study, 88% of the cases the time from bite to medical care were no longer than 3 h. Eighty eight percent of the patients received AV. The number of vials received ranged between one and 10 (mean 8.06) (Table 5). Four patients presented neurological manifestations, but received less than the recommended minimal dose of five vials, and one patient presented numbness and neurological systemic manifestations, but did not receive the AV. In the cases reported after the new protocol being published (year 2014), of the seven cases classified as mild, two showed systemic manifestations, therefore they should be classified at least as moderate. From the 16 cases classified as severe, one did not show systemic signals, and should be classified at least as moderate. Two cases were considered mild, but received AV. One of the cases with underdosage of AV was classified as severe but the patient received less than half the number of vials indicated in such cases. This may indicate that health professionals are generally not well trained to apply the SAE, that they do not recognize the signals and symptoms of each level of gravity, or that there is a lack of AV in the hospitals in the region. Out of the four cases with underdosage, three evolved without complications and one did not report them; two evolved to cure and two did not report the outcome; one spent 9 days at hospital, two spent four days, and one did not report how many days were spent in the hospital. The only case without use of AV did not have any complication and evolved to cure; the patient spent one day in the hospital.

Table 5: Therapeutic data from the coral snake bites reported by the Brazilian Information System of Notifiable Diseases (SINAN), between 2010 and 2015. The data are restricted to probable cases (n = 34).

Therapeutic data	Number of cases	%
Time to medical care (h)		
0 – 1	11	32%
1 – 3	19	56%
3 – 6	3	9%
6 – 12	1	3%
> 12	0	0%
Number of vials used		
0	0	0%
1 – 5	10	29%
10	20	59%
> 10	0	0%
Ignored or unfilled	4	12%
Number of vials used (mean)	8.06	

Intensive Care Units (ICU) sometimes are needed to give support in severe cases, when mechanical support is needed for the patient. In Amazonia, there are 204 medical centres with ICUs. Of those, 131 (64%) are concentrated in the capitals. There are 3613 facilities, with 2512 (69%) concentrated in the capitals. Of the 3459 municipalities in the region, 85% do not have any ICU facility (AMIB 2016). This concentration in a vast area with difficulties in transportation, often by boat, could mean a large number of people have no access to immediate intensive care in case of severe envenoming by *Micrurus*.

Recommendations:

1. Promote educational actions directed to health professionals, aiming to teach them how to recognize the clinical manifestations of coral snake bites, the new gravity classification in Brazil, and the recommended therapeutic, including the correct antivenom, number of vials for each case, as well as support treatment.
2. Study seroneutralization in experimental models to support the venom pool used to immunize animals for AV production, considering the absence of Amazonian *Micrurus* venoms in these pools. Experimental studies should indicate the need for inclusion of new venoms. A new AV manufactured together with other countries in the region could be a perspective for future research. Clinical and epidemiological data should validate any new AV.
3. Investigate adverse reactions in patients treated with *Micrurus* AV, identify the main reactions, their frequency and how to deal with them.
4. Inspect whether all the municipalities in the region have the AV for *Micrurus* bites available, check if the lots are well conditioned and if they are enough for the population in the area.
5. Increase the number of the ICUs in the area to fill the geographic gaps in the cover in order to prevent deaths in the severe cases where ventilatory support is needed.

7. **Preventive measures**

Micrurus are colorful animals, drawing the attention due to their combination of red, yellow and black rings. This may lead people, especially young children and people under use of alcohol and illegal drugs to manipulate these animals (Pardal et al., 2010; Risk et al., 2016). In our search in FMT-HVD records, we came across with at least three cases when alcohol use was involved in *Micrurus* bites. Manipulation due to misidentification with false coral snakes also plays a role in accidents (Strauch et al., 2018). Some studies have shown a tendency of bites in the upper limbs, but not always related to manipulation (Bucaretchi et al., 2006). Many other studies, however, have shown that bites by *Micrurus* are more common in the lower limbs. Therefore, they may be much more an accidental case, with people stepping on the animal, or even putting their hands without seeing it (de Roodt et al., 2013; Risk et al., 2016; Mendonça-da-Silva et al., 2018). The higher number of bites in lower limbs (71%) reported in Amazonia seems to indicate that the latter is the case. It is well known that simple measures, such as the use of boots and gloves, can significantly reduce the chances of snakebite (Bernarde, 2014). In Amazonia, traditional populations like indigenous or riverines seldom have access to such methods. Being the most affected group by this kind of burden, they should receive preference in snake- bite prevention policies.

In Amazonia, time to medical care was one of the factors associated with higher risk of severity and death by snakebite (Feitosa et al., 2015b). Assuming that the same neuroparalytic manifestations can be delayed for over 12 h, it is important to keep the patient in observation for at least 24 h, with the medical support ready for use, if needed. Our data suggest that underdosing of antivenom in the region seems to occur. Improvement in the access to health facilities and systematic professional training on diagnosis, specific therapy, and clinical management of complications could have a significant impact in preventing poor outcomes (Oliveira et al., 2016).

Educational programs should be conducted towards both professionals and general population in order to make them be able to recognize at least the main groups of coral snakes in the region, and how to differentiate them from false coral snakes. This could reduce significantly the number of snakebites due to misidentification. Professionals should also receive training regarding the correct use, both about the dosage (number of vials administrated) and specific AV (Oliveira et al., 2016). The use of traditional medicine, very widespread in the region, should be avoided, once it can delay the departure to hospital, worsening the clinical condition (Brasil 2001). Educational programs telling about the risks of a late hospital departure and the ineffectiveness of these methods are also advisable.

Recommendations:

1. Perform educational programs with local populations and health professionals, teaching them how to recognize at least the main species of *Micrurus* in the region, how to differentiate them from false coral snakes, how to avoid snakebites, the recommended first aids and therapy in case of a bite and the importance of fast departure to a medical center.
2. Identify the risk groups in the region and promote public politics towards them in order to avoid further accidents, including the distribution of boots and gloves for the prevention of bites.

8. Final remarks

Research about snakebites in the Amazonian region has made a good progress in the recent years. However, many gaps still remain in the understanding of this problem, especially when involving elapid snakes. Coral snakes are difficult to see and study and cause relatively few snakebites per year in a sparsely populated region. Additionally, underreporting is a major problem, making it hard to determine any pattern about this type of accident. Therefore, evidences of treatment and clinical profile are based solely on case reports and cases from other geographic regions. There is a huge gap in Amazonia regarding this kind of accident, and further research with series of confirmed cases will certainly improve our knowledge on epidemiological and clinical aspects of these accidents in the region.

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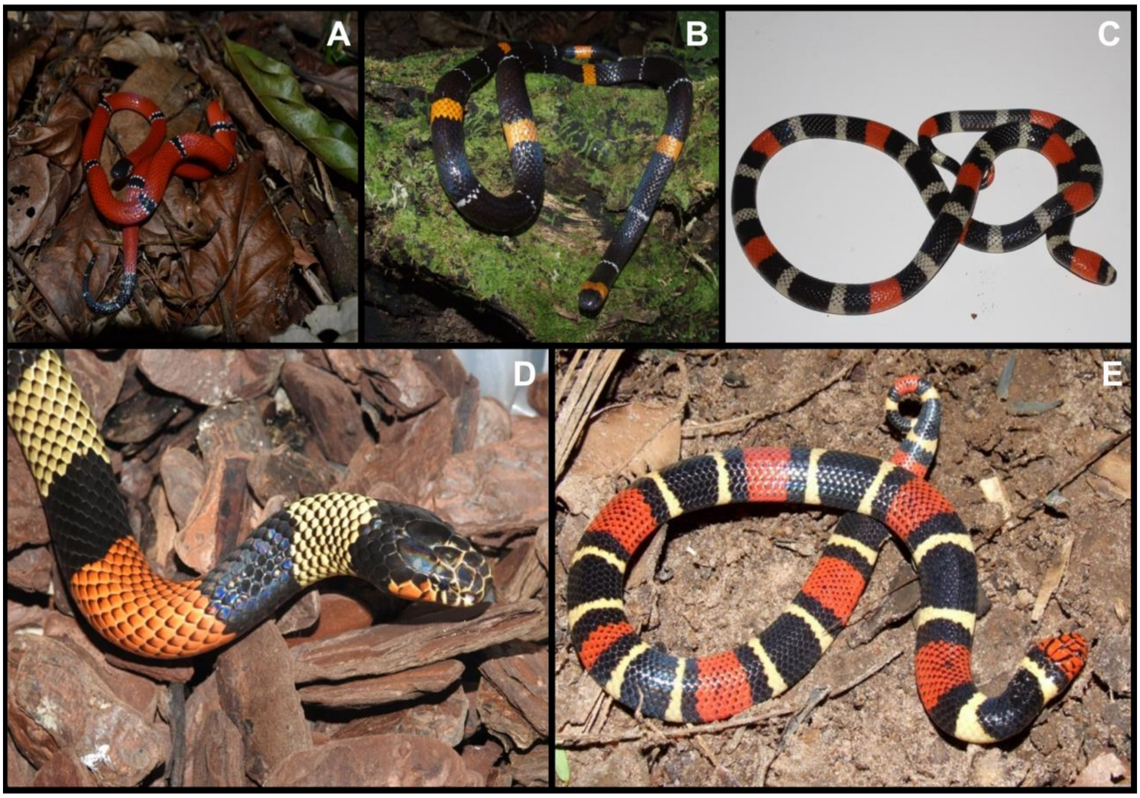

CAPÍTULO 2

Bisneto P. F., Araújo B. S., Pereira H. S., Silva I. M., Sachett J. A. G., Bernarde P. S., Monteiro W. M., Kaefer I. L. **Envenomations by coral snakes in an Amazonian metropolis: Ecological, epidemiological and clinical aspects**. Artigo publicado na revista Toxicon em outubro de 2020. **DOI: 10.1016/j.toxicon.2020.07.009**

Envenomations by coral snakes in an Amazonian metropolis: ecological, epidemiological and clinical aspects

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Abstract: Envenomation by coral snakes represents a little known burden in Brazilian Amazonia. So far, details on clinical and epidemiological aspects remain obscure in the region. We gathered data from medical charts and from the scientific collection of snakes from *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*, finding 26 cases of envenomation by five species of *Micrurus* in Manaus region, between 1987 and 2018. They represent 0.7% of the snakebites treated in the hospital since the records began, in 1979. *Micrurus lemniscatus* was responsible for most of the bites (10), followed by *M. hemprichii* (five), *M. spixii* (three), *M. surinamensis* (three) and *M. averyi* (one). There was no difference between the sexes of the snakes that caused bites. Patients were mostly males, and most of the cases were reported in urban areas. Bites predominated in dry season, and there was a clear geographical segregation among species. We describe seven cases of envenomation, three mild and four severe, all of which evolved to cure. Paresthesia (six), pain (five) and edema (four) were the most common local symptoms. Systemic features such as dyspnea/shallow breath (four), palpebral ptosis (four), blurred vision (three), dysarthria (three) and difficulty to walk (three) were also detected. Two patients bitten by *Micrurus* sp. and *M. hemprichii*, showed slight increased serum levels of creatine kinase (reference level <190 U/L), 1,184 U/L and 1,229 U/L, respectively, indicative of mild systemic myotoxicity. This is the first report of myotoxic manifestation in the envenomation by *M. hemprichii*. No patient developed respiratory failure, though one bitten by an adult *M. spixii* required intubation and mechanical ventilation due to decreased level of consciousness during evolution, probably related to induced sedation caused by concurrent alcohol intoxication. All patients were treated with Brazilian *Micrurus* antivenom (*soro antielapídico*, median = 10 vials). Six patients were pretreated intravenously with H1 and H2 antagonists and steroids, with two patients developing early adverse reactions. The median length of hospital stay was four days. Envenomations by coral snakes in Manaus region are clinically severe, but rare and sparsely distributed over time, making the detection of epidemiological and clinical patterns a challenge for public health.

1. Introduction

In Brazil, the only representatives of the family Elapidae are the coral snakes (genera *Micrurus* and *Leptomicrurus*) (Silva Jr. et al. 2016). Coral snakes inhabit a wide range of habitats, from tropical forests to open dry areas, and from undisturbed areas to disturbed crops and pastures, including urban areas in large cities (Martins and Oliveira 1998, Campbell and Lamar 2004, Marques et al. 2009, Bernarde 2014, Almeida et al. 2016). They cause a rather little number of envenomations in the country, about 1%

each year (SINAN 2020, Bucaretchi et al. 2016a), due a combination of factors: non-aggressive behavior, fossorial habits, tiny fangs, small mouth gape, and small amount of venom they can yield and inject (Melgarejo 2009, Gutiérrez et al. 2016). Although it is thought that they need to "chew" to inject venom, quick bites can also deliver an amount of venom enough to cause serious envenomations (Morgan et al. 2007, Pardal et al. 2010). In Brazilian Amazonia, seven species of coral snakes, all in the genus *Micrurus*, were found causing human envenomations. Coral snakebites in the Amazonia correspond to only 0.05%, most of them in open spots of the biome and in urban areas, mostly affecting adult males (Bisneto et al. 2020).

Micrurus venoms have neurotoxic action, which is responsible for most of the clinical manifestations, and myotoxic and mild edematogenic effects (Vital Brazil and Fontana 1984, Vital Brazil 1987, Barros et al. 1994, de Roodt et al. 2012, Gutiérrez et al. 2016, Greene 2020). Myotoxic manifestations are related to the increase in plasma levels of creatine kinase and myalgia (Bucaretchi et al. 2016a, Greene 2020). Recent reports demonstrated that in some cases, thrombocytopenia, coagulopathy and electrocardiographic alterations may also be present (Manock et al. 2008, Heckmann et al. 2017, Mota-da-Silva et al. 2019). Neurotoxic manifestations include paresthesia, pain, palpebral ptosis, dizziness, ophthalmoplegia (and visual disturbances related to both, like blurred vision and diplopia), muscular weakness, dyspnea, dysarthria, dysphagia, difficulty to walk, drooling and respiratory failure, which is the main cause of death (Bucaretchi et al. 2016a, Bucaretchi et al. 2016b, Bisneto et al. 2020, Greene 2020). Although rare, severe neuroparalytic manifestations may be of early appearance, meaning the patient may need ventilatory support within minutes (Pardal et al. 2010). On the other hand, those same symptoms may take hours to manifest, regardless of other manifestations (Kitchens and Van Mierop 1987). This possibility often makes health professionals to automatically classify all coral snake envenomation as severe and use the highest antivenom (AV) dosage recommended. Until recently, this was the case in Brazil. But aiming to avoid the waste of antivenom, a new classification with appropriate use of AV in each case has been proposed (Brasil 2001, Brasil 2014, Bucaretchi et al. 2016b).

Until a few years ago, data coming from Brazilian Amazonia has been limited to a few case reports, but new epidemiological data from the *Sistema de Informação de Agravos de Notificação* – SINAN (Brazilian Information System of Notifiable Diseases) started to fill gaps in the knowledge about this burden in the region (Bisneto et al. 2020). However, SINAN database does not contain precise data about clinical conditions of the patients, information about the snakes, precise geographical location of the bites, adjunctive treatments and other information useful to evaluate more precisely specific cases. In this study, we aimed to use information from hospital records from a referral health center in Brazilian Amazonia to describe ecological, epidemiological, and clinical characteristics of coral snake envenomations in Manaus region, Brazilian Amazonia.

2. Material and Methods

2.1. Study area and design

This study includes coral snakebites admitted to the hospital *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado* (FMT-HVD). FMT-HVD is the referral hospital in the Amazonas state for the treatment of envenomed patients, most of them bitten by venomous snakes and stung by scorpions in Manaus and surroundings. FMT-HVD maintains a scientific collection of animals, including offending venomous and non-venomous snakes brought by the patients to the hospital. This study was approved by the Ethical Committee of the FMT-HVD (approval number 713.140/ 2014).

Manaus is the capital of the Amazonas state, northern Brazil, located in the Central Amazonia. Its metropolitan zone comprises the municipalities of Autazes, Careiro, Careiro da Várzea, Iranduba, Itacoatiara, Itapiranga, Manacapuru, Manaquiri, Novo Airão, Presidente Figueiredo, Rio Preto da Eva and Silves. The population in the area is estimated in 2.67 million inhabitants in 2019 (IBGE 2019) in an area of 127,287.789 km^2 (IBGE 2018) (Figure 1). The weather is seasonal, with a dry season spanning from May to October and the rainy season from November to April, with an annual rainfall index around 2,300 mm and an average annual temperature of 27 °C (INMET 2020).

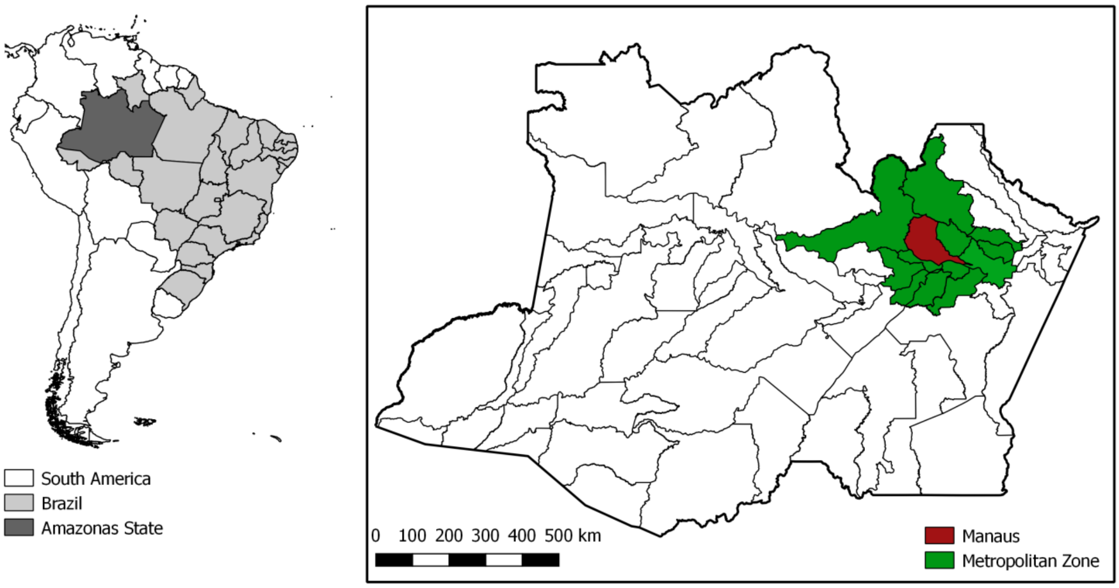

Fig. 1: Location of Amazonas state and metropolitan zone of Manaus in the context of South America.

