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Effects of climate change on *Aedes aegypti*

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To my mom.

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General abstract

Climate emergency is currently recognized in the world, due to the high concentration of greenhouse gases (GHG) in the atmosphere. Temperature increase is one of the main consequences of climate change and it differently affects biodiversity. As ectothermic organisms, insects are more susceptible to changes in temperature and many studies investigate the effects of temperature increase in insects, especially species vectors of pathogens because they threaten human health. However, the combined effect of temperature increase and CO_2 concentration – the main GHG – on insect vectors is understudied. In this thesis, I investigated the effects of climate change on *Aedes aegypti*, species that is the primary vector of the viruses that cause Zika, chikungunya, and dengue, and it occurs in almost all tropical and subtropical regions of the world. The thesis is divided in three chapters. In the first chapter, I investigated the global pattern of research collaboration that assess "effect of temperature or climate change on *Aedes aegypti*", using bibliometric analysis. Studies that investigated climate change effects on *Aedes aegypti* had an exponential increase in the last 15 years. Brazil and Argentina, two developing countries, appeared among the top five countries with higher publication, while other developing countries (e.g. India and Paraguay) that face health problems related to diseases transmitted by the species had few or no publication in the area. Then, it is essential to reinforce the international collaboration, including these countries. In the second and the third chapters, I designed experiments in a microcosm that simultaneously simulates the increase in temperature and CO_2 concentration for 2100 in Manaus, Amazonas, Brazil. Four simulated climate change scenarios (SCCS) compose the microcosm, one is the current climatic condition in Manaus (Control), and the remaining three SCCS (Light, Intermediate and Extreme) simulate the B1, A1B, and

A2 climate scenarios predicted by the Fourth Assessment Report of Intergovernmental Panel on Climate Change (IPCC). In the second chapter, I evaluated the effects of SCCS and predation risk on larvae survivorship, and adult emergence pattern of *Aedes aegypti*. *Aedes aegypti* larval survivorship was not affected by SCCS and predation risk, but adult emergence pattern was affected by SCCS. Warmer scenarios accelerated the emergence of *Aedes aegypti* adults, and the Intermediate SCCS showed a peak emergence. In the third chapter, I evaluated the antioxidant defense system (ADS) of *Aedes aegypti*. I tested two main enzymes of ADS, catalase (CAT) and superoxide dismutase (SOD) in *Aedes aegypti* larvae and adults of both sexes reared in SCCS. The ADS responses of *Aedes aegypti* larvae and adult females were similar, and the activity of two enzymes did not differ according to SCCS. However, enzyme activity of adult males was affected by SCCS. In summary, results from the three chapters allow me to suggest an increase in international collaboration networks to the global network, mainly connecting countries with few or no researches in this area and that may be affected by the species in future climate change scenarios. The results also agreed with predictions regarding an increase in mosquito population in a close future, and indicated that energy allocation in *Aedes aegypti* may differ between life stages and sexes. Furthermore, vector control and mitigation measures to reduce greenhouse gases emission should be taken seriously, to reduce the contact of mosquitos and humans, and avoid the consequences to human health.

Resumo geral

Devido à alta concentração de gases de efeito estufa (GHGs) na atmosfera, é consenso que, atualmente, estamos vivendo uma emergência climática. O aumento da temperatura do planeta é uma das principais consequências das mudanças climáticas e impacta a biodiversidade de diferentes formas. Por serem organismos ectotérmicos, os insetos são mais suscetíveis a mudanças de temperatura, e muitos estudos têm investigado os efeitos do aumento da temperatura em insetos, especialmente em espécies que são vetores de patógenos, porque eles ameaçam a saúde humana. No entanto, o efeito combinado do aumento de temperatura e da concentração de CO_2, o principal GHG, em insetos vetores é pouco estudado. Nessa tese, eu investiguei os efeitos das mudanças climáticas em *Aedes aegypti*, espécie que é vetor primário de vírus que causam Zika, chikungunya e dengue, e que ocorre em quase todas as regiões tropicais e subtropicais do mundo. A tese é dividida em três capítulos. No primeiro capítulo, eu investiguei o padrão global de colaboração em pesquisas que avaliam "efeitos da temperatura ou de mudanças climáticas em *Aedes aegypti*", através de uma análise bibliométrica. Estudos que investigam os efeitos de mudanças climáticas em *Aedes aegypti* tiveram um aumento exponencial nos últimos 15 anos. Brasil e Argentina, dois países em desenvolvimento, aparecem entre os cinco países com maior número de publicações nessa área, enquanto outros países (por exemplo Índia e Paraguai), que também enfrentam problemas de saúde relacionados a doenças transmitidas pela espécie, têm pouca ou nenhuma publicação na área. Assim, é essencial que as colaborações internacionais incluam esses países. No segundo e terceiro capítulos, eu delineei experimentos em um microcosmo que simula o aumento simultâneo de temperatura e da concentração de CO_2 para 2100 na cidade de Manaus, Amazonas, Brasil. O microcosmo