2.2. Data collection and classification of the cases

We performed a search in the FMT-HVD records, looking for medical charts related to coral snakes envenomations in the period of study. Perpetrating snakes were dissected, in search of information about sex and diet, and we measured their snout-vent length (SVL) with a measuring tape (±0.1 cm accuracy). We retrieved information on the medical charts about the conditions involved in each case (time of day, month and year, if the patient tried to handle the snake or if it was an accidental bite and if there was use of drugs or alcohol), geographical location, zone (urban or rural), age and sex of the patient, pre-hospital historic, treatment given, adverse reactions to treatment, clinical manifestations, laboratorial tests, and outcome of the case. The single case by

Micrurus averyi was described by Mendonça-da-Silva et al. (2018) and was used only in ecological and epidemiological data.

We classified the cases both in probability and severity. Cases were classified as a) confirmed: when the snake responsible for the bite was identified, regardless of the symptoms presented by the patient; b) suspect: when the patient did not bring or photograph the snake, but showed clinical features associated to *Micrurus* spp. snakebites, such as local paresthesia, local pain, palpebral ptosis, blurred vision, skeletal muscle weakness, inability to walk, or superficial (shallow) breath/dyspnea; c) doubtful: when the snake was not identified neither the patient presented any symptom related to envenomation by coral snakes (Casais-e-Silva & Brazil, 2009). Doubtful cases were excluded from the analyses. We classified the severity of the cases following Rosenfeld (1971) and Brazilian Ministry of Health (2014) as a) dry-bites: without envenomation; b) mild: local symptoms only; c) moderate: beyond local manifestations (that may be absent), acute myasthenia without paralysis; d) severe: acute myasthenia with signs of intense muscle weakness, such as paralysis, including signs of respiratory distress.

3. Results

3.1. Frequency of coral snakebites and biology of the perpetrating specimens

A total of 3688 cases of snakebites were found, from 1979 to 2018. Of those, we found 26 cases of bites by coral snakes (25 confirmed and one suspect) that were included in the epidemiological analyses. Twenty-three snakes could be found in the collection and were included in biological and ecological analyses. Seven cases (six confirmed and one suspect) could be described based on the medical charts that could be found. For the cases where medical charts were not found, only the data present in the book of records in the collection were recovered, so we could not describe them in clinical details. The 26 cases represent 0.7% of all snakebites treated in the hospital in the period of study. We also found three doubtful cases where the patient received antivenom against coral snake.

Five species were involved in the confirmed cases: *Micrurus averyi, M. hemprichii, M. lemniscatus, M. spixii* and *M. surinamensis* (Figure 2). Among those, *M. lemniscatus* was involved in almost half of the cases (10), *M. hemprichii* in five, *M. spixii* and *M. surinamensis* in three cases each, and *M. averyi* in one case (reported in Mendonça-da-Silva et al. 2018). The difference among sexes was almost non-existent (eight males and nine females). Six individuals could not be sexed (Table 1). In two confirmed cases caused by the same animal, the snake was identified as *Micrurus* sp. both in the book of records and in the medical charts (cases 5 and 6), but the specimen could not be found.

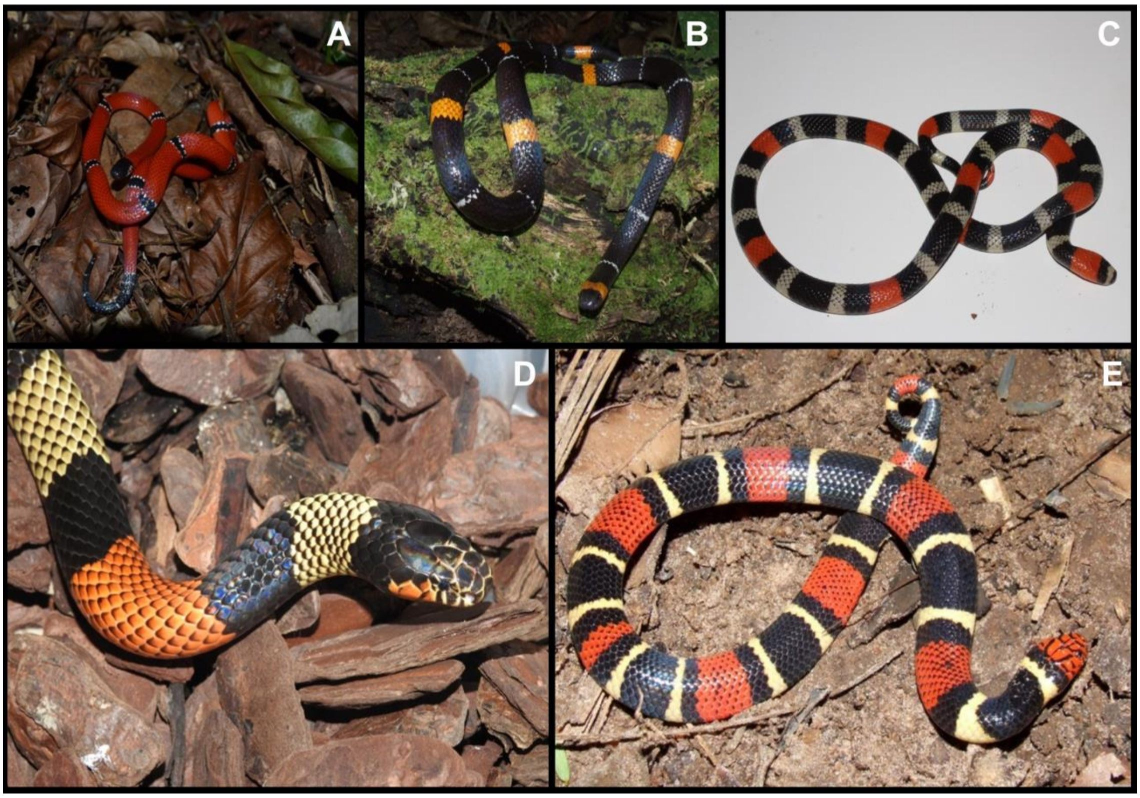

Fig. 2: The species of coral snakes involved in envenomations in Manaus region. A: *Micrurus averyi*; B: *M. hemprichii*; C: *M. lemniscatus*; D: *M. spixii*; E: *M. surinamensis*. Credits: A: Gabriel Masseli; B, D and E: Paulo Sérgio Bernarde; C: Pedro Bisneto.

Only two individuals had food remains in the gut, one containing the remains of a squamate, another containing an ant, possibly from secondary digestion from a lizard prey. The largest individual was an unsexed *M. spixii* (1160 mm SVL) and the smallest was a female of *M. lemniscatus* (190 mm SVL) (Table 1).

Table 1: Ecological data of specimens of *Micrurus* responsible for snakebites in Manaus region, Brazilian Amazonia.

Case	**Specimen**	**Sex**	**SVL (mm)**	**Zone of procedence**	**Food content**
1	*M. averyi*	Male	390	Urban	No
2	*M. hemprichii*	Female	323	Rural	Squamate
3	*M. hemprichii*	Male	694	Rural	No
4	*M. hemprichii*	Female	375	ND	No
5	*M. hemprichii*	Male	555	ND	No
6	*M. hemprichii*	ND	308	Rural	No
7	*M. lemniscatus*	Female	860	Rural	No
8	*M. lemniscatus*	ND	235	Urban	No
9	*M. lemniscatus*	ND	ND	Urban	No
10	*M. lemniscatus*	Male	475	ND	No
11	*M. lemniscatus*	Male	640	Urban	No

12	*M. lemniscatus*	Female	620	Urban	No
13	*M. lemniscatus*	Male	500	Rural	No
14	*M. lemniscatus*	ND	ND	Urban	No
15	*M. lemniscatus*	Female	190	Urban	No
16	*M. lemniscatus*	Female	610	Urban	No
18	*M. spixii*	ND	1160	Rural	Ants
19	*M. spixii*	Male	840	Rural	No
20	*M. spixii*	Female	910	Rural	No
21	*M. surinamensis*	Male	620	Urban	No
22	*M. surinamensis*	ND	ND	Urban	No
23	*M. surinamensis*	Female	440	Urban	No

Abbreviations: ND: not determined. SVL: snout-vent length. SVL measures were taken only from individuals without any missing part of the body. Data used only for the 23 specimens found in the collection.

3.2. Annual and seasonal distribution of the snakebites and sex of the patients

The 26 cases reported from 1987 to 2018 represented an average of one case about each 14 months. Most of the years passed without cases or with just one case each. The peak in the number of cases was from the middle 1990s to middle 2000s (Figure 3A).

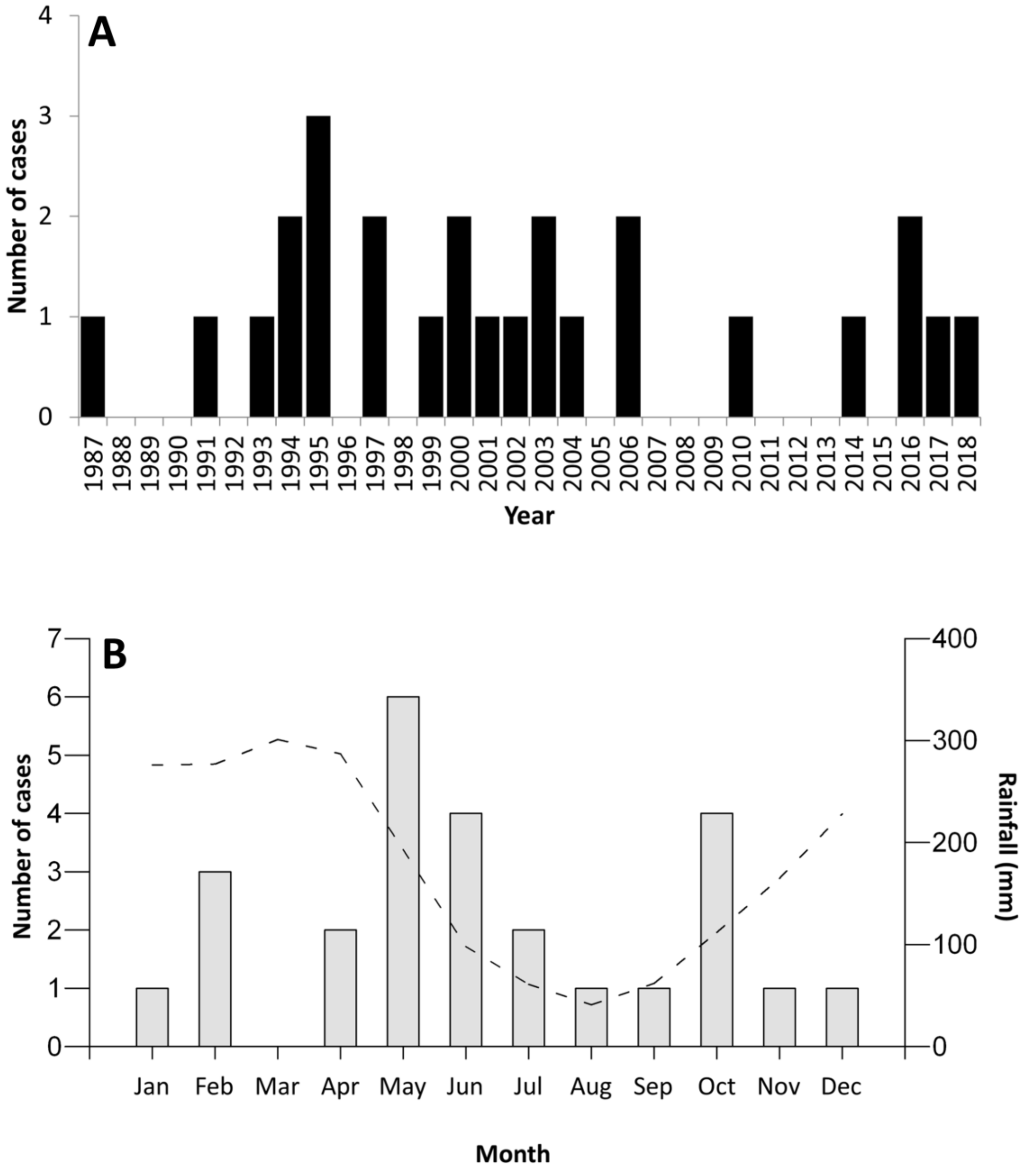

Fig. 3: Annual (A) and monthly (B) distribution of patients bitten by venomous coral snakes admitted at *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*, Manaus, Brazil. Vertical bars represent number of cases, and dashed line represents mean monthly rainfall. Rainfall data retrieved from Leopoldo et al. (1987).

Eighteen cases occurred in the dry season (May to October), and eight in the rainy season (November to April). The months with the highest number of cases were May, June and October. About half the bites occurred between April and July. Bites were not reported in March (Figure 3B). Of the 23 patients whose sex could be determined, 16 were males and seven were females.

3.3. Geographical distribution of the snakebites

Among the cases, one lacked the origin, and one occurred in the state of Pará, without further description of the location. In the metropolitan zone of Manaus, envenomations were distributed in three municipalities: Manaus (20 cases), Rio Preto da Eva (two cases) and Presidente Figueiredo (two cases). *Micrurus hemprichii* and *M. spixii* caused bites only in rural zone, while all cases of *M. surinamensis* and all but one cases of *M. lemniscatus* occurred in urban zone (Figure 4). The single case of *M. averyi* occurred in urban zone (see Mendonça-da-Silva et al. 2018). All cases where the exact address or geographic location in urban zone could be recovered occurred near or within forest fragments. Of the 21 cases whose locality is known, 15 occurred in urban zone and six occurred in rural.

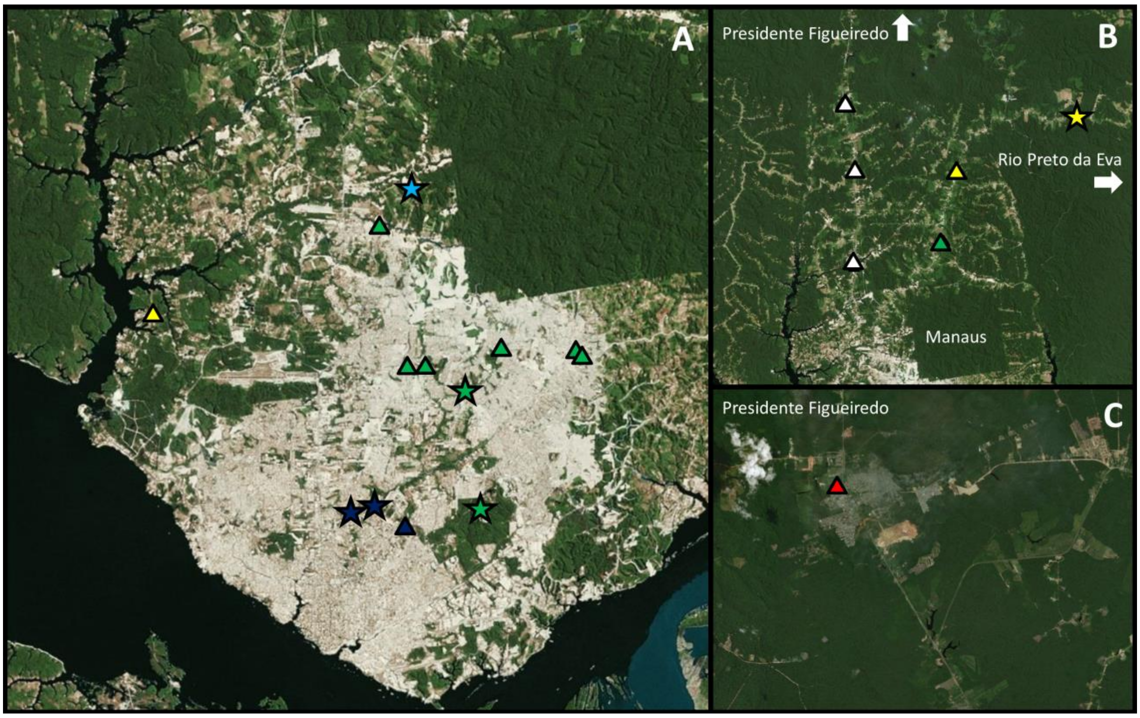

Fig. 4: Geographical distribution of confirmed snakebites by coral snakes in Manaus region. A: Satellite view of the urban zone of Manaus. B: View of adjacent areas of Manaus, including the two main roads exiting from it: AM-010 to the east (going to Rio Preto da Eva) and BR-174 to the north (going to Presidente Figueiredo). Directions of both municipalities are given by the arrows. C: View of Presidente Figueiredo. Colors refer to species responsible for each case: dark blue: *Micrurus surinamensis*; green: *Micrurus lemniscatus*; light blue: *Micrurus* sp.; red: *Micrurus averyi*; white: *Micrurus spixii*; yellow: *Micrurus hemprichii*. Triangles represent approximate locations of the cases. Stars represent exact locations. The light blue star represents a double envenomation caused by the same snake (see cases 5 and 6 in section 3.4).

3.4. Case series

A summary of the seven cases described here is given in Table 2. Among these seven cases, one was caused by *Micrurus lemniscatus*, two by *M. hemprichii*, one by *M. spixii* (Figure 5), two by *Micrurus* sp. and one was suspect (the snake was not brought to the hospital or photographed to be identified). Alcohol ingestion was involved in three of the cases, intentional manipulation of the snake in two, and one case was work-related. Two cases evolved with late systemic neurological manifestations, three evolved with early systemic neurological manifestations and two showed no systemic neurological manifestation. In all cases, local manifestations were present. They include bleeding, edema, erythema, paresthesia and pain (both local and radiated). Paresthesia, pain and edema were the most common local symptoms, present in six, five and four cases, respectively. Patients from cases 1 and 3 showed progressive edema. In case 1 extending from the right hand to the elbow joint. Two patients showed mild myotoxic manifestations (slight increased levels of blood creatine kinase). Other systemic clinical features and laboratory changes detected included abdominal pain, blurred vision, chest pain, diplopia, difficulty to stand, difficulty to walk, dizziness, dysarthria, dysphagia, dyspnea/shallow breathing, headache, leukocytosis, lowering of the level of consciousness, nausea, pneumopathy, palpebral ptosis, somnolence, thrombocytopenia, vomiting and weakness. The most common systemic symptoms were dyspnea/shallow breath (four), palpebral ptosis (four), blurred vision (three), dysarthria (three) and difficulty to walk (three). The patient of case 3 showed some of these symptoms, but his pre-admission history suggests caution in interpreting these manifestations (see Table 2 and section 4.3.).

All patients received *Micrurus* antivenom (*soro antielapídico bivalente*, Instituto Butantan, São Paulo, Brazil, Fab'2). Five received 10 vials, one received 15 vials and one received 5 vials (mean = 10 vials). One of these patients received 10 vials of AV against *Bothrops*, due local symptoms presented and lack of the specific antivenom. Two patients developed early adverse reaction for AV, including one of the patients that received only *Micrurus* antivenom. Four cases were classified as severe and three as mild. The median length of hospital stay was four days.

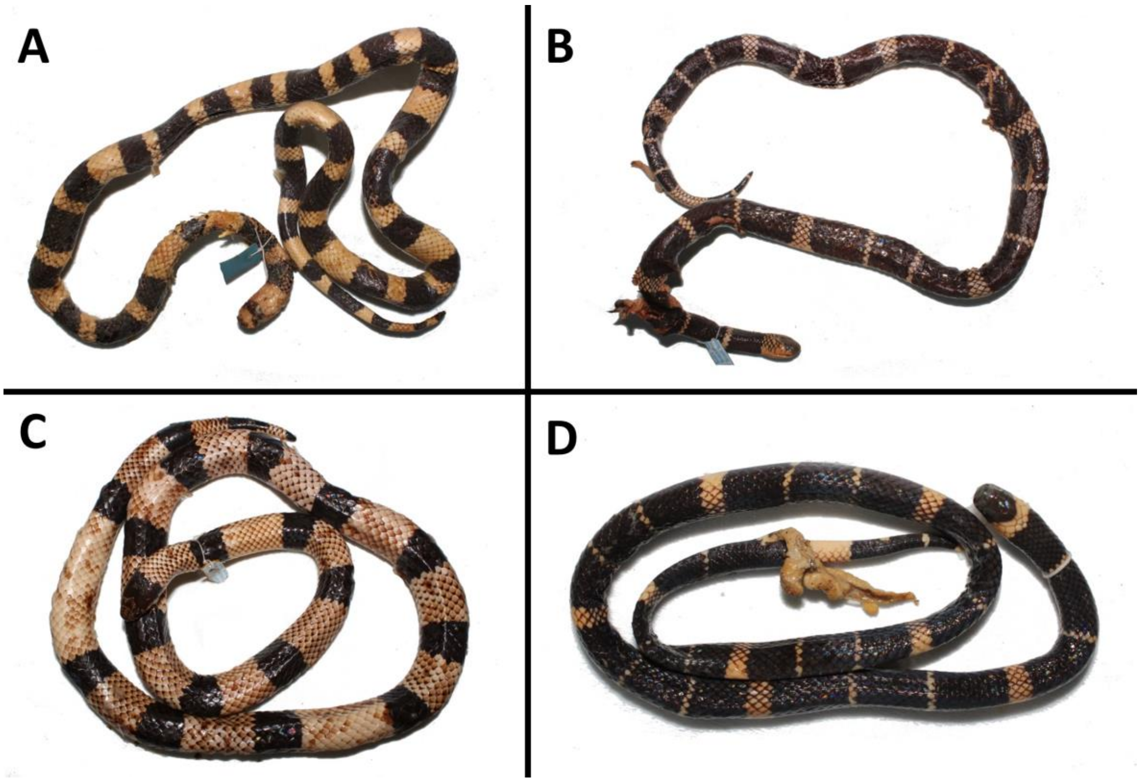

Fig. 5: Preserved specimens responsible for confirmed cases of envenomations by coral snakes admitted at *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*, Manaus, Brazil, that were clinically described in this study. A: *Micrurus lemniscatus* responsible for envenomation in case 1. B: *M. hemprichii* responsible for envenomation in case 2. C: *M. spixii* responsible for envenomation in case 3. D: *M. hemprichii* responsible for envenomation in case 4.

Table 2: Summary of cases of envenomation by coral snakes attended in *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado* (FMT-HVD) in Manaus, Brazil, for which clinical data was available.

Number of case, local, date and hour	Snake data	Clinical history and treatment	Reported effects	Time from bite to first signals	Classification
Case 1: Manaus; 30th April 1994; 7 p.m.	*Micrurus lemniscatus*; female; 860 mm of SVL	48-year-old male, *pardo*, logger, bitten on the right hand. Admitted in the hospital fifteen hours after the bite. Received PrTr, 10 vials of SAB and further 5 vials of SAE. Developed EAR against the AV, received further H1 antagonists and adrenaline. Blood and urine tests normal. Discharged after five days without complications.	**Local:** Edema; Erythema; Pain; Radiated pain **Systemic:** Abdominal pain; Blurred vision; Chest pain; Diplopia; Difficulty to walk; Dysarthria; Dyspnea/ shallow breathing; Palpebral ptosis; Somnolence	**Local:** few minutes **Systemic:** 15 h	Confirmed; severe

Case 2: Manaus; 19th June 1995; 8 p.m.	*Micrurus hemprichii*; male; 694 mm of SVL	49-year-old female, *parda*, farmer, bitten on the left heel. Made use of traditional medicine (scraping of *Jatropha curcas*). Admitted in the hospital one hour and forty five minutes after the bite. Received PrTr and 5 vials of SAE. Developed serious EAR (dyspnea and tachycardia), and the use of AV was suspended. After use of steroids, further 10 vials of SAE were administrated. Blood and urine tests normal. Discharged after four days without complications.	**Local:** Bleeding; Pain; Paresthesia **Systemic:** Blurred vision; Headache	**Local:** just after bite **Systemic:** 4 h 45 min	Confirmed; mild

Case 3: Manaus; 15th May 2006; 10 a.m.	*Micrurus spixii*; female; 910 mm of SVL	48 year-old male, *pardo*, logger, drinking alcohol, bitten on the right thumb while trying to grab the snake, with intense blood loss in the site. Admitted in the hospital seven and half hours after the bite, showing local manifestations and drunk. Received PrTr, Captopril and 10 vials of SAE. Presented a drop in the level of consciousness and was sedated and intubated in the ICU. Thrombocytopenia (platelets count= 36,000/mm^3) and leucocytosis (WBC= 12,000/mm^3) were also detected. Mucous secretion was aspirated from the upper respiratory tract. After 3 days he was extubated and treated with antibiotic due to clinical suspicion of aspiration or nosocomial pneumonia. Discharged after 11 days without further complications.	**Local:** Bleeding; Edema; Paresthesia **Systemic:** Abdominal pain*; Leucocytosis; Lowering of the level of consciousness*; Palpebral ptosis*; Thrombocytopenia	**Local:** just after bite **Systemic:** 12 h 30 min	Confirmed; mild**

Case 4: Rio Preto da Eva; 24th April 2014; 2 p.m.	*Micrurus hemprichii*; unsexed; 308 mm of SVL	18 year-old male, unknown race, military from the army, bitten on the left middle finger while manipulating dead leaves in a military basement. Admitted in the hospital 45 minutes after the bite. Received PrTr, anticholinergic drug and 10 vials of SAE. Showed slight increased CK serum level (1,229 U/L). Discharged after one day without complications.	**Local:** Edema; Erythema; Paresthesia **Systemic:** Mild myotoxicity	**Local:** 45 min **Systemic:** 5 h***	Confirmed; mild
Case 5: Manaus; 28th May 2016; late afternoon	*Micrurus* sp.; same specimen responsible for case 6	14 year-old male, *pardo*, unknown occupation (P5). Since the early morning was drinking with the patient of case 6 (P6). Both men later ate and slept until late afternoon, when P5 stepped on a coral snake and was bitten on the right big toe. He went to a nearby hospital and later transferred to FMT-HVD, where he arrived about one and half hour after the bite. Received PrTr and 10 vials of SAE. Blood and urine tests normal. Discharged after one day without complications.	**Local:** Pain; Paresthesia; Radiated pain **Systemic:** Difficulty to stand up and to walk; Dysarthria; Dyspnea/ shallow breathing; Palpebral ptosis; Weakness	**Local:** 1h 45 min*** **Systemic:** 1h 45 min***	Confirmed; severe

Case 6: Manaus; 28th May 2016; late afternoon	*Micrurus* sp.; same specimen responsible for case 5	23 year-old male, *pardo*, unknown occupation (P6). Pre-envenomation history similar to P5. After the snake bit P5, P6 tried to grab the animal and was bitten on the left thumb. He went to a nearby hospital and later transferred to FMT-HVD, where he arrived about one and half hour after the bite. Received PrTr and 10 vials of SAE. Showed slight increased CK serum level (1,184 U/L). Discharged after one day without complications.	**Local:** Pain; Paresthesia; Radiated pain **Systemic:** Difficulty to stand up and to walk; Dysarthria; Dyspnea/ shallow breathing; Increased levels of blood creatine kinase; Palpebral ptosis; Weakness	**Local:** 1h 45 min*** **Systemic**: 1h 45 min***	Confirmed; severe
Case 7: Presidente Figueiredo; 27th December 2018; in the morning	The snake was not taken to hospital, described or photographed.	42 year-old female, unknown race, retired, bitten on the left hand in a waterfall bathing area. Was taken to the local hospital where she received 10 vials of SAE. Was transferred by ambulance to FM-HVD. Blood and urine tests normal. Discharged after five days without complications.	**Local:** Edema; Erythema; Pain; Paresthesia **Systemic:** Blurred Vision; Chest Pain; Dizziness; Dysphagia; Dyspnea/ shallow breathing; Headache; Nausea; Vomiting	**Local:** few minutes after bite **Systemic:** few minutes after bite	Suspect; severe

Abbreviations: Snake Data: SVL: snout-vent length. **Clinical history and treatment:** AV: antivenom; CK: creatine kinase; EAR: early adverse reactions; PrTr: pretreatment i.v. before AV infusion: H1 (promethazine or dexchlorpheniramine) and H2 (cimetidine or ranitidine) antagonists, and steroids (hydrocortisone); SAB: *soro antibotrópico pentavalente,* Instituto Butantan, São Paulo, Brazil; SAE: *Micrurus* antivenom (*soro antielapídico bivalente*, Instituto Butantan, São Paulo, Brazil, Fab'2); WBC= white blood cells. *Symptoms possibly related to alcohol ingestion; **Severity classification based on the uncertainty of the envenomation-related clinical condition due to the pre-admission history; ***Time estimated when exact times of the first symptoms were not reported in the medical charts.

4. Discussion

4.1. Frequency of envenomations and biological aspects

Since the earliest studies, it was clear the low incidence of envenomations by coral snakes in Brazil. The low frequency (usually about 1%) is found not only in the country as whole, but in regional or local studies, within or outside the Amazon region (Feitosa et al. 1997, Borges et al. 1999, Nascimento 2000, Vilar et al. 2004, Moreno et al. 2005, Bucaretchi et al. 2006, Casais-e-Silva & Brasil 2009, Bucaretchi et al. 2016a, Oliveira et al. 2018, Bisneto et al. 2020). However in some cases, this number could be overestimated due to confusion with many genera and species of harmless “false” coral snakes (*e.g.*: *Anilius scytale, Apostolepis, Atractus latifrons, Erythrolamprus aesculapii, Oxyrhopus*, *Phalotris, Phimophis, Pseudoboa*) that mimicry the color, and sometimes behavior of the “true” coral snakes (Almeida et al. 2016). In cases when patients describe a red, white and black snake, or even bring the animal to the hospital, where health professionals are not always able to identify the species, AV may be unnecessarily used.

Among the species of coral snakes found in Manaus region, the five species responsible for the cases are the most commonly found (Martins & Oliveira 1998, Fraga et al. 2013, Masseli et al. 2019). All of them are known for causing envenomations in humans (Pardal et al. 2010, Bucaretchi et al. 2016a, Mendonça-da-Silva et al. 2018, Roriz et al. 2018). In the scientific collection of FMT-HVD, most of the specimens kept are of *M. lemniscatus*. It is also the most common coral snake in Manaus region and is known for being more prone to bite when handled than other species of *Micrurus* (Martins & Oliveira 1998). The higher frequency of this species within the genus and its behavior may explain why it is the main cause of bites in Manaus area. In studies on snakebites where biological data about the snakes are used, usually there is a bias towards one of the sexes, usually associated with reproductive factors (Arbolea et al. 1999, Medeiros et al. 2010, Risk et al. 2016). In our study, unlike the finds of Risk et al. (2016) for Southeast Brazil, we found no differences among sexes of the snakes responsible for those bites. However, the low number of sexed snakes could explain that, and these results should be treated carefully. The mean sizes of each species responsible for the bites, plus the generally big size of the smallest individuals we measured (bearing in mind that this is a group that seldom grows more than one meter long) may be the reflex of the difficulty that the youngest/smallest individuals have to open their mouths wide, puncture their tiny fangs through the skin and inject a minimum amount of venom.

4.2. Epidemiological and ecological aspects

Despite the high diversity of coral snakes in Brazil, and particularly in Amazonia, most of the previous studies on the subject were performed on case reports (eg, Pardal et al. 2010, Mendonça-da-Silva et al. 2018, Mota-da-Silva et al. 2019). Although useful and with merits on their own, it is not possible to detect patterns about epidemiological aspects related to envenomations by coral snakes, hence the importance of addressing the problem more broadly.

The low frequency of bites reflects in a series of sparsely arranged cases, where in most of the years no case was reported. In comparison, during the rainy season, when most of snakebites are attended in FMT-HVD, up to 3 cases of snakebite by *Bothrops* can arrive in the hospital in a single day (*personal observation*). The population in the area was estimated in 820,087 inhabitants in 1980 and in 1.19 million inhabitants in 1991, around the time when the first records began (IBGE 1983, IBGE 1991). During the years when there was the peak of cases (Figure 3), Manaus almost doubled its population, from 1.01 million inhabitants in 1990, to 1.80 million in 2010 (IBGE 2010). This urban expansion meant that many areas of native forest were cut down and invaded for housing construction, not always in an orderly manner. This phenomenon possibly meant greater contact of people with snakes. Snakebites seasonal pattern in Amazonia is strongly associated with the rainy season (Feitosa et al. 2015a, Alcântara et al. 2018). This is attributed to increase in prey availability or rising levels or the rivers, pushing these animals closer to human contact (Oliveira & Martins 1998, Borges et al. 1999, Moreno et al. 2005, Alcântara et al. 2018, Oliveira et al. 2018). Interestingly, as we found here, a previous study reported that snakebites by coral snakes in Amazonia seem to occur more often in the dry season (Bisneto et al. 2020). As in other studies, males are the most affected group, probably because they are more at risk due work-related activities developed in areas where the snakes are more easily found (Wen et al. 2015, Alcântara et al. 2018, Oliveira et al. 2018, Santos et al. 2019, Bisneto et al. 2020), but other factors may play a role in this particular type of snakebite: coral snakes are colorful, and their coloration draw attention of people unaware of the danger they pose, like children and people under influence of alcohol or other drugs, or when they are wrongly identified as a harmless "false" coral snake (Kitchens & van Mierop 1987, Abo et al. 2018, Strauch et al. 2018). Three of our cases, in which alcohol ingestion was involved, illustrate this phenomenon. Besides that, as seen in both cases 5 and 6 and in literature, alcohol ingestion may lead to situations where people show behavior that may lead to multiple envenomation (Bucaretchi et al. 2019). Unlike other studies that show that most of snakebites occur in the rural area (de Roodt et al. 2013, Wen et al. 2015, Alcântara et al. 2018, Oliveira et al. 2018, Santos et al. 2019), our data clearly shows not only a concentration of cases in urban area, but that there was a clear division between geographical zones among most of the species (Figure 5). *Micrurus lemniscatus* and *Micrurus surinamensis* are known to inhabit disturbed areas in the largest cities in Amazonia, Manaus and Belém (Almeida et al. 2016). Both species also inhabit many types of microhabitats, being aquatic, semiaquatic (in the case of *M. surinamensis*), cryptozoic, terrestrial, fossorial, and even aquatic (in the case of *M. lemniscatus*) (Martins & Oliveira 1998). The ability to live in such environments, plus their adaptability to disturbed areas means that they can be found closer to people, posing more risk inside the urban area. *M. hemprichii* and *M. spixii* are considered snakes typical of forested areas (Martins & Oliveira 1998, Masseli et al. 2019), and although we have found a few of the *M. spixii* in the collection coming from urban areas, most of them, and all of *M. hemprichii*, come from forested areas. This suggests that there are habitat preferences and tolerances that are reflected in the distribution of the bites caused by them. The cases in the urban area occurred near forest fragments, indicating that coral snakes are usually close to forested areas, and that people living or working near them are more likely to encounter these animals.