é composto por quatro cenários simulados de mudanças climáticas (SCCS), um deles simula as condições climáticas atuais em Manaus (cenário Controle), e os outros três SCCS (Brando, Intermediário e Extremo) simulam os cenários climáticos B1, A1B e A2 preditos no Quarto Relatório de Avaliação do Painel Intergovernamental sobre Mudanças Climáticas (da sigla em inglês IPCC). No segundo capítulo, eu avaliei os efeitos do SCCS e do risco de predação na sobrevivência das larvas e no padrão de emergência de adultos de *Aedes aegypti*. A sobrevivência das larvas de *Aedes aegypti* não foi afetada pelos SCCS ou pelo risco de predação, mas o padrão de emergência dos adultos foi afetado pelos SCCS. Cenários mais quentes aceleraram a emergência de *Aedes aegypti* adultos, e um pico de emergência foi observado no SCCS Intermediário. No terceiro capítulo, eu avaliei o sistema de defesa antioxidante (ADS) de *Aedes aegypti*. Eu testei as duas principais enzimas do ADS, catalase (CAT) e superóxido dismutase (SOD) em larvas e adultos de ambos os sexos de *Aedes aegypti*, criados nos SCCS. As respostas do ADS de larvas e fêmeas adultas de *Aedes aegypti* foram similares, e a atividade das duas enzimas não diferiu em nenhum SCCS. Porém, a atividade enzimática de machos adultos foi afetada pelo SCCS. Como resultados dos três capítulos, eu sugiro que haja um aumento das redes de colaboração internacional, principalmente conectando à rede global, países com pouca ou nenhuma pesquisa na área e que possam ser afetados pela espécie em cenários futuros de mudanças climáticas. Os resultados também estão de acordo com as predições sobre o aumento das populações de mosquitos em um futuro próximo, e indicam que a alocação de energia em *Aedes aegypti* pode diferir entre os estágios de vida e sexo. Além disso, o controle de vetores e as medidas de mitigação para reduzir a emissão de gases de efeito estufa devem ser levados a sério, dessa forma é possível reduzir o contato de mosquitos e humanos, e evitar as consequências para a saúde humana.

General Introduction

"By fuel combustion man has added about 150,000 million tons of carbon dioxide to the air during the past half century. The author estimates from the best available data that approximately three quarters of this has remained in the atmosphere" (Callendar 1938). G.S. Callendar was one of the first scientists to indicate that global temperature had increased as a result of an increase in CO_2 emissions, which are mostly caused by human actions. More than 70 years after those statements, the influence of human actions on climate was highlighted in the Fifth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC 2014a). Anthropogenic CO_2 emissions and other greenhouse gases (GHGs), such as methane and nitrous oxide, continued to increase in the past 30 years and are responsible for climate change (Friedlingstein et al. 2020, United Nations Environmental Programme 2020). China and the USA are the largest GHGs emitter and their emission is mainly due to fossil fuels burning (IPCC 2014b). In Brazil, the main activities responsible for GHGs emissions are land use changes, mainly deforestation, followed by agriculture, energy, waste, and industries (Albuquerque et al. 2020). CO_2 emissions is predicted to decrease up to 7%, due to the confinement generated by the pandemic of COVID-19 (Le Quéré et al. 2020). However, the amount of GHGs in the atmosphere remains high and because of that, a climate emergency is recognized (United Nations Environmental Programme 2020).