4.3. Clinical aspects

Micrurus venoms are a complex cocktail of toxins, mainly composed by Phospholipases A2 (PLA_2) and three-finger toxins (3FTx) (Alape-Girón et al. 1996, Correa-Netto et al. 2011, Sanz et al. 2019). These groups of toxins are the main responsible by clinical manifestations presented by the patients bitten by these animals. Our results showed that pain and paresthesia are the most common local symptoms, which also has been reported in the literature (Kitchens and Van Mierop 1987, Bucaretchi et al. 2006, de Roodt et al. 2013, Bucaretchi et al. 2016a; Bisneto et al. 2020, Greene 2020). Among systemic manifestations, the most common are related to neurotoxic activity, including palpebral ptosis, dizziness, weakness, vision disorders (like diplopia and blurred vision), dyspnea, inability to walk and myasthenia (Bucaretchi et al. 2016a), all of whom were present in the cases we described. Myotoxic manifestations are related to myotoxic activity in the venoms of many species of coral snakes, like *Micrurus hemprichii, M. lemniscatus* and *M spixii* (Gutiérrez et al 1992, de Roodt et al 2012). They manifest as an increasing in the levels of blood CK (Bucaretchi et al. 2016a). In species from Central and South America, this increase is only slight, but two cases reported for the eastern coral snake (*M. fulvius*) in Florida showed rhabdomyolysis (levels of CK of 7,000 U/L and 18,000 U/L), in addition to severe paralysis (Kitchens and Van Mierop 1987). For Amazonian species, only *Micrurus lemniscatus* have previously been associated to myotoxic manifestations (Manock et al. 2008). Here, we were able to report two further cases in the region with patients showing increased levels of CK: one bitten by a *M. hemprichii* (case 4, being the first case for the species with such manifestation), and another one bitten by an unidentified species of *Micrurus* (case 6). Case 6 occurred in urban zone, in a housing development possibly not inhabited by the forest dweller *M. hemprichii* (Martins & Oliveira 1998). The only two species of snakes that caused envenomations in the urban zone were *M.*

lemniscatus and *M. surinamensis* (see section 3.3). *M. surinamensis* does not show myotoxic activity (Gutiérrez et al. 1992), so it is probable that the responsible for that double envenomation was a *M. lemniscatus*.

Leukocytosis and thrombocytopenia were observed in this study and have been previously reported in envenomation by *M. lemniscatus helleri* in Ecuador (Manock et al. 2008), while thrombocytopenia also was observed in an envenomation by *M. annellatus bolivianus* in the state of Acre, Western Brazilian Amazonia (Mota-da-Silva et al. 2019). Leukocytosis is interpreted as signal of early inflammatory response, while thrombocytopenia may be result of the action of C-type lectins found in the venoms of some species of *Micrurus* (Manock et al. 2008). C-type lectins are platelet-agglutinating toxins found in the venoms of some groups of snakes (Gartner & Ogilvie 1984), and although found in low concentrations in most of Brazilian *Micrurus*, some species in Amazonia showed high concentrations of this toxin. This means that this toxin can play a role in the envenomations (Aird et al. 2017).

The proportion of adverse reactions in patients treated with the *Micrurus* antivenom observed by us was similar to that found in another study for the State of São Paulo, in Brazil (Bucaretchi et al. 2006). Both studies comprised a low number of patients (seven in this and 10 in the study in São Paulo), so the proportion should be taken with care. Both studies saw only early manifestations, but we found more serious manifestations (dyspnea and tachycardia), even with use of premedication. Health professionals should watch more carefully the appearance of these symptoms to avoid a worsening in clinical condition in patients already at risk of suffering neurological manifestations. In two of the cases, systemic neurological manifestations were observed many hours after the bite (seven and fifteen hours). Both patients evolved to severe clinical condition, and one had to be intubated. Although the patient described as case 3 needed mechanical ventilation due to important lowering of the level of consciousness, his pre-admission history (the patient was admitted at the hospital drunk, uncooperative, agitated, disoriented and hypertensive), the use premedication with sedative side-effects (H1 and H2 antagonists and captopril) and the presence of only local symptoms related to envenomation (see Table 2) suggest a mild envenomation whose clinical course was due to factors not associated with the envenomation itself. Patients bitten by coral snakes should seek medical help and be kept on observation for at least 24 hours, even if they do not show any sign at all, once late symptoms still can evolve to severe manifestations (Kitchens and Van Mierop 1987). Medical help also should be searched for as fast as possible, in face of early appearance of the same systemic manifestations (Pardal et al. 2010). Administration of the AV is the recommended treatment for snakebite, with anticholinesterase drugs being very useful in some severe cases caused by species whose venoms are rich in postsynaptic neurotoxins (Bucaretchi et al. 2016a). Case 2 illustrates the use of traditional medicine used by local people. These products, in addition to being unhelpful in the treatment, can worsen the local condition and can delay the arrival at the hospital, worsening the prognosis, a delay that could be fatal (Feitosa et al. 2015b).

With the new classification proposed in Brazil for the treatment of bites by coral snakes, the number of vials for mild, moderate and severe cases was changed to zero, five and 10 vials, respectively (Brasil 2014). Older cases followed the former classification, which classified all cases as severe and instructed health professionals to use 10 vials of AV (Brasil 2001). The number of cases without paralytic manifestations shows that bites by coral snakes are not always severe, and that the use of 10 vials of AV in this series of cases was not always necessary. Besides that, there is no inherent risk in withholding the use of AV in patients with asymptomatic or mild cases until the first systemic signals start to manifest (Wood et al. 2013). In the case where AV against *Bothrops* was used, its use was justified for the medical team because of the lack of AV for *Micrurus* available at the time when the patient arrived, and to fight the local symptoms. However, local symptoms from *Bothrops* bites vary significantly from those of *Micrurus* (Oliveira et al. 2018): this AV does not act on systemic manifestations, and its use could mean that a patient bitten by a *Bothrops* could go without treatment. Further, the patient in question developed early adverse reaction against the antivenom, as already reported in other cases (Pardal et al. 2004, Mendonça-da-Silva et al. 2017, Alves et al. 2018). These cases indicate that such approach should be avoided at all costs. The same can be said about the use of AV in bites by harmless “false” coral snakes. Without the identification of the perpetrator animal (either by picture or bringing it to the hospital), or the appearance of neurological manifestations related to envenomation by coral snakes, the case should be considered a “dry bite” (bite without envenomation) or a bite by a harmless snake, without unnecessary use of AV.

Studies about envenomation by coral snakes are difficult to deal with because so few cases occur and can be reported. Although we present new data that is relevant to the study of envenomation by coral snakes in Brazilian Amazonia, some limitations are present in this study. Clinical and epidemiological data could be recovered from only a few cases we know to have occurred in the study area, making it difficult to explain some of our findings. We do not know, for example, why, unlike other kinds of snakebites, envenomations by coral snakes occur more often in urban zone and in dry season. We also cannot explain if the lack of relationship between these envenomations with work-related activities was due the absence of such association or if it was influenced by our relatively restricted number of observed cases. The total influence of human behavior (alcohol ingestion or snake handling), ecological aspects (the exact location of many of the bites reported and landscape configuration at the time of the bites), and the clinical aspects (symptoms and their proportions in total of cases, treatment given and outcome) cannot be fully understood given the limited available data.

5. Conclusions

Envenomation by coral snakes in Manaus region is rare and sparsely distributed over time. Unlike other kinds of snakebites, the urban area is more affected, and species of *Micrurus* living in urban zone are more likely to be a cause of such event. Alcohol ingestion is not an overriding factor, but can lead to dangerous behavior that may put more than one person in danger or confuse the diagnosis. Most of the cases were clinically severe, with serious systemic manifestations developing either in few minutes or many hours after the bite. Antivenom administration must follow the most recent protocols established by the Brazilian Ministry of Health and the diagnosis should be based on the confirmed identification of the snake or on the appearance of manifestations typical of envenomation by coral snakes. For the first time, increased level of blood creatine kinase was reported for envenomation by *Micrurus hemprichii*. Further studies in other medical centers might help to fill in the knowledge about this type of burden in the Amazon region.

Ethical statement

The current study was approved by the Ethical Committee of the *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado* (approval number 2014/713.140). The study used only medical records and specimens deposited in a scientific collection. No human subjects were recruited during the research and no data in the manuscript allows the identification of any patient, respecting the rights of privacy.

CRediT authorship contribution statement

Pedro Ferreira Bisneto: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Investigation, Visualization. **Bruno dos Santos Araújo:** Investigation. **Handerson da Silva Pereira:** Investigation. **Iran Mendonça da Silva:** Investigation, Writing - original draft, Writing - review & editing. **Jacqueline de**

Almeida Gonçalves Sachett: Resources, Writing - original draft, Writing - review & editing, Project administration. **Paulo Sérgio Bernarde:** Writing - original draft, Writing - review & editing. **Wuelton Marcelo Monteiro:** Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration, Supervision, Funding acquisition. **Igor Luis Kaefer:** Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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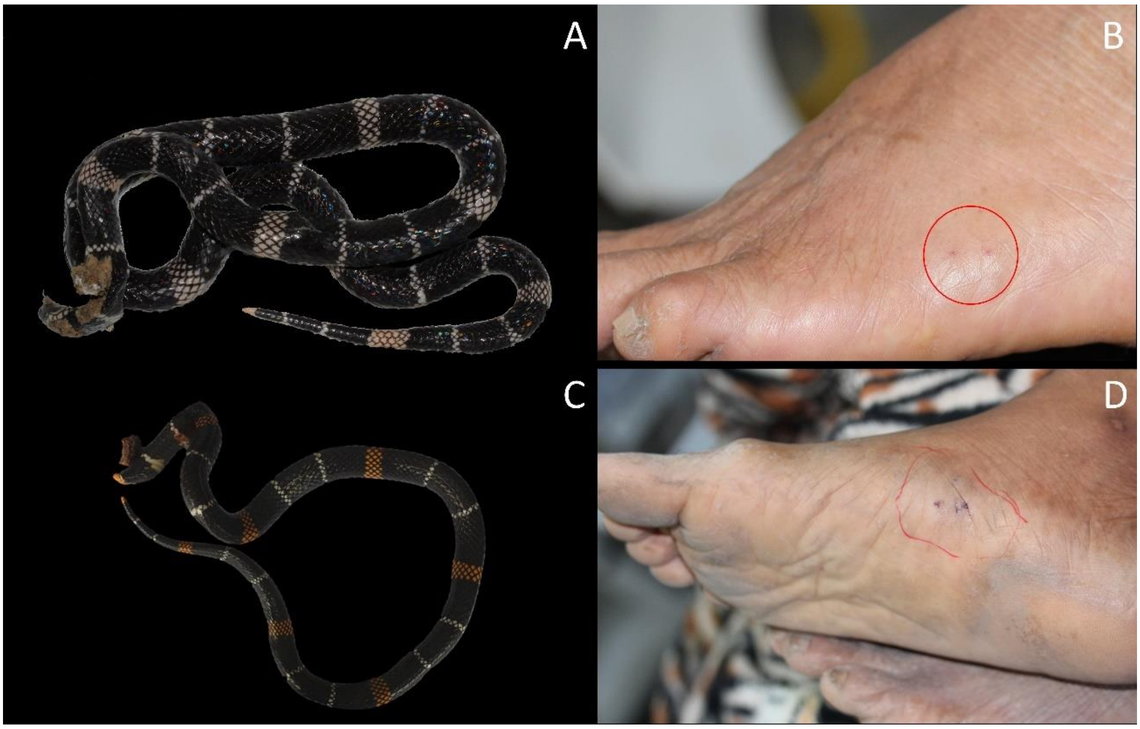

CAPÍTULO 3

Bisneto P. F., Pereira H. S., Sachett J. A. G., Kaefer I. L, Monteiro W. M.. **Envenomation by *Micrurus hemprichii* in Brazilian Amazonia: a report of two cases**. Manuscrito em preparação para a Revista da Sociedade Brasileira de Medicina Tropical.

Envenomation by *Micrurus hemprichii* in Brazilian Amazonia: a report of two cases

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Running title: Envenomation by *Micrurus hemprichii*

Abstract: We report two separate new cases of human envenomations by *Micrurus hemprichii* for Amazonia, a biome where envenomations by *Micrurus* are seldom reported. Two women were bitten after stepping on the snakes in peridomicile, rural areas. The first case evolved mainly to local symptoms, but the patient was discharged before the identification of the snake and had to be called back for observation before being discharged. The second case presented dyspnea and was discharged after four days in hospital. Cases like these show the importance of knowing local venomous snakes in order to provide a correct hospital conduct.

Keywords: Coral Snakes. Elapidae. Snakebites.

Introduction

Envenomations by coral snakes are uncommon, but can be severe and potentially lethal (1,2). Although these snakes can be found in all Brazilian territory, most of the cases are reported from the most populated areas in southeastern region (1). Amazonia contains the largest number of species, yet very few cases are reported there (1,3–6). Case series show that *Micrurus lemniscatus* is the main species involved in envenomations in Brazilian Amazonia, but other species of medical importance include *M. averyi, M. bolivianus, M. filiformis, M. hemprichii, M. spixii* and *M. surinamensis*

(4,5), and some of these species can live sympatrically in the Amazonian biome (7,8). *Micrurus* are seldom seen in relation to other snakes, in both pristine and anthropically-disturbed areas (4,6).

Less than 1% of the snakebites reported in Brazil are related to coral snakes (1,2). This is usually associated with a combination of relatively small body size, burrowing habits, low level of aggressiveness, small fangs and small gape of mouth (1,2). In Brazil, the frequency of envenomation by coral snakes is lower in Amazonia compared to other regions, and envenomations are highly spaced over time (4,5). Confusion with false corals (harmless mimicking species) can also make diagnosing *Micrurus* envenomation difficult (9).

Manifestations can progress severely in a short time, requiring intubation and mechanical ventilation (1,2,6). A variety of local and systemic symptoms have been described in envenomations caused by different species of *Micrurus* (1,2), and the symptomatology for many species in Midwestern, Northeastern and Southeastern Brazil are relatively well known (9). However, for several species, especially in Brazilian Amazonia, there are only a few reported clinical cases and additional reports are necessary to evaluate clinical, biological and toxinological aspects (5,9), thus allowing comprehensive studies and medical applications. This is the case for *Micrurus hemprichii* (Jan, 1858), the species involved in the cases described here.

This study was performed in accordance with the Helsinki Protocol and was approved by the Ethical Committee of the *Universidade do Estado do Amazonas* (approval number 713.140/2014).

Case reports

Case 1: On 3rd June 2021, a woman, *parda* (with mixed ethnic ancestry), 59 years old, resident of the *Ramal Santo Antônio*, rural area of Manaus, Brazil (Figure 1A; B), was at home, about 10 p.m., moving to the bathroom outside the residence, situated in an area near the forest, when she accidentally stepped on a male *Micrurus hemprichii* (Figure 2A) with a snout-vent length (SVL) estimated in 690-700 mm due to head damage. The snake bit the dorsolateral region of the left foot of the woman, leaving fang marks (Figure 2B). The victim reported that the snake bit and released. After the bite, she reported local numbness, which extended to the lower part of the thigh, after 30 minutes. Her family took her immediately to the *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado* (FMT-HVD), the reference hospital in Manaus, where she arrived three hours later. Upon arriving at the hospital (at about 1 a.m.) the patient showed pain, hyperaemia, paresthesia, lymphocytopenia (percentage of lymphocytes = 15%) and leukocytosis (leukocyte count = 13570 /mm^3). Blood tests were otherwise normal, and she received only pain relievers. As the patient had only local symptoms and the snake was not immediately identified as a coral snake, she was discharged from the hospital in the morning (about 11 a.m.). After the correct identification of the animal, the patient was asked to return on the same day to the hospital to stay in observation. Upon returning, the patient reported only local pain, cold sensitivity and hyperaemia. After a few hours under observation, the patient was discharged without use of antivenom or complications. The manifestations presented classified the case as mild (2).

Case 2: On 19th April 2022, a woman, *parda*, 43 years old, resident of the *Ramal do Pau Rosa*, rural area of Manaus (Figure 1A; C), situated in an area surrounded by forest, was cooking at home about 6:30 p.m. She was leaving the cooking table, located on the ground floor outside the house, when she accidentally stepped on a male *Micrurus hemprichii* (Figure 2C) with a SVL estimated between 642-650 mm due to head damage. The snake bit once the lower right side of the right foot, leaving fang marks (Figure 2D). Tourniquet was used. She reported having felt local numbness immediately and arrived at FMT-HVD three hours later, showing erythema at the bite site, intense pain (eight or nine on a scale of ten) radiating to the waist, muscle tremors in the body, especially in the limbs, numbness in the whole leg and irradiated edema to the upper leg, that gradually decreased until disappearing on the third day of hospitalization. In the first day of hospitalization, she presented dyspnea. She received ten vials of antivenom for coral snakes about four hours after the bite, hydrocortisone, pain relievers and diazepam. In the first and second days of hospitalization, the patient had lymphocytopenia (percentage of lymphocytes = 16.1% and 8%, respectively). Other blood parameters were normal. The pain gradually decreased until 22nd April, when the patient was discharged without complications. The manifestations presented classified the case as severe (2).

The snakes were deposited as voucher specimens in the FMT-HVD scientific collection (Case 1: FMT-HVD 4311; Case 2: FMT-HVD 4317).

Discussion

Two cases of envenomation by *Micrurus hemprichii* are reported here. *Micrurus hemprichii* is considered a strictly-forest species, thus uncommon in urban zones (7,8). Both cases occurred in areas surrounded by forest. In Manaus, an ecological difference in coral snake envenomations has been reported: species adapted to urban areas typically cause bites there, while specialist forest-dwelling taxa such as *M. hemprichii* are involved in cases from forested areas (4).

In Brazil, most of the rare cases of bites by coral snakes are attributed to *M. corallinus*, *M. frontalis* and *M. lemniscatus* (1,4). However, 15 species from Brazil are considered of greater medical importance, based on the probability of causing human envenomations (9). Among the species from Amazonia, *Micrurus hemprichii* is included in that list, based on its large distribution, number of cases reported and possibility of severe manifestations (3,4,9). Manifestations caused by this species include classic neurotoxic symptoms, such as vomiting, pain, paresthesia and blurred vision (1,3–5). A recently described case also presented a slight increase in blood levels of creatinine kinase, evidence of mild myotoxic envenomation (4). Creatinine kinase exams are not necessarily routine in victims of coral snake bites, but the fact some species in the region, including *M. hemprichii*, have venoms with myotoxic activity (10) or are known to cause this manifestation (2) indicates that this exam should be part of the routine care for this type of patient.

Case 1 showed only local manifestations, restricted to the affected limb, that lasted only a few hours. In Brazil, a significant part of the cases of coral snake envenomation is considered as mild (1,2). Currently, the Ministry of Health protocol classifies coral envenomations in three categories: mild, moderate or severe. Only the last two should receive antivenom, and mild cases should be treated only symptomatically (2). The manifestations related to severity, indicative of paralysis, can manifest more than 12 hours after the bite (4,11). Because of that, it is important to keep the victim under observation for at least 12 hours, regardless of symptoms (1,2,4). Victim of case 1 was discharged from the hospital because the medical team was unable to identify the snake, since many harmless species mimic coral snakes (9), and also because the patient did not show any systemic manifestation at arrival. Only after the snake was taxonomically identified as a *Micrurus*, the patient was called back to the medical center. On the other hand, severe manifestations can be of early appearance (2,4,6). Patient of case 2 arrived in hospital already showing dyspnea and in need of receiving the maximum amount of antivenom required for envenomation by *Micrurus* in Brazil (2).

Correct identification of snakes involved in envenomations might avoid irrational use of antivenom, as in the case of a bite by a harmless snake or using the correct dosage according to the severity of the case. It will also avoid incorrect medical procedures, such as in case 1. Species identification is especially difficult when dealing with mimicry systems composed by *Micrurus* and several other non-venomous snakes genera. On the other hand, people living in areas with higher risk of snakebites should get encouraged to adopt preventive measures to minimize the risk of bites, adopt proper first-aid actions and, when possible, facilitate species identification of the specimen involved in the case [e.g., through photographs or use of field guides (12)], thus allowing a taxonomic-informed medical assistance.

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Conflict of interest

None.

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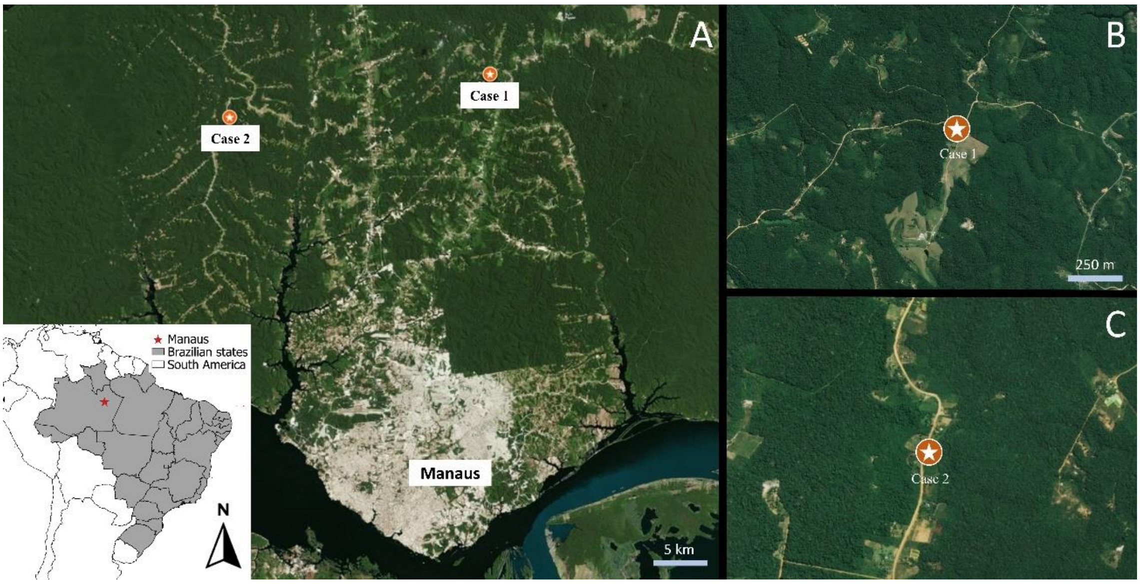


Figure 1: City of Manaus in the context of South America and satellite view of the area of reported cases. Location of cases is approximate. A: General view of Manaus and surroundings. B: Detail of the area of case 1. C: Detail of the area of case 2. Note the extensive forest cover in the areas of both cases.

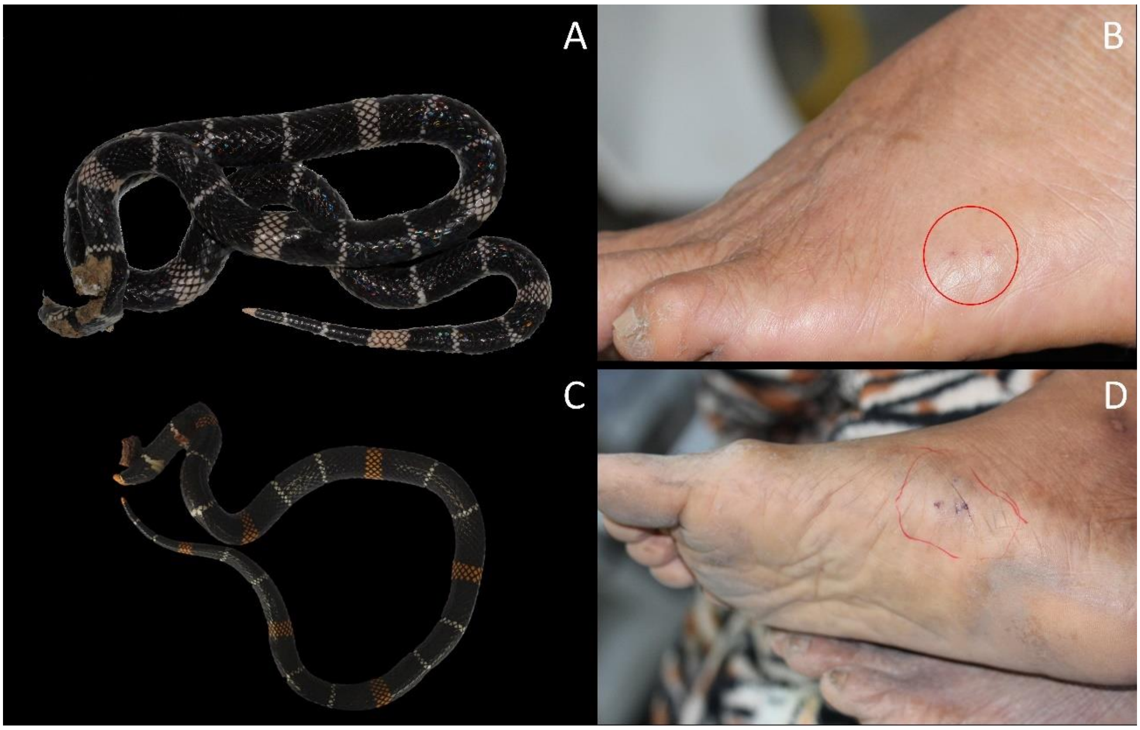
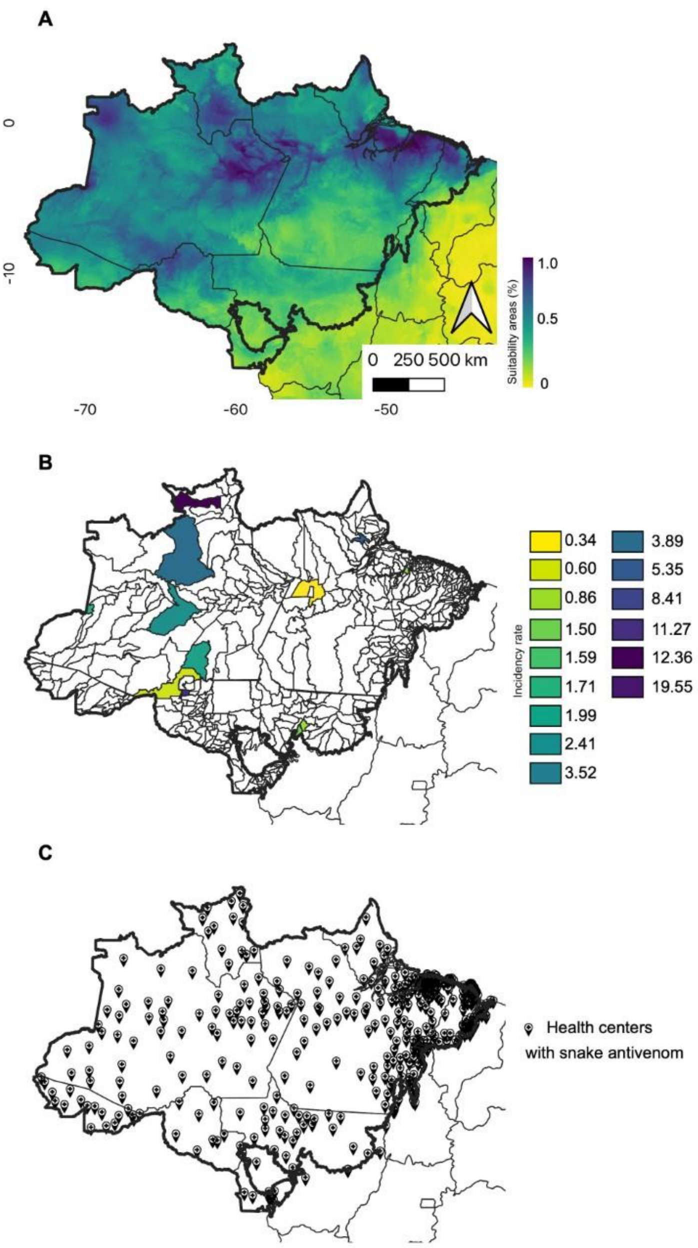


Figure 2: Snakes involved in the cases and bite sites. A: *Micrurus hemprichii* from case 1. B: Bite site of case 1. C: *M. hemprichii* from case 2. D: Bite site of case 2. Fang marks are situated within the red marks.



CAPÍTULO 4

Bisneto P. F., Frazão L., Ceron K., Sachett J., Monteiro W. M., Kaefer I. L., Guedes T. B. **The challenge of detecting risk areas of snakebite when case rates are low: the case of Amazonian coral snakes**. Manuscrito em preparação para a revista Toxicon.

The challenge of detecting risk areas of snakebite when case rates are low: the case of Amazonian coral snakes

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Running title: Risk areas for coral snakebite in Amazonia

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Abstract: Identifying risk areas for human envenomation by animals is relevant for public health policies such as strategic distribution of health centers with availability of antivenoms. Coral snakes are highly diverse in the vast Amazonia, inhabit both pristine and human-modified environments, and the outcome of the clinical condition after accidents tends to be serious and potentially lethal mainly due to neurotoxic effects of its venom. By integrating species' geographical records and environmental variables, we used species distribution modeling to predict the distribution of medically important coral snake species in the Brazilian Amazonia. We also analyzed these results with data on envenomation in the region, in order to propose actions to reduce the number of envenomations by *Micrurus* and to provide tools for better policy of public health. We conclude that i) the entire Amazonia shows high environmental suitability for coral snakes to occur; ii) such high suitability explains little about the incidence of cases in the region. This is probably due to the low human density in Amazonia, but also to coral snake traits such as cryptic habits and kind of defensive behavior. Differently from many other medically-important snake species, the ecological and epidemiological scenario regarding coral snakebites precludes the detection of prominent geographical areas of concern and demands a broad and equitable availability of health centers throughout the Amazonia.

Keywords: Elapidae, Human health, Neglected Tropical Diseases, Ophidism, *Micrurus*, species distribution modeling

1. Introduction

Snakebite envenomation (hereafter SBE) is considered a non-infectious neglected tropical disease that requires urgent funding for research and public policy actions integrating ecological, epidemiological and clinical aspects at wider geographical contexts (Chippaux 2017a, Martín et al. 2022). In Brazil, 430 species of snakes are recorded, of which 70 species (16.27%) are venomous (families Viperidae and Elapidae) (Melgarejo 2009, Costa et al. 2021). Although they represent the minority of species, venomous snakes were responsible for an annual average of ~30,000 snakebites/year. Between 2010 and 2020, the Brazilian Amazonia (hereafter Amazonia) region concentrated 42.6% of snakebites reported in Brazil (SINAN 2022), with 0.6% of case-fatality between 2000 and 2016 (Fan & Monteiro 2018). Given that most of the human displacement in the immense Amazonian territory is done by boats, and the fact that the closest health centers can be hours or days away, a strategic distribution of health centers containing antivenoms for the cases that occur in this region is vital to reduce the chances of human mortality.

Snake antivenoms are considered the only effective treatment against SBE (WHO 2018). In many parts of the world, antivenoms are expensive, scarce and poorly distributed, and countries with difficulties in purchasing and strategically distributing them have the highest mortality (Gutiérrez et al. 2006, Harrison et al. 2009). One of the challenges in addressing the lack of antivenoms involves specifying their requirements at an operational, local level, through the collection of epidemiological data (Chippaux 2017a). An example are the Americas, where in the last decade reporting of SBE for many countries became mandatory, and better epidemiological data became available (Chippaux 2017b). In Brazil, a system for providing antivenom based on epidemiological information was established, according to the estimated demand for each state (CNZCAP 1991, Gutiérrez et al. 2009, Fan & Monteiro 2018). With the advent of this system, there was a considerable decrease in the annual mortality rate resulting from snakebites (Cardoso and Wen 2009).

One of the groups of venomous snakes in the country is represented by the coral snakes (family Elapidae, genera *Leptomicrurus* and *Micrurus*), represented by 38 species widely distributed in the national territory and occurring in all kinds of natural (and sometimes even disturbed) landscapes (Silva Jr. et al. 2016, Costa et al. 2021). In Amazonia, they occur in forested, open and disturbed areas, and at least two species (*Micrurus lemniscatus* and *M. surinamensis*) are found in urban environments (e.g. Martins and Oliveira 1998, Rodrigues et al. 2016, Almeida-Correa et al. 2020). Only 13.3% of the Brazilian population resides in Amazonia, however the states of the region concentrated 42.6% of the snakebites reported for the country between 2010 and 2020 (SINAN 2022). Although coral snakes cause less than 1% of the snakebite accidents in the region, the outcome of the clinical condition tends to be serious: several of the cases reported in Amazonia are considered severe and some of them evolve with early neuroparalytic manifestations (Bisneto et al. 2020a, Bisneto et al. 2020b). In general, symptoms presented by victims bitten by coral snakes in Amazonia include: erythema, pain, paresthesia, numbness, palpebral ptosis, salivation, blurred vision, dysarthria, dysphagia, diplopia, dyspnea and muscular weakness (Bisneto et al. 2020a, Bisneto et al. 2020b).

Amazonia has a long history of land use, especially in the southern/eastern borders (Margulis 2004), and deforestation in the area has been associated with increased risk of snakebites (Ferreira e Ferreira 2020). However, envenomation by coral snakes in Amazonia are rare and sparse amongst long intervals of time, making it difficult to detect epidemiological patterns (Bisneto et al. 2020a). Normally, snakebite risk assessments are based on the relationship between abundance and species richness of venomous snakes related to human aspects, such as population density (Ochoa et al. 2021, Glaudas 2021, Martín et al. 2022). In Latin America, most of the snakes involved in accidents are viperids (*Crotalus* and *Bothrops*), and coral snakes are commonly left out from epidemiological analyses (Yañez-Arenas et al. 2014, Yañez-Arenas et al. 2018). In Amazonia, there are numerous poorly-accessible areas, research centers concentrated in few cities, that along with the secretive (fossorial) life habits of *Micrurus* result in a lack of detailed data on species' ranges, which is known as the Wallacean shortfall (Whittaker et al., 2005). *Micrurus* represents a clear example as the knowledge about species distributions is very incomplete (Terribile et al. 2018, Nogueira et al. 2019).

In recent years, Species Distribution Modeling (hereafter SDM) procedures have been used to predict geographic distribution areas for species (Elith & Leathwick 2009, Peterson et al. 2011, Araújo et al. 2022). In the context of venomous snakes and SBE, this method can be used to predict the distribution of species of medical importance, help planning an adequate antivenom distribution policy, including production logistics, prevention policies and monitoring of risk areas (Yañez-Arenas et al. 2018, Citeli et al. 2020). The use of ecological data is especially relevant when there is a lack of information of the species distribution (i.e., fossorial species), allowing the prediction of species distribution and thus identifying high risk areas of snakes envenoming. The objective of this study is, by integrating updated species' geographical records and environmental variables, to use species distribution modeling to predict the distribution of medically important coral snake species in the Amazonia. We also aimed to analyze these results with data on envenomation in the region, in order to propose actions to reduce the number of envenomations by *Micrurus* and to provide tools for better policy of public health.

2. Material and methods

2.1. Study area

The Amazonian biome (Figure 1) contains the largest tropical forest in the world with ca. 6 million km^2, and almost 60% of its territory lies within the Brazilian border (Coca-Castro et al. 2013). It is characterized by its forest integrity where vegetation is composed mostly of dense ombrophilous forest (IBGE 2012). The climate in Amazonia is hot and wet. The monthly thermal amplitude is low, ranging 2º C along the year. The average rainfall is 2300 mm per year, showing a heterogeneous temporal and spatial distribution, but in most of the region the rainy season occurs between November and March, the dry season between May and September (Figueroa & Nobre 1990, Fisch et al. 1998, INMET 2022). Currently, 47.2% of Amazonia is covered by indigenous territory or protected natural areas (RAISG 2020) (Figure 1B).

Amazonia covers totally or partially municipalities in nine Brazilian states: Acre, Amapá, Amazonas, Maranhão, Mato Grosso, Rondônia, Roraima, Pará and Tocantins (SUDAM 2007, IBGE 2020a). The population in the study area was estimated at 22.39 million people in 2015 (IBGE 2013), of which about a fifth is concentrated within the five largest cities, with a density of 5.60 inhabitants/km² (IBGE 2020b). It is also evident that there is a high concentration of indigenous people due to the abundance of indigenous territories (Figure 1D), which comprise 2,376,140 km², equivalent to 27.5% of the entire biome (RAISG 2020). Since 1970, the main drive of land-use in Amazonia has been expansion of the area devoted to planted pasture (Margulis 2004) (Figure 1B). Other pressures threatening the region include crops, mines, hydroelectric dams and the presence of roads (Margulis 2004, MMA et al. 2007, Lees et al. 2016, Ferrante & Fearnside 2020, Ferrante et al. 2021).