Climate change affects biodiversity, threatening different biodiversity components, from biomes to organisms (Bellard et al. 2012). Among organisms, insects are especially susceptible to the consequences of climate change, such as temperature, because they are ectothermic (Christiansen-Jucht et al. 2014, Leonel et al. 2015, Zapletal et al. 2018, Piovezan-Borges et al. 2020). Climate change can spread insects distribution (Hertig 2019, Iwamura et al. 2020); temperature increase may accelerate their development (Couret et al. 2014) consequently generate adults with smaller body size (Nedvd 2009, Tseng et al. 2018); and may modifying species interactions, through phenological mismatches (Damien & Tougeron 2019).

The effects of climate change, mainly temperature increase, are well studied in species vectors of pathogens, due to the risks to human health (Davis et al. 2017, Ezeakacha & Yee 2019, Fouque & Reeder 2019). Mosquitoes are among the main vectors of pathogens (Rozendaal 1997), and the increase in mosquitos population in the tropics is predicted by the IPCC (IPCC 2014a). Climate change may affect vector physiology (Zhao et al. 2010, Sivan et al. 2017), behavior (Reiskind & Janairo 2018), development (Couret et al. 2014, Zapletal et al. 2018), which may result in changes in vector distribution (Liu et al. 2019, Khan et al. 2020). Pathogens transmission by vectors is also positively associated with increase in the global temperature (Mbaika et al. 2016, Tesla et al. 2018). These pattern may alter the incidence, transmission, and spread of diseases caused by vectors, causing impacts on human health (Siraj et al. 2017, Winokur et al. 2020).

Among the vectors of pathogens, *Aedes aegypti* (*Ae. aegypti*) occurs in almost all tropical and subtropical regions of the world and is the primary vector of the viruses that cause Zika, chikungunya and dengue. Annually, 96 million dengue cases are estimated globally, with 40.000 deaths and more than 3.9 billion people are at risk of contracting this disease (WHO 2020). Due to the wide distribution and the impact on public health, arboviruses transmitted by *Ae. aegypti* pose a global health threat (Kraemer et al. 2015).

The effects of temperature in life-history characteristics, and in vectorial capacity of *Ae. aegypti* are well-know. For example, larval development rate is faster with temperature increase (Couret et al. 2014); the percent of egg hatching increases in 24-25ºC compared to higher temperatures (Mohammed & Chadee 2011); extrinsic incubation period of Zika virus decreases in high temperature (Winokur et al. 2020); dengue epidemic potential increases in temperature up to 29ºC (Liu-Helmersson et al. 2014). However, the combined effect of temperature and CO_2 concentration – the main GHG – on *Ae. aegypti* is understudied, and considering that this species has complex life cycle, it is essential to evaluate these effects during their different life stages. This knowledge is critical because the experience lived during the larval stage can lead to consequences for adult stage, a mechanism known as carry-over effect (O'Connor et al. 2014). Therefore, understanding how climate change affects the interspecific interaction, development, and physiology of *Ae. aegypti* is a fundamental to support mitigation measures.

In this way, this thesis investigates the effects of climate change on *Ae. aegypti* considering three scales: i) global: patterns and international collaborations of studies that assess the effects of temperature and climate change on *Ae. aegypti* through bibliometric analysis ; ii) developmental characteristics: evaluating how simulated climate change scenarios (SCCS) affect larval survivorship and pattern of adult emergence of *Ae. aegypti* at predation risk; iii) physiological level: evaluating how SCCS affect antioxidant defense system of *Ae. aegypti* larvae and adult.

This thesis was organized in three chapters. In the first chapter, "Global patterns of studies on climate change effects on *Aedes aegypti*: collaboration expanded, despite some critical countries stay behind", I aim to investigate the global pattern and international collaborations of studies on “effect of temperature or climate change on *Ae. aegypti*”. I also assessed the relationships between number of publications by country, dengue cases and socio-economic index of these countries.