2.2. Target species and occurrence data

It is known that 30 species of two genera (*Micrurus* and *Leptomicrurus*) of coral snakes are found in Amazonia (Silva Jr. et al. 2016b, Costa et al. 2021, Silva Jr. et al. 2021). However, in Brazil, only those species of the genus *Micrurus* are known to have caused envenomation in humans (Bisneto et al. 2020b). We considered in our study those species of *Micrurus* with at least one point occurrence inside the limits of the Amazonia (Fig. 1); those species with at least 20 point records distant ~3 km from each other (see details below in the species distribution model section); and those with typical forested distribution, i.e., we excluded species from the Cerrado that showed with few records inside Amazonia (e.g. *Micrurus frontalis*).

We obtained occurrence data of species of coral snakes (genus *Micrurus*) (Appendix S1, Supporting Information) from Table S2 provided by Nogueira et al. (2019). These distribution data are based on vouchered specimens examined in natural history museums or obtained from literature records (see Nogueira et al. 2019 for further details). After identifying the species occurring within Amazonia, we expanded the occurrence database of these species beyond the region boundaries using data provided by Nogueira et al. (2019). This approach was used because the better we detail the distribution of species, the better we characterize their climatic niches, thus generating more reliable models (Phillips et al., 2004).

2.3. Species distribution modeling

We performed a Species distribution modeling (SDM) (Guisan and Thuiller 2005) to estimate the geographic distribution of *Micrurus* species based on environmental suitable areas for the species in Amazonia. The SDM uses the association of environmental variables with occurrence data of a species to map their predicted distribution (Guisan and Thuiller 2005).

We obtained 20 variables (being 19 bioclimatic and one of elevation) from the WorldClim database (see http://www.worldclim.org/ for variable descriptions) at a resolution of 5 arc-min (Fick and Hijmans 2017), averaged over the 1970–2000 period. To avoid overprediction and low specificity, we cropped the environmental layers to span from latitude -90 to -30 and longitude -50 to 15 (values in decimal degrees). To reduce autocorrelation among occurrence data and potential for overfitting we eliminated one of each pair of records falling within single grid cells (~3 km) using the package 'spThin' (Aiello-Lammens et al. 2015). To avoid problems related to the multicollinearity of the environmental explanatory variables, we calculated the Variance Inflation Factor (VIF) values for variables to each species. All values that were highly correlated (VIF > 5) were removed through a stepwise procedure, using the 'usdm' package (Naimi 2013). In general, eight variables were selected for the species: mean diurnal range (BIO2), isothermality (BIO3), temperature seasonality (BIO4), mean temperature of wettest quarter (BIO8), precipitation of wettest month (BIO13), precipitation seasonality (BIO15), precipitation of warmest quarter (BIO18) and precipitation of coldest quarter (BIO19) (Appendix S2). The variable most frequently chosen as the most important for each species according to the models was temperature seasonality (BIO4).

We performed species distribution modeling to each *Micrurus* species using nine different algorithms implemented in the 'biomod2' package (Thuiller et al. 2016) in R computational environment (R Core Team 2020) including the following: three regression methods [GAM: general additive model (Hastie and Tibshirani 1990), GLM: general linear model (McCullagh and Nelder 1989), MARS: multivariate adaptive regression splines (Friedman 1991)]; three machine learning methods [GBM: generalized boosting model (Ridgeway 1999), MAXENT: Maximum Entropy (Phillips et al. 2006), RF: random forest (Breiman 2001)], two classification methods [(CTA:

classification tree analysis (Breiman 1984), FDA: flexible discriminant analysis (Hastie et al. 1994)], and one envelope model [SRE: Surface Range Envelop (Booth et al. 2014)]. To meet the criteria of having absence (or pseudo-absence) data for most of these models (except SRE), we generated two equal-sized (to the true presence records) sets of random pseudo-absence (PA) points across the model background (500 PA points in each set). The models were calibrated using 70% of randomly selected data. The other 30% of the data were used for intrinsic model evaluation.

Individual model performance was evaluated using two metrics: true skill statistic (TSS) and the area under the curve of receiver operating characteristics (ROC) implemented in the 'biomod2' package. TSS is calculated as "sensitivity + specificity - 1" and ranges from -1 to +1, where +1 indicates perfect agreement, a value of 0 implies agreement expected by chance, and a value of less than 0 indicates agreement lower than expected by chance. Models with high predictive accuracy (TSS > 0.8) were used for the projection of snakes distribution. We constructed ensemble maps based on the median of two runs of all the selected models in which individual accuracy had TSS value equal to or greater than 0.8. Continuous predictions of ensemble models were transformed into a predicted bivariate map of potential presence versus absence of the species using a threshold approach. Variable importance in the ensemble prediction was evaluated with a permutation procedure (see Thuiller et al. 2016 for details).

2.4. Mapping suitable areas for coral snakes and testing snakebite risk in Amazonia

To characterize the predicted distribution of coral snakes in Amazonia, we created a generalized map of predicted distribution showing the environmental suitability for the genus. The generalized predicted distribution map was made using QGIS version 3.16 (QGIS Development Team, 2020).

To analyze the risk of venomous snakebites caused by *Micrurus*, we constructed a spreadsheet for each Brazilian municipality of the biome containing data on the number of SBE, the value of predicted snake distribution, and human population density (Appendix S3). The data of the SBE in each municipality of Amazonia caused by *Micrurus* were gathered from the Brazilian Ministry of Health, through the *Sistema Nacional de Agravos de Notificação* – SINAN (Brazilian Information System of Notifiable Diseases), considering the period between 2010 and 2015 and selecting the type of snakebite by "coral snake". To avoid possible confusion with bites by "false" coral snakes (non-venomous species that mimic *Micrurus*), we excluded from the analysis cases that could not be associated with coral snake envenoming, following the classification of bites from Casais-e-Silva & Brazil (2009) and Bisneto et al. (2020b). The values of predicted snake distribution were collected automatically, on QGIS (QGIS Development Team, 2020), from a generalized map of predicted distribution (in raster format) using the centroid of each municipality of the Amazonia. The values of population density were obtained from Centro de Dados Socioeconômicos e Aplicações (CIESIN, 2021) also using the centroid of each municipality. We obtained human population density in Amazonia, and the number and incidence rate (given in cases/100,000 inhabitants) of cases.

We tested which variables were related to incidence of Elapidae SBE in Amazonia. For this, we ran the Generalized Linear Models (GLM) using the incidence rate of snakebites as the response variable and the interaction between distribution of Elapidae snakes (i.e., risk) and human population density (CIT) as predictor variables. The model families were selected after inspecting the distributions of the response variables in the diagnostic plots generated in the DHARMa package in the R environment (Hartig, 2022; R Core Team, 2021). The model that best explained the data was the Quasi-Poisson distribution. We ran the GLMs using the glmmTMB package (Brooks et al., 2017) and visualized the results using the package modelsummary (Arel-Bundock, 2020) in R environment (R Core Team, 2021). For spatial visualization and better discussion of our results, we also provided a map of health care centers with snake antivenom. We used the centroid of each municipality of the Amazonia and the list of health care centers with snake antivenom provided by Citeli et al. (2018).

2.5. Ethics statement

This study was evaluated, approved and authorized by the National Research Ethical Committee through the Plataforma Brasil and Ethical Committee of the *Núcleo de Medicina Tropical* of the *Universidade de Brasília* (approval number 1.652.440/2016).

3. Results

3.1. Distribution of coral snakes in Amazonia

We recorded 23 species of *Micrurus* with at least one record in Amazonian limits. After filtering, fourteen species were selected for the SDM (see Target species and occurrence data), totalizing 3,539 occurrences (Figure 1, Appendix S1, S2, S4). Our database of occurrences of coral snakes is uneven. Most records are concentrated around major cities and river channels (Figure 1A). The number of records is also uneven. For example, *M. lemniscatus* has over 1000 records, and many others have hundreds, while species like *M. diutius*, *M. nattereri* and *M. psyches* have less than 100 records (Appendix S2). A few of the species not used in the analyses are known only from the type specimens (e.g. *M. pacaraimae* and *M. tikuna*) (Silva Jr et al. 2021).

Maps for all the species analyzed are available in Appendix S4, Supporting Information. Suitable areas for *Micrurus albicinctus* were concentrated in southwest Amazonia, in the Amazonas/Rondônia/Mato Grosso border, but also south of Rondônia and in most of the Amazonas. *Micrurus annellatus* showed suitability in western Amazonia, mainly in Acre, but also in western Rondônia and southwestern Amazonas. The most suitable areas for *Micrurus averyi* are located in the northern half of Amazonia, mainly in the north of the Amazon river, from western Amazonas, through Roraima to Amapá and eastern Pará to Maranhão. *Micrurus diutius* had greater environmental suitability for the northern half of Amazonia, from the western Amazonas to Maranhão, with a few areas of suitability in western Amazonas. *Micrurus* *filiformis* showed suitability in most of Amazonia, especially in a central corridor from east to west from Acre to Maranhão, following the Amazon river channel and its main tributaries. The suitability areas for *Micrurus hemprichii* were located in most of the Amazonia, specially most of Amazonas, Acre and Roraima, central and eastern Pará, and in the north of the states of Maranhão, Rondônia and Mato Grosso.

Micrurus langsdorffi had greater environmental suitability for the northwestern Amazonia, almost solely in Amazonas, but with suitable areas in western Acre, northern Rondônia and southern Pará. *Micrurus lemniscatus* has a pan Amazonian distribution, with suitable areas being found in almost the entire region, with a few exceptions in Amazonas, Pará and Mato Grosso. For *Micrurus nattereri*, suitability was concentrated in the known area of occurrence, at the northwest end of the Amazonia, with a few patches scattered in the other states, except for Acre. *Micrurus obscurus* showed suitability for the western Amazonia, with many areas without records showing high probability of occurrence, and a few areas of less probability in Pará and Amapá. *Micrurus paraensis* showed suitability in a diagonal area from Maranhão and eastern Pará to Mato Grosso and Rondônia, with areas in the northern Amazonia. Suitable areas for *Micrurus psyches* were in the northern half, mainly in northern Pará, Roraima and Amapá, but also in areas in eastern and central Amazonas. *Micrurus spixii* showed the largest suitable areas among the species analyzed. Almost all the region, but especially northern Rondônia and eastern Pará, showed high suitability for the species. *Micrurus surinamensis* also showed a large suitable area in Amazonia, with an exception in central Amazonas.

3.2. Mapping suitable areas for coral snakes and testing snakebite risk in Amazonia

The general map of predicted distribution indicated areas of suitability for coral snakes in an extensive area in Amazonia (Figure 2A), with a pattern of high suitability toward the east. The highest suitability areas were located in eastern and western Pará, eastern and northwestern Amazonas (with an area in the far west, near the border with Peru and Colombia), northern Maranhão, northern Rondônia (with areas in the south of Amazonas, near the border of both states), and southern Roraima. Areas with medium suitability were found in most of Amazonas, northern half of Pará, northern half of Roraima and good portions of Acre, Amapá and Mato Grosso. Areas of less suitability were found in southern Maranhão, southern half of Pará, open areas in northern Roraima, Tocantins and southern Amazonian regions of Rondônia and Mato Grosso (Figure 2A).

Between 2010 and 2015, twenty cases of SBE by coral snakes were reported for the 772 municipalities in the study area for all states, except the state of Acre. The highest incidence rates were found in the municipalities of Goianorte (Tocantins; 19.55 cases/100,000 inhabitants), Alto Alegre (Roraima; 12.36 cases/100,000 inhabitants), Alto Paraíso (Rondônia; 11.27 cases/100,000 inhabitants) and Presidente Juscelino (Maranhão; 8.41 cases/100,000 inhabitants) (Figure 2B).

We observed no direct relationship between reported SBE cases by *Micrurus* and human population density ($p > 0.05$) (Figure 3). We also did not observe a relationship between reported SBE cases with the interaction between human population density and the risk of snakebites ($p > 0.05$). However, we observed a positive and significant correlation between incidence of Elapidae SBE and the risk of SBE (i.e., suitability value for the presence of Elapidae snakes) ($z = 2.41$, $df = 555$, $p = 0.04$) (Figure 3).

Of the 559 municipalities in the Amazonia, 368 (65.8%) are listed to have health centers with available snake antivenom (Figure 2C). Together, they contain ~18.65 million inhabitants, which represent 83.2% of the population in the area. States with the largest proportional coverage of the population with antivenom were, in decreasing order: Amazonas (98,97%), Pará (96.86%), Roraima (96.8%), Amapá (90.29%), Acre (85.3%), Tocantins (73.18%), Maranhão (68.69%), Rondônia (51.35%) and Mato Grosso (45.82%).

4. Discussion

4.1. Distribution of coral snakes in Amazonia

One of the main goals of this study was to map the predictive distribution of species of coral snakes in the Amazonia. *Micrurus* are mostly small size species (snout-vent length ~1000 mm), with cryptic/fossorial habits, few species were recorded in urban areas, and the chances of encountering and biting humans, even in densely populated areas, are low (Bisneto et al. 2020a, Marques & Sazima 2021, Risk et al. 2021). Of the 38 species of coral snakes in Brazil, 23 occur in the Amazonian biome (Nogueira et al. 2019, Costa et al. 2021, Silva Jr. et al. 2021). However, studies on the distribution and/or composition of species in the area tend to be local or regional (e.g. Prudente et al. 2010, Fraga et al. 2013, Bernarde et al. 2017, Silva et al. 2019), which makes it difficult to characterize the real distribution of the coral snakes. We can point out that *Micrurus lemniscatus* is the most recorded coral snake in Amazonia, and despite its widespread distribution, yet there is a huge gap in its distribution in the southern half of Amazonia, where it certainly occurs. It is also interesting to note that for most of suitable areas of *M. annellatus* there are no occurrence record for the species (Appendix S4, Supporting information) (Nogueira et al. 2019, Silva Jr. et al. 2021).

Large sampling gaps for *Micrurus* are found in several areas, especially in southern Pará, Amapá, southern Rondônia, Roraima and southwestern Amazonas (Figure 1A). Many records are close to major cities (e.g., Manaus, Belém) and rivers (e.g. Madeira, Tapajós). In Amazonia displacement is difficult: frequently there are no roads nearby and many places are days away from the nearest cities, or are in indigenous territory and/or protected areas, whose biodiversity has not been not explored. It is also noteworthy that snakes are inconspicuous animals, difficult to detect and collect (Bernarde et al. 2012, Frazão et al. 2020), especially in densely vegetated tropical forests (Fraga et al. 2014). Small sized and fossorial/semi-fossorial reptiles, such as *Micrurus* have samples biased (largely toward accessible areas and large population centers) or are underassessed (Couto et al. 2007, Bland & Böhm 2016, Tingley et al. 2016). Therefore, some studies may simply not have observed the presence of coral snakes, since low detectability of snakes results in false absences reported by field works (Fraga et al. 2014).

The climatic variables related to the distribution of venomous snake species were mostly associated with temperature and precipitation. Snakes, as ectotherms, should be strongly influenced in distribution by the climate, since temperature directly affects their metabolic activity and tend to be more important to reptile species richness (Qian et al. 2007, Kafash et al. 2020). Precipitation can also play an important role in constraining reptiles activity, distribution and dispersion, (Fraga et al. 2017; Kearney et al. 2018). Climate conditions also seem to modulate daily activity of at least some species of coral snakes. *Micrurus fulvius* has a peak of activity in the early morning and late afternoon, which indicates that this species avoids the warmer parts of the day (Jackson & Franz 1981), while *Micruroides euryxanthus* is active at night on the surface during or after rains (Vitt & Hulse 1973).

The Brazilian notification system for SBE has a history of underreporting issues (Fiszon & Bochner 2008, Wen et al. 2015) related, for example, to failures during the completion of forms by health professionals (Bernarde 2014). In the case of coral snakes, another problem could be related to confusion with false coral snakes (families Aniliidae, Colubridae and Dipsadidae; several genus e.g. *Anilius, Apostolepis, Atractus, Erythrolamprus, Oxyrhopus, Phalotris, Phimophis, Pseudoboa*) which in some cases may be responsible for an over-reporting of bites due to both morphological confusion and the fact that they are more common and cause much more bites than coral snakes (Bucaretchi et al. 2021). On the other hand, the need to filter data as we did in this work means that some cases actually caused by *Micrurus* were left out of the analyses. Another aspect that deserves attention is that of the 14 species analyzed, only half are involved in bites in Amazonia, and only three or four seem to be involved in most of the cases (Bisneto et al. 2020a, Bisneto et al. 2020b). Many species of *Micrurus* may not influence the risk of bites due to being rarer, having a more restricted geographic range or being more sensitive to human disturbance — and therefore coming into less contact with humans.

4.2. Mapping suitable areas for coral snakes and testing snakebite risk in Amazonia

Our potential distribution models showed high TSS and ROC indices (>0.9), indicating a robustness of the constructed maps (Guisan et al. 2017). Our results indicate that the entire Amazonian biome is suitable for the distribution of coral snakes. Areas with the highest suitability for these venomous snakes are located near major cities like Manaus, Belém, Santarém and Porto Velho (Figure 2A). As explained above, this may be due to the tendency of rare animals to be found more frequently near large urban centers. However, there are notable exceptions, such as areas in western and northwestern Amazonas, northern Amapá, southern Roraima and western Marajó island, where urbanization is much more limited. Many species of coral snakes are associated with forests, and are hardly found in deforested or urbanized areas (Martins & Oliveira 1998, Santos-Costa et al. 2015, Bisneto et al. 2020a), and those areas may fit in the ecological requirements of the group, even if poorly sampled. In Maranhão state, areas in Amazonia have been associated with higher suitability for coral snakes compared to more open Cerrado areas (Araújo et al. 2022).

We observed that the potential presence of coral snakes is the only variable that could be associated with risk areas. There was a wide variation in confidence intervals, as a result of which in many areas suitable for the occurrence of coral snakes, bites were not recorded, while in others there was a high incidence of SBE. For SBE, assessments of risk areas range from the probability of encounters between humans and venomous snakes (Yañez-Arenas et al. 2018) to analyzes that use ecological data from snakes and socioeconomic data from humans (Martín et al. 2021, Martín et al. 2022). These analyzes have in common the premise that snakebites are dependent on the frequency of contact between humans and snakes (i.e. where there are more humans and snakes, there are more bites) (Bravo-Vega et al. 2019, Martín et al. 2022). In Maranhão, one of the Brazilian states that compose the Amazonian biome, risk of snakebite had positive and significant correlation with human population density, but viperids had greater weight in the analyses (Araújo et al. 2022). In Brazil, species of this family, especially from the genus *Bothrops*, are known to be frequently found, in addition to adapting well to altered areas, with some species entering the urban zona (Bernarde 2014). Elapids are difficult to assess by these measures because of their low number of cases (Bisneto et al. 2020a).

In general, states from in the area have health care centers with antivenom in most (if not all) of their municipalities, and the distribution of health care centers tends to follow the distribution of municipalities. Most of the municipalities without antivenom available are small (<20,000 inhabitants). A notable case is Rondônia, whose only half of its population lives in municipalities with health care centers. The population of Mato Grosso inside Amazonia is also poorly covered by health care centers. The municipality of Alto Paraíso (Rondônia), had an incidence rate above 11 cases/100,000 inhabitants, however it does not have a health center with antivenom available. It is difficult to access adequate health care in Amazonia: victims of snakebites often seek traditional therapeutic practices or take too long to realize the severity of their cases, which delay or prevent their arrival in health care centers; some of them need to travel for hours/days in various means of transport to reach the health care centers, and not all hospitals officially listed as health centers against snakebites have antivenoms available (Cristino et al. 2021, Salazar et al. 2021). Intensive care units, sometimes needed to assist victims of envenomations by coral snakes, also have low coverage in the area (Bisneto et al. 2020b).

Underreporting of cases or deaths is also a major problem in Amazonia. In some rural areas, most of the victims never reached a health center, so their cases were not reported in the official databases (Salazar et al. 2021). In Brazil, the distribution of antivenoms is based on epidemiological data (Gutiérrez et al. 2009). As a result, decision making regarding the regional distribution of antivenom depends on the number of cases detected by the official surveillance system (Monteiro et al. 2020).

However, cases of coral snakes are rare, it's difficult to obtain epidemiological data from them (Bisneto et al. 2020a). Because of that, at least two states (Acre and Amazonas) have an antivenom distribution policy to provide at least ten vials in each municipality (Deugles Cardoso and Thais Marques, personal communication). Antivenom distribution depends also on the conditions for cold storage and the availability of hospital facilities and proper medical supervision, both unavailable in rural or remote areas of Amazonia. Traditional populations are particularly vulnerable as they are more exposed to bites but have less access to antivenom (Monteiro et al. 2020, Salazar et al. 2021). One option to mitigate these risks is the decentralization of distribution of antivenom, through production of antivenoms that do not require cold storage (Monteiro et al. 2020).

5. Conclusions

Our potential distribution maps are important because they contain geographical information on poorly known venomous snake species in a poorly sampled area. Moreover, our study is pioneer in using data of distribution and SBE of a rare group of venomous snakes to assess risk areas for human envenoming involving these species.

All the Amazonian biome is suitable for occurrence of *Micrurus*, with areas of highest suitability converging to the east. Here, we found that risk areas are those with higher suitability for coral snakes, but this high suitability alone explains very little the low incidence of cases in the region. States in the area have, in general, good coverage of antivenom, but some states should expand their coverage of health care centers to attend to a greater number of inhabitants. Rural and traditional populations are particularly vulnerable due to the unavailability of proper medical care and/or the delay in reaching a health care center. Because of the low incidence of cases and high suitability for coral snakes in Amazonia, antivenom distribution should not be based on epidemiological data, but instead a minimum supply of antivenom against Micrurus should be distributed to all municipalities, including antivenom options that do not require refrigeration for storage.

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Author contributions

Conceptualization: ILK, LF, TBG; **Data curation:** PFB, LF, TBG; **Formal analysis:** LF, TBG; **Funding acquisition:** TBG; **Investigation:** PFB, ILK, LF, KC, TBG; **Methodology:** LF, TBG; **Project administration:** TBG; **Resources:** TBG; **Software:** TBG; **Supervision:** WMM, ILK, TBG; **Validation:** TBG; **Visualization:** TBG; **Writing – original draft:** PFB, ILK, LF, JS, WMM, TBG; **Writing – review & editing:** PFB, ILK, JS, WMM, KC, LF, TBG;

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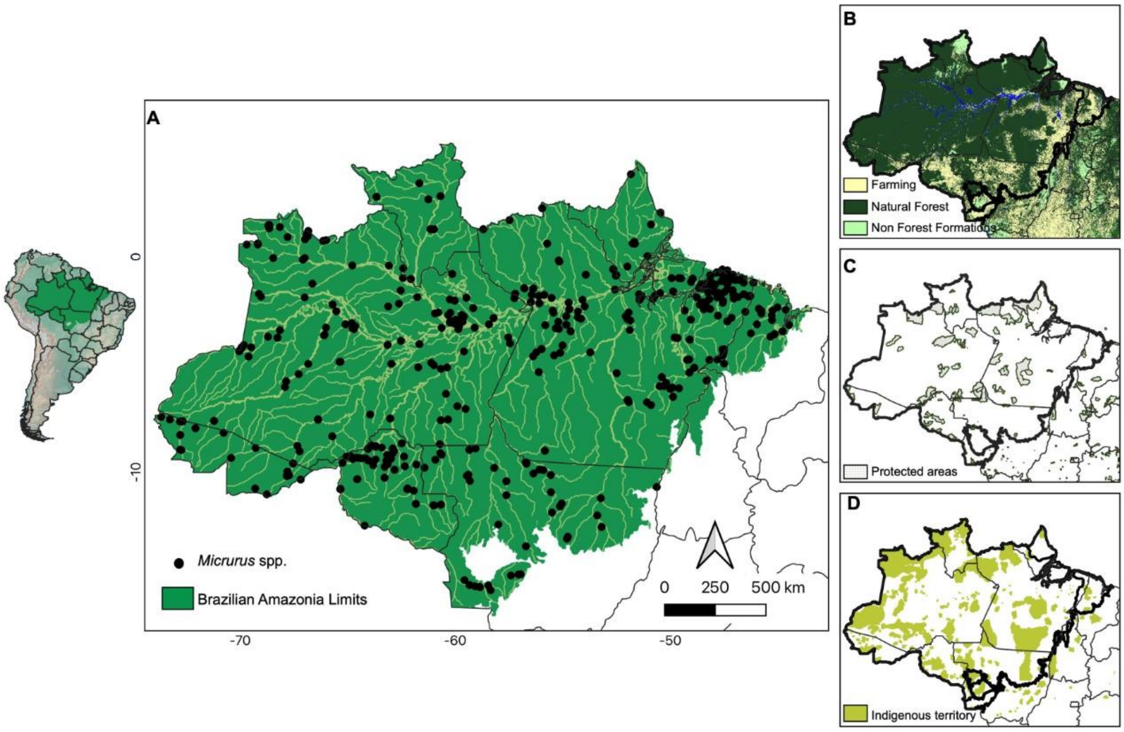


Figure 1: Coral snakes in Amazonia. A. Limits of the Brazilian Amazonia (merged from IBGE 2019 and Eva & Huber 2005), showing the records for the selected species of coral snake (from Nogueira et al., 2019). B. Natural habitat remnants, and land cover changes (collection 4, Souza Jr. et al. 2020, MapBiomas 2021). C. Protected areas (CEM 2021). D. Indigenous territory (Funai 2019).

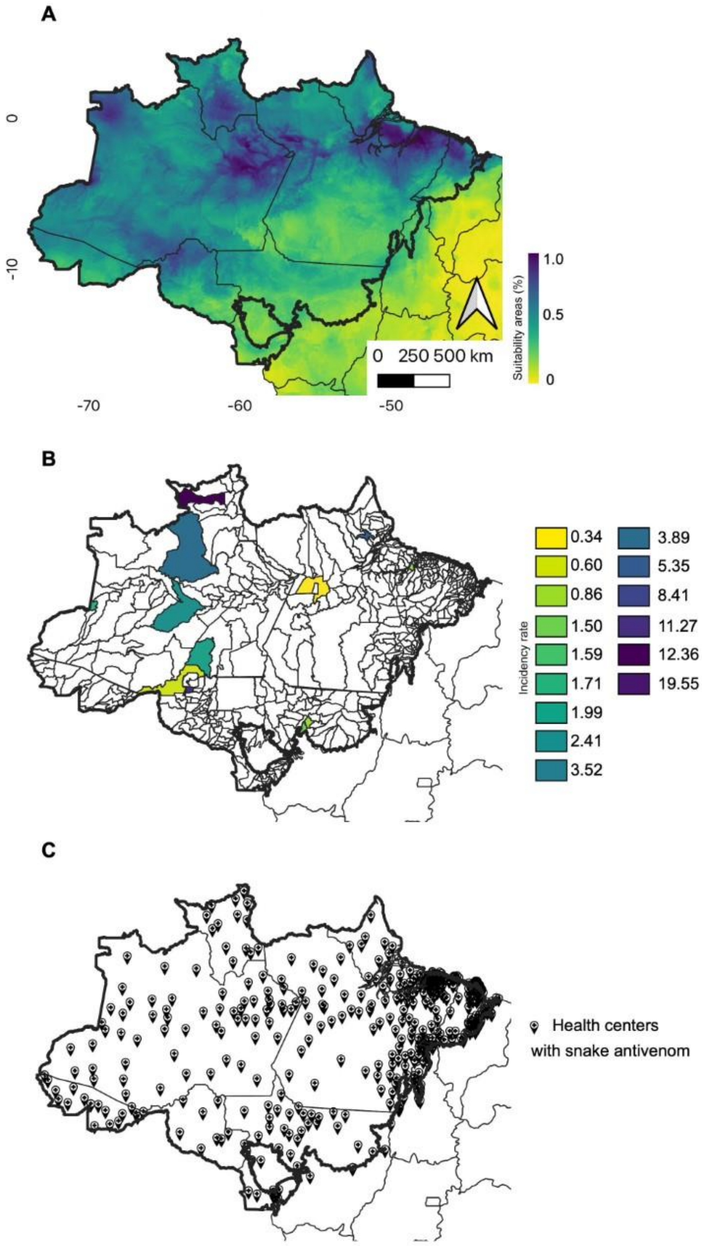


Figure 2: Maps of predicted distribution of coral snakes in Brazilian Amazonia (A), incidence rates among municipalities (B) and distribution of health care centers with antivenom against snakebites in the study area (C).

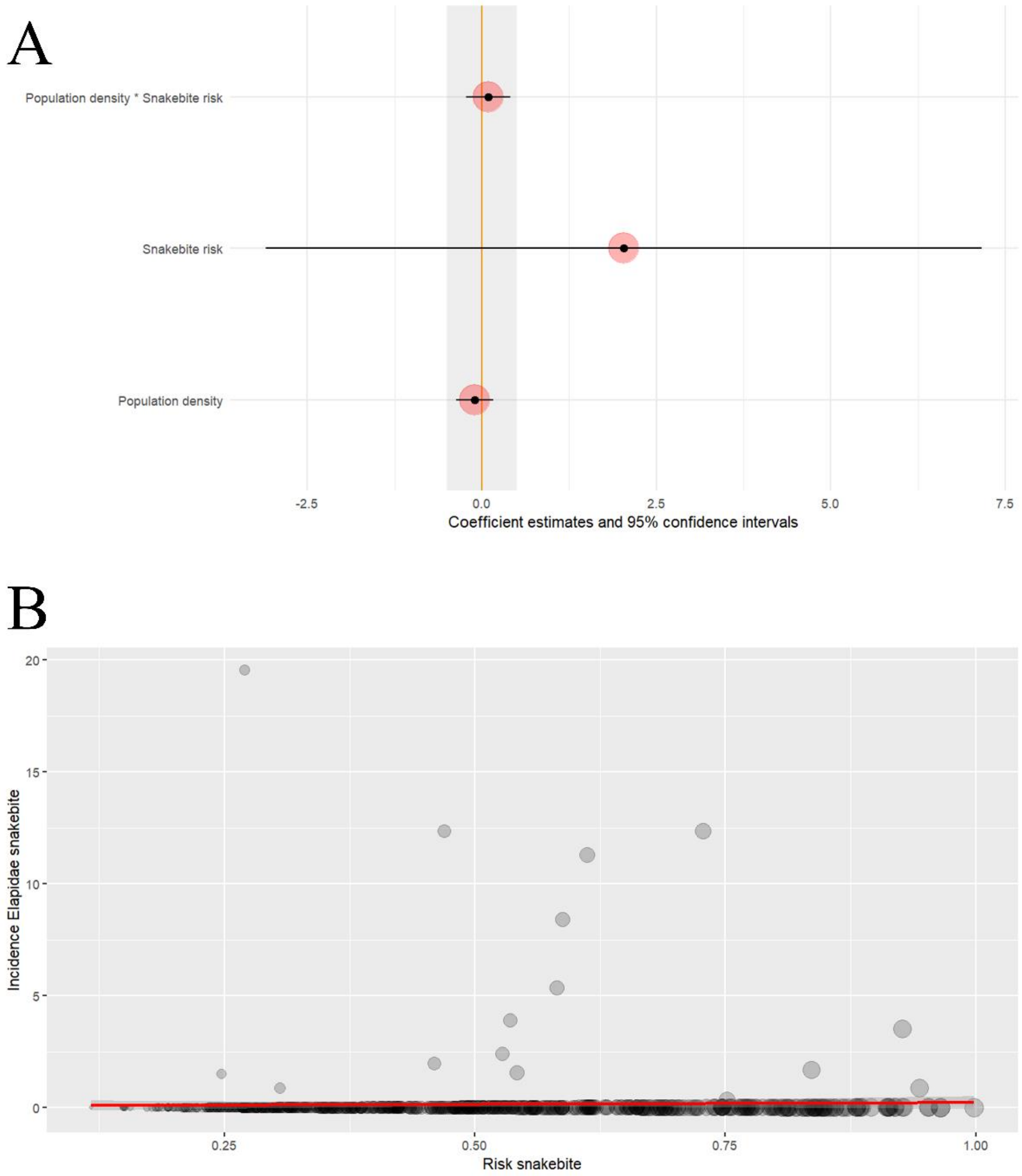


Figure 3: Result of the Generalized Linear Model (GLM), where A) Regression coefficient summary plot for the incidence rate of Elapidae snakebites in Amazon. Points show estimate medians; bars show 95% confidence intervals; B) Relation between incidence rate of Elapidae snakebites in Amazon and the risk of snakebites (i.e., suitability value for the presence of Elapidae snakes) ($z = 2.41$, $df = 555$, $p = 0.04$).

Supporting information

Appendix S1. Occurrence records of coral snake genus *Micrurus* (family Elapidae) considered in this study to run species distribution modeling.

Available in: https://docs.google.com/spreadsheets/d/1c-eLooJL7O91eF7dYWykUP4xT_1ugJP4/edit?usp=sharing&ouid=105371806218653374083&rtpof=true&sd=true

Appendix S2. Number of total number of occurrences and number of records after eliminating records falling within single grid cells (~3 km) (thinning), average performance of the SDM (ROC/TSS) generated and variables selected for the analyzed coral snake genus *Micrurus* (family Elapidae) in Brazilian Amazonia.