The second chapter, “Simulated climate change, but not predation risk, accelerates *Aedes aegypti* emergence in a microcosm experiment in western Amazonia” was published in vol. 15 of the PLOS ONE in 2020. The main aim was to assess larval survivorship and pattern of adult emergence of *Ae. aegypti* reared in SCCS at predation risk, using *Toxorhinchites haemorroidalis* larvae as predator.

In the third chapter, “Simulated climate change scenarios reveal distinct responses in antioxidant defense system of *Aedes aegypti* larvae and adult” aim to evaluate the antioxidant defense system (ADS) of *Ae. aegypti* larvae and adults reared in SCCS, to understand the responses of ADS of different life stages (larva and adults) and sexes (adult males and females) of *Ae. aegypti*.

Chapter 1

Global patterns of studies on climate change effects on *Aedes aegypti*: collaboration expanded, despite some critical countries stay behind

Abstract

Over the years, many studies have investigated the effects of temperature and climate change on life-history characteristics, epidemiological aspects, and distribution expansion of *Aedes aegypti* (*Ae. aegypti*). These effects can modify the species life cycle, infection rates, and distribution of the species, and increase the risks caused to human health. Despite this accumulated knowledge, studies are not always carried out in countries that suffer from diseases caused by *Ae. aegypti*, or these countries are not involved in the published studies. In this way, we use bibliometric analysis to investigate the pattern of global publications and international collaborations in studies that address the effect of temperature or climate change on *Ae. aegypti*. Our results showed that the number of studies on climate change has been increasing over the years, and currently this topic has received more attention from studies than the temperature effect on *Ae. aegypti*. Among the top five countries with the largest number of publications in the area, three are developed countries (USA, UK, and Australia) and two are developing countries from South America (Brazil and Argentina). The South America countries can serve as hubs to boost publications in the Global South. We observed that some countries in critical regions (e.g. Bolivia, Myanmar, Paraguay, Portugal, and Taiwan) are staying behind in scientific production or collaboration. These countries need to strengthen international collaborations because *Ae. aegypti*

occurrence and dengue cases are very high and they are in regions in which the expansion of *Ae. aegypti* distribution, or their occurrence is expected in future climate change scenarios. We also observed that at least one country on each continent (Australia, China, UK, South Africa, Brazil and USA) has a high number of international partnerships. These countries can serve as a hub for boosting research on their own continent. To improve international collaboration there are some existing mechanisms that can be considered (e.g. research networks, internationalization programs). These collaborations will be important to improve the knowledge on *Ae. aegypti* in countries with few or no publications, and to arrange management actions in future climate change scenarios.

Resumo

Ao longo dos anos, muitos estudos investigaram os efeitos da temperatura e das mudanças climáticas em características da história de vida, aspectos epidemiológicos, e expansão da distribuição de *Aedes aegypti* (*Ae. aegypti*). Esses efeitos podem modificar o ciclo de vida, as taxas de infecção e a distribuição dessa espécie, e assim aumentar os riscos causados a saúde humana. Apesar do conhecimento acumulado, estudos nem sempre são realizados em países que sofrem de doenças causadas pelo *Ae. aegypti*, ou esses países não estão envolvidos nesses estudos publicados. Dessa forma, através de uma análise bibliométrica nós investigamos o padrão global de publicações e as colaborações internacionais em estudos que avaliam o efeito da temperatura ou mudanças climáticas em *Ae. aegypti*. Nossos resultados mostraram que o número de estudos em mudanças climáticas tem aumentado ao longo dos anos e, atualmente, esse tópico tem recebido mais atenção em estudos do que o efeito da temperatura em *Ae. aegypti*. Entre os cinco países com o maior número de publicações na área, três são países desenvolvidos (EUA, Reino Unido e Austrália) e dois são países da América do Sul (Brasil e Argentina). Os países da América do Sul podem servir como "hubs" para impulsionar as publicações no Sul Global. Nós também observamos que alguns países em regiões críticas (por exemplo, Bolívia, Mianmar, Paraguai, Portugal e Taiwan) estão ficando para trás na produção e colaboração científica. Esses países precisam fortalecer as colaborações internacionais já que a ocorrência de *Ae. aegypti* e o número de casos de dengue são muito altos, e eles estão em regiões nas quais a expansão da distribuição de *Ae. aegypti* ou a ocorrência da espécie é esperada em cenários futuros de mudanças climáticas. Nós também observamos que pelo menos um país em cada continente (Austrália, China, Reino Unido, África do Sul, Brasil e EUA) tem um alto número de

parcerias internacionais. Esses países podem servir como “hubs” para impulsionar pesquisas em seus próprios continentes. Para melhorar a colaboração internacional existem alguns mecanismos que podem ser considerados (por exemplo, redes de pesquisa, programas de internacionalização). Essas colaborações são importantes para melhorar o conhecimento sobre *Ae. aegypti* em países com pouca ou nenhuma publicação, e para organizar ações de gestão em cenários futuros de mudanças climáticas.

Introduction

Aedes aegypti (*Ae*. *aegypti*) is one of the main disease vector in the world, transmitting Zika, chikungunya and dengue virus (Powell 2018, Souza-Neto et al. 2019). Changes in climatic variables, such as temperature increase, induce alterations in *Ae. aegypti* development (Bar-Zeev 1958, Rueda et al. 1990, Carrington et al. 2013), reproduction (Costa et al. 2010, Carrington et al. 2013), and behavior (Rowley & Graham 1968). Several studies investigated and predicted the effect of temperature or future climate change scenarios in life-history traits or epidemiological factors related to the *Ae. aegypti* (Couret et al. 2014, Liu-Helmersson et al. 2014, Leonel et al. 2015, Mordecai et al. 2017, Piovezan-Borges et al. 2020). These studies showed that increase in temperature accelerated the development (Carrington et al. 2013) and adults emergence (Piovezan-Borges et al. 2020), decrease the period of extrinsic incubation (development period of pathogen inside the vector until it is able of being transmitted) (Winokur et al. 2020), and wide the distribution of *Ae. aegypti* in future climate change scenarios (Kamal et al. 2018, Iwamura et al. 2020). These findings are key pieces to increasingly understand how *Ae. aegypti* respond to climate changes and its consequence for human health.

Overall, developing countries that have adequate climatic conditions for *Ae. aegypti* development, struggle with diseases transmitted by the species. This may be related to the lack of basic health conditions, precarious public health structures, population growth, and intensive and uncontrolled urbanization (Reiter et al. 2003, WHO 2003, Parham et al. 2015). Climate change can intensify these problems, with increase in the frequency and occurrence of extreme events, such as prolonged droughts or floods, harming local communities in affected areas (Garbero & Muttarak 2013).

Developing and least developed countries and poor people are likely to be more affected by climate change effects (United Nations Development Program 2020), for example the rise in temperature that will expand the number of diseases, such as vector-borne diseases, water-borne epidemics, and cardiovascular disease (WHO 2003). Evaluate the patterns of studies on climate change effects on *Ae. aegypti* is essential to understand where the studies are being developed, and detect international scientific collaborations, which are important to face the challenges caused by climate change in vector pathogen species.

International scientific collaborations are beneficial to improve researches quality, through increasing in critical mass (Boekholt et al. 2009), enabling publication in high impact journals, generating greater visibility to the studies (McManus et al. 2020). Furthermore, the establishment of good relationship among countries through research collaboration, can generate partnerships to future researches or opportunities for students, and solve problems (Boekholt et al. 2009). Historically, the USA and Europe have the largest research collaboration networks (Adams 2012), which may be the result of 'helicopter research', that wealthy countries collect data from low-income countries, and involve local scientists in research (Minasny & Fianti 2018). However, this is not necessarily true or homogeneous, and, in recent years, other developed countries from different continents or developing countries have shown an advance toward internationalization, and collaboration between national and foreign researchers has been encouraged by science policies of governmental or private funding agencies (McManus et al. 2020).

Understand the global pattern of studies with *Ae. aegypti* in the context of climate change is essential because it can help to improve global strategies to manage

Ae. aegypti and anticipate uncontrolled diseases transmission caused by the species. The lack of participation of some countries may lead to a misalignment of the accumulated knowledge and the reality of the country. This is true not only for developing countries located in the regions with the highest occurrence of the species (Campbell-Lendrum et al. 2015), but also for developed countries where the species does not currently occur, but where the species is projected to expand distribution in future climate change scenarios (Iwamura et al. 2020). To provide this overview, we explore studies using bibliometric analysis and summarize global pattern about the effect of temperature or climate change on *Ae. aegypti*, including publications growth, studies trends, and collaborations network. Furthermore, considering the number of publication in a country may vary according to aspects related to human health (e.g. number of dengue cases), and with socio-economic factors of the country, we assessed the relationship between number of publication per country and dengue cases, the most common disease caused by the primary vector *Ae. aegypti*, and socio-economic index (Gini coefficient, including gross domestic product (GDP) per capita and human development index (HDI)).

Methods

Literature search, inclusion and exclusion criteria

We performed a search using the ISI Web of Science (WoS) database, retrieve all articles from the first insertion until October 2020, using the following terms: ("climate change" OR temperature OR warming) AND "A* aegypti". We filtered the results in documents type, including all articles, notes, early access papers and data papers written in English. Our inclusion criteria were studies that: i) assessed how temperature or climate change affects *Ae. aegypti* at any life stage, and any species behavior (e.g. thermal preference, vectorial capacity); ii) include *Ae. aegypti* in studies of multiple species and iii) evaluated *Ae. aegypti* distribution. Thus, fieldwork, laboratory, or modeling studies were considered in our search. We excluded studies that: i) do not evaluate effects of temperature or climate change *per se*; ii) do not show statistical relationship between temperature or climate change on *Ae. aegypti* characteristic; iii) without access to the full text and the abstract content is not enough to consider the study; and vii) show only effect of CO_2 concentration on *Ae. aegypti*. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process steps and the filtering criteria (Moher et al. 2009) are available in Supplementary material (SM1).

Data analysis

To analyze global collaboration network and keyword network, we conducted a bibliometric analysis using *VOSviewer* version 1.6.15 (Jan van Eck & Waltman 2010). A collaboration network of co-authors was generated using country form affiliation as unit of analysis. Nodes size represent publication number. To extract information on the number of publications by country, considering the country of the first author, we use the *bibliometrix* R package. We merge England, North Ireland, Scotland and Wales in United Kingdom, in order to converged country names used in the two bibliometric analysis programs (*VOSviewer* and *bibliometrix* R package). A keywords network was created using author keywords cited at least 2 times and excluded the obligatory term '*Ae. aegypti*' and similar (e.g., '*Aedes-aegypti*', '*Aedes aegypti*'). We chose to keep in the network terms such as ‘temperature’ and ‘climate change’. Although these terms are part of the search terms, we seek to understand their connection to the other keywords. In this network, similar terms were merged (SM2), in this way, it is possible to have a better view of the main topics covered in the documents. The nodes size in this network represents the number of occurrences of keywords. For normalizing the strength of the links between items in the cluster in both networks (global collaboration and keyword), we used the association strength method.

The *bibliometrix* R package (Aria & Cuccurullo 2017) and *biblioshiny* interface were used to analyze annual growth in publication, and keywords temporal dynamic. Publication years was obtained by *bibliometrix* and the graph was constructed using GGPlot 2 package (Wickham 2016).

In order to know the numbers of dengue cases and the socio-economic indices of each country, we use the most recent data published by global organizations. Dengue data were gathered from WHO (World Health Organization) of 2017. From Human Development Report (United Nations Development Program 2020), we used data of human development index (HDI) of 2019 and Gini coefficient of 2010-2018 (data of most recent year available during this period). Gross domestic production (GDP) per capita data of 2019 was extracted from World Bank. To evaluate the correlation among number of publication by country, and dengue cases, and socio-economic indices (HDI, Gini coefficient and GDP per capita), we used Pearson correlation. For correlation analysis, we used the first author affiliation country. Countries without complete information regarding dengue cases or socioeconomic indices did not enter in the correlation analysis. Data regarding the number of publications, number of dengue cases, and the socio-economic indices of each country are available in SM3.The analysis were carried out in the R environment (R Core Team 2020).

Results

Annual growth in publications

The search returned 1361 records, of these we found 317 studies that evaluated the effects of climate change on *Ae. aegypti* after inclusion and exclusion criteria. We observed an increase in the number of studies for the period 1951-2020, mainly after 2000. The majority of papers (n = 249) were published in the last 11 years (Fig. 1). The average number of publications between the period of 1951-1999 was 1.59 articles/year, but this average more than doubled in the following years (2000-2020). From 2000 to 2008, 3.56 articles/year were published, and a great increase in publications started in 2009 (average of 20.75 articles/year from 2009 to 2020). The year with the highest number of publications was 2019 (n = 40), although we assessed studies 2020 until October. The rate of annual scientific production was 7.26%.

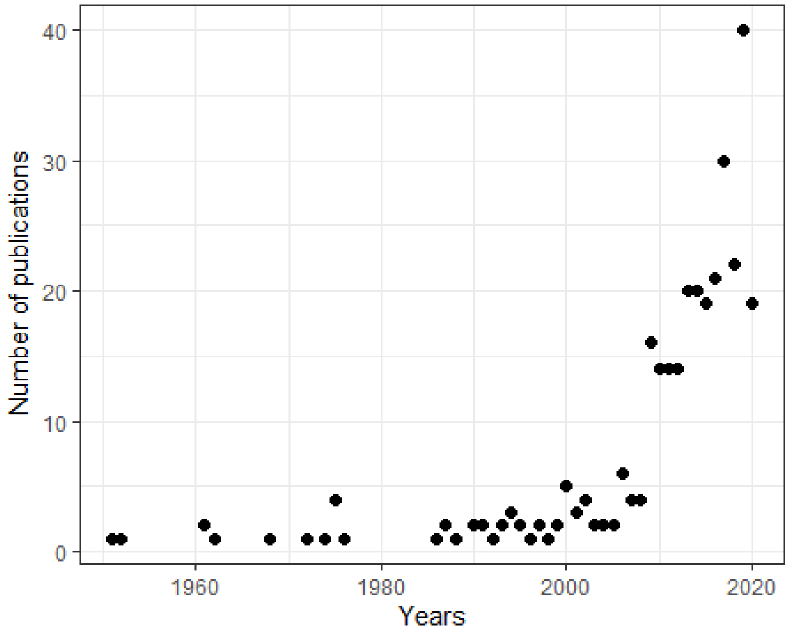


Figure 1. Annual production of studies about temperature or climate change effects on *Aedes aegypti* from 1951 to 2020.

Keywords network and trend of use over time

The keywords network consisted of 111 items, and 13 clusters (Fig. 2a). Five terms were highlighted in the center of keywords network: ‘dengue’, ‘temperature’, ‘mosquito’, ‘climate change’ and ‘*Aedes albopictus*’. When analyzing links among terms, we observed that those related to diseases such as 'infection' and 'transmission' belong to the same cluster of 'dengue' (total links: 53). The term 'temperature' had 46 links and were connected with keywords related to species characteristic, such as 'survival' and 'development time', as well as 'mosquito' that is connected to 'larval habitats' and 'abundance' (mosquito total links: 30). Whereas ‘climate change’ had more links (total links: 25) with terms that refer to mathematical models, statistical analysis (e.g., mechanistic model, kurtosis) and with ‘vectorial capacity’ (Fig. 2a). The cluster formed by ‘*Aedes albopictus*’ includes terms related to ‘competition’, ‘arbovirus’ and ‘vector competence’. The only term related to human health were 'public health' and despite not being in the same cluster, this term were a linked with 'climate change'.

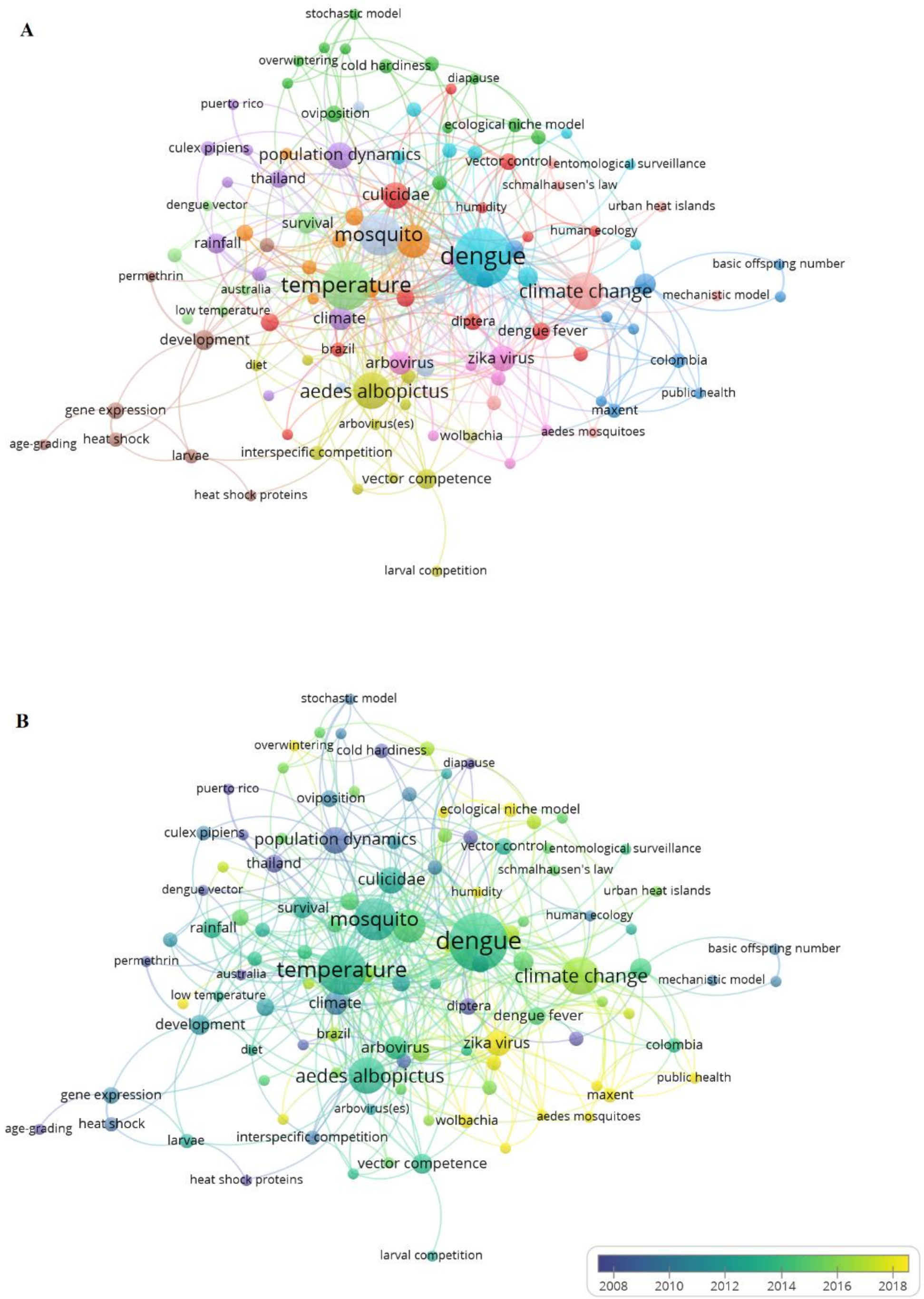


Figure 2. Keywords network a) with cluster colors; b) over time. We consider keywords cited at least 2 times, and excluded the term '*Aedes aegypti*' and similar. The nodes size represents the number of occurrences of keywords, and the links indicate the connections between keywords.

By focusing on the main pathogens transmitted by *Ae. aegypti*, ‘dengue’ received a lot of scientific attention in 2013, while studies focused on ‘chikungunya’ and ‘Zika’ was mainly produced in 2017 and 2018, respectively (Fig. 2b). Two of the topics of interest in our research, ‘temperature’ and ‘climate change’, also have been focused in different years. Studies with ‘temperature’ were mainly published in 2013, while ‘climate change’ was study topic of 2016-2017 (Fig. 2b). We found some remarkable changes in the temporal dynamics of the 10 most cited keywords over almost 30 years (1991-2020). The publications number with ‘climate change’ is increasing, especially in the last 11 years (Fig. 3). ‘Dengue’ and ‘