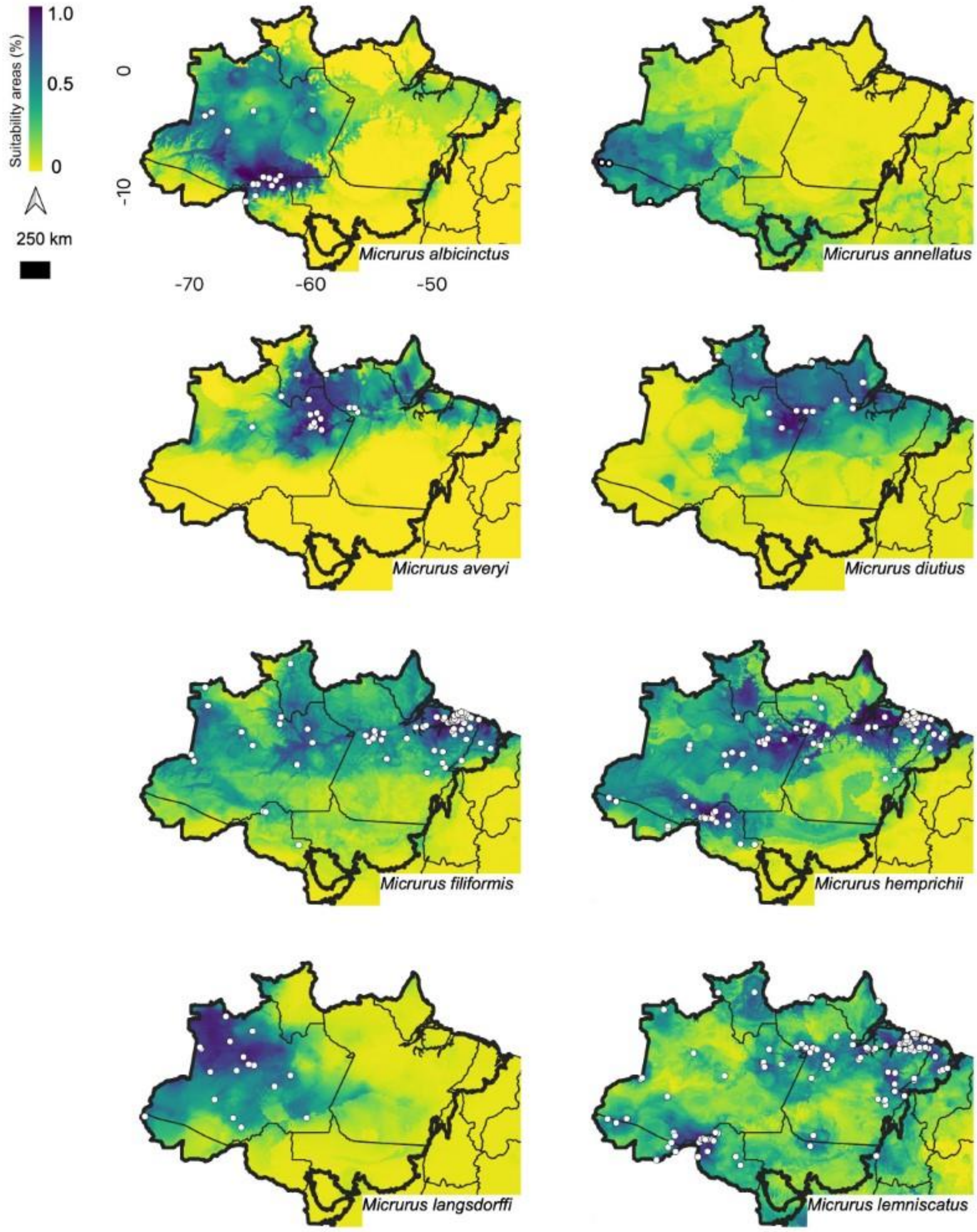
Species analyzed	**Total of occurrences (records after thinning)**	**TSS values**	**ROC values**	**Variables selected**
Micrurus albicinctus Amaral, 1925	329 (20)	0.967	0.996	BIO3; BIO4; BIO8; BIO13; BIO18; BIO19
Micrurus annellatus (Peters, 1871)	85 (54)	0.954	0.996	BIO4; BIO5; BIO18; BIO19
Micrurus averyi Schmidt, 1939	67 (23)	0.969	0.996	BIO2; BIO3; BIO9; BIO13; BIO14; BIO19
Micrurus diutius Burger, 1955	50 (30)	0.948	0.995	BIO1; BIO3; BIO4; BIO7; BIO13; BIO15; BIO18; BIO19

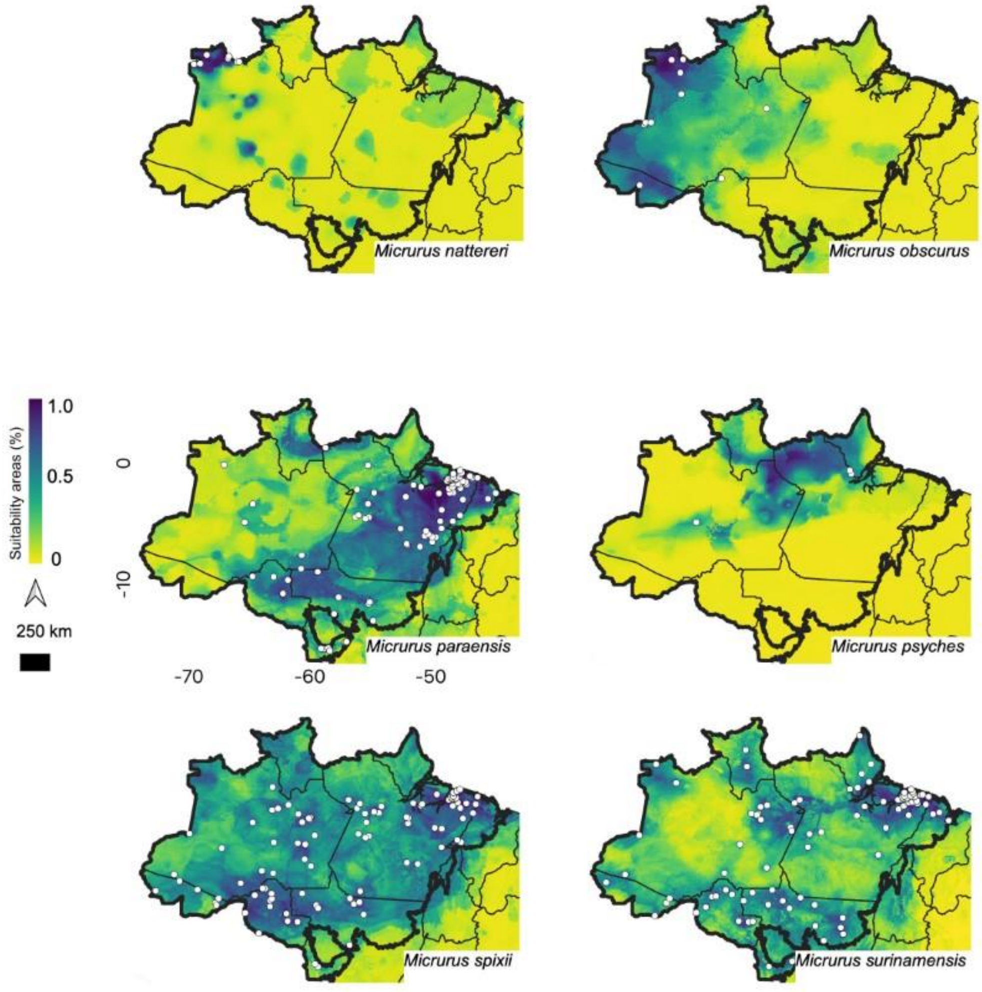
Micrurus filiformis (Günther, 1859)	282 (97)	0.932	0.991	BIO2; BIO3; BIO4; BIO12; BIO13; elevation
Micrurus hemprichii (Jan, 1858)	329 (121)	0.928	0.987	BIO2; BIO4; BIO13; BIO14; BIO18; BIO19; elevation
Micrurus langsdorffi Wagler, 1824	109 (59)	0.918	0.986	BIO2; BIO3; BIO4; BIO15; BIO18; BIO19; elevation
Micrurus lemniscatus (Linnaeus, 1758)	1127 (441)	0.921	0.993	BIO2; BIO4; BIO8; BIO13; BIO15; BIO18
Micrurus nattereri Schmidt, 1952	30 (19)	0.975	0.994	BIO2; BIO4; BIO8; BIO12; BIO13
Micrurus obscurus (Jan & Sordelli, 1872)	121 (62)	0.897	0.978	BIO2; BIO4; BIO8; BIO15; BIO18; BIO19
Micrurus paraensis Cunha & Nascimento, 1973	248 (87)	0.899	0.988	BIO4; BIO5; BIO8; BIO12; BIO15; BIO18; BIO19
Micrurus psyches (Daudin, 1803)	50 (39)	0.963	0.993	BIO3; BIO4; BIO7; BIO8; BIO14; BIO15; BIO18; BIO19
Micrurus spixii Wagler, 1824	335 (127)	0.937	0.993	BIO2; BIO3; BIO4; BIO8; BIO16; BIO18; BIO19

Micrurus surinamensis (Cuvier, 1817)	377 (177)	0.958	0.997	BIO2; BIO3; BIO4; BIO13; BIO15; BIO18; elevation
Total	**3539 (1356)**			

Appendix S3. Data used to analyze the risk of coral snakebites: number of snakebites (2010–2015, from the *Sistema de Informação de Agravos de Notificação*), snake distribution (from generalized map of predicted distribution for all coral snake species in the Brazilian Amazonia; Fig. 2), and human population density in the Amazonia (from the *Centro de Dados Socioeconômicos e Aplicações*; CIESIN; SEDAC 2018). Available in: https://docs.google.com/spreadsheets/d/1TdF8gpp027FUcRBCgZNTfqB8hqrV-8Pb/edit?usp=sharing&ouid=105371806218653374083&rtpof=true&sd=true

Appendix S4. Maps of predicted distribution of each coral snake genus *Micrurus* (family Elapidae). The points represent occurrence records and color gradients represent degrees of suitability of the predicted distribution of each species across the Brazilian Amazonia.


Suitability areas (%)
1.0
0.5
0
250 km
0
-10
-70
-60
-50
Micrurus albicinctus
Micrurus annellatus
Micrurus averyi
Micrurus diutius
Micrurus filiformis
Micrurus hemprichii
Micrurus langsdorffi
Micrurus lemniscatus



Micrurus nattereri
Micrurus obscurus
Suitability areas (%)
1.0
0.5
0
0
-10
250 km
Micrurus paraensis
Micrurus psyches
-70
-60
-50
Micrurus spixii
Micrurus surinamensis

Conclusões

Acidentes por cobras-corais na Amazônia possuem baixa frequência e incidência. Os principais sintomas locais apresentados nos casos reportados para a região são dor, edema e parestesia. Sintomas sistêmicos geralmente não associados a envenenamentos por cobras-corais, como coagulopatia e trombocitopenia, têm sido relatados. Poucas espécies na região parecem estar associadas com este tipo de acidente. Ao contrário do que geralmente acontece em acidentes ofídicos, a maioria dos acidentes por *Micrurus* ocorre na estação seca e na zona urbana, e os aspectos ecológicos dessas serpentes, como diferenças nos tipos de habitats, se refletem diretamente na distribuição dos acidentes entre áreas naturais e antropizadas. Os casos confirmados na região de Manaus demonstram que as características sistêmicas mais comuns são dispneia, ptose palpebral, visão turva, disartria e dificuldade para andar. Toda a Amazônia apresenta alta adequabilidade ambiental para a ocorrência de cobras-corais, mas essa alta adequação explica pouco sobre a incidência de acidentes na região. Isso provavelmente se deve à baixa densidade humana na Amazônia, mas também às características das cobras-corais, como hábitos crípticos. Diferentemente de muitas outras espécies de serpentes de importância médica, o cenário ecológico e epidemiológico das picadas de cobras-corais impede a detecção de áreas geográficas proeminentes de preocupação e exige uma disponibilidade ampla e equitativa de centros de saúde em toda a Amazônia.

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Anexos

A: Parecer substanciado do CEP UNB (1.652.440/2016)

UNB - FACULDADE DE MEDICINA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Aspectos epidemiológicos e econômicos dos acidentes ofídicos na Amazônia Brasileira

Pesquisador: Maria Regina Fernandes de Oliveira
Área Temática:
Versão: 1
CAAE: 57968416.2.0000.5558
Instituição Proponente: Núcleo de Medicina Tropical
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.652.440

Apresentação do Projeto:
Por meio de um estudo epidemiológico observacional, transversal analítico, ecológico analítico misto e análise de custo/doença período de tempo específico pretende-se avaliar: a carga epidemiológica e econômica relacionadas ao ofidismo na Região Amazônica, revelando um problema de saúde coletiva cujas informações ainda são fragmentadas e limitadas.

Objetivo da Pesquisa:
Descrever e analisar a casuística de acidentes ofídicos ocorridos na Amazônia Brasileira no período de 2010 a 2015 e estimar os custos associados no ano de 2015.

Avaliação dos Riscos e Benefícios:
O estudo utilizará dados secundários não nominais da base de dados do SINAN quanto para a base de dados do SIM.E pelo metodologia proposta não acarretará qualquer malefício à população estudada e poderá trazer benefícios do ponto de vista coletivo.Ademais, os autores comprometem-se a garantir o sigilo e a privacidade dos participantes da pesquisa.

Comentários e Considerações sobre a Pesquisa:
Os resultados da pesquisa poderão gerar conhecimento sobre os aspectos epidemiológicos e

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econômicos dos acidentes ofídicos na Amazônia brasileira. Tais informações podem auxiliar o mapeamento das regiões com altas taxas de incidência e também contribuir com a implementação de medidas preventivas que objetivam promover uma maior segurança para a população de risco para este tipo de acidente e diminuição de gastos com pacientes acometidos.

Considerações sobre os Termos de apresentação obrigatória:

O projeto encontra-se bem instruído com TCLE adequado, riscos e benefícios e metodologia bem delineada.

Recomendações:

Projeto instruído adequadamente e de acordo com a resolução do CNC 466/12.

Conclusões ou Pendências e Lista de Inadequações:

Parecer pela aprovação do projeto

Considerações Finais a critério do CEP:

Projeto apreciado na Reunião Ordinária do CEP-FM-UnB. Após apresentação do parecer do Relator, aberta a discussão para os membros do Colegiado. O projeto foi Aprovado por unanimidade.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_717317.pdf	04/06/2016 20:21:36		Aceito
Outros	Lattes_Samara.pdf	04/06/2016 20:20:56	Maria Regina Fernandes de Oliveira	Aceito
Outros	Lattes_Maria_Regina.pdf	04/06/2016 20:08:57	Maria Regina Fernandes de Oliveira	Aceito
Folha de Rosto	Folha_Rosto.pdf	31/05/2016 08:25:55	Maria Regina Fernandes de Oliveira	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Ofidismo_finalCEP.pdf	27/05/2016 15:58:25	Maria Regina Fernandes de Oliveira	Aceito
Outros	ficha_acidentes_animais_peconhentos.pdf	27/05/2016 15:55:42	Maria Regina Fernandes de Oliveira	Aceito
Outros	encaminhamento.pdf	27/05/2016 15:49:07	Maria Regina Fernandes de	Aceito

Outros	encaminhamento.pdf	27/05/2016 15:49:07	Oliveira	Aceito
Declaração de Instituição e Infraestrutura	termo_concordancia.pdf	27/05/2016 15:42:50	Maria Regina Fernandes de Oliveira	Aceito
Declaração de Pesquisadores	Termo_responsabilidade.pdf	27/05/2016 15:39:53	Maria Regina Fernandes de Oliveira	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TERMO_DE_CONSENTIMENTO_LIVRE_E_ESCLARECIDO.pdf	27/05/2016 15:24:19	Maria Regina Fernandes de Oliveira	Aceito
Declaração de Instituição e Infraestrutura	CartaAnuencia.pdf	27/05/2016 01:48:59	Maria Regina Fernandes de Oliveira	Aceito
Cronograma	Cronograma.pdf	27/05/2016 01:42:47	Maria Regina Fernandes de Oliveira	Aceito
Orçamento	Orcamento.pdf	27/05/2016 01:39:12	Maria Regina Fernandes de Oliveira	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BRASILIA, 27 de Julho de 2016

Assinado por:
Florêncio Figueiredo Cavalcanti Neto
(Coordenador)

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B: Parecer substanciado do CEP UEA (713.140/2014)

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Acidentes envolvendo animais peçonhentos: avaliação da notificação do agravo na rede de atenção a saúde do Amazonas

Pesquisador: Jacqueline de Almeida Gonçalves Sachett

Área Temática:

Versão:

CAAE: 30390613.9.0000.5016

Instituição Proponente: Escola Superior de Ciências da Saúde da Universidade do Estado do

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 713.140

Data da Relatoria: 16/05/2014

Apresentação do Projeto:

Trata-se de um estudo epidemiológico, prospectivo, contemporâneo dos acidentes envolvendo animais peçonhentos na rede de atendimento do município de Manaus e 14 municípios do estado do Amazonas mediados pela tecnologia da Telessaúde/UEA.

Objetivo da Pesquisa:

Objetivo Primário:

- Avaliar a notificação dos acidentes com animais peçonhentos agravo na rede de atenção a saúde do Amazonas

Objetivo Secundário:

- Identificar os dados registrados referente a ocorrência dos acidentes envolvendo animais peçonhentos no Estado do Amazonas por meio dos
dados contidos na ficha de notificação do SINAN. - Rastrear os acidentes envolvendo animais peçonhentos na atenção básica de municípios do
estado do Amazonas utilizando a Telessaúde/UEA; - Avaliar os aspectos sócio-demográficos e clínicos das vítimas de acidentes envolvendo animais
peçonhentos atendidos na Rede de atenção à saúde ¿ Atenção Básica e Fundação Medicina Tropical

Doutor Heitor Vieira Dourado; - Comparar os
acidentes ocorridos nas redes de atenção com as notificações ocorridas no SINAN do estado do Amazonas.
- Monitorar e Identificar os fatores que
influenciam para a notificação destes acidentes na Rede de atenção à saúde - Atenção Básica e Fundação Medicina Tropical Doutor Heitor Vieira

Avaliação dos Riscos e Benefícios:

Riscos:

Esta pesquisa possui riscos mínimos por se tratar de levantamentos de dados dos registros de saúde.

Benefícios:

- Contribuição para a qualidade do atendimento às vítimas de animais peçonhentos; - Estímulo e valorização do Sistema de Informação em Saúde. Notificação dos acidentes com animais peçonhentos pelos profissionais de saúde; - Fortalecimento da rede de atenção a saúde e a referência e contra-referência em acidentes com animais peçonhentos do Amazonas Fundação de Medicina Tropical Doutor Heitor Vieira Dourado - Produção de cunho científico referente as avaliações e indicadores observados durante a execução das ações do propostas pelo projeto; - Transformação da percepção dos profissionais da área da saúde, diante dos acidentes. - Articulação interdisciplinar na prevenção dos eventos relacionados a animais peçonhentos, como ponto mediador para a qualificação da assistência a saúde do indivíduo. - Mecanismos de acompanhamento e avaliação, indicadores: A avaliação ocorrerá de forma continuada com a participação dos atores envolvidos nos projetos, tanto da área acadêmica quanto da assistencial. Diante dos achados, será avaliado o alcance dos objetivos propostos em cada projeto, bem como a necessidade de intervenção. A partir desta premissa, será realizado oficinas com os pesquisadores e profissionais assistenciais para fomentar discussões e construir propostas para transformação e qualificação do serviço prestado. Propõe-se avaliar a situação, com a utilização de indicadores de avaliação, como: número de acidentes notificados; número de acidentes não notificados; número de reuniões realizadas; número de pesquisadores e profissionais atuantes no desenvolvimento das atividades, bem como adesão dos mesmos.

Comentários e Considerações sobre a Pesquisa:

Projeto relevante para a formação acadêmica e para avaliação da notificação do agravo na rede de atenção a saúde do Amazonas.

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos foram apresentados.

Recomendações:

Ajustar o cronograma.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Aprovado.

MANAUS, 09 de Julho de 2014

Assinado por:
Manoel Luiz Neto
(Coordenador)

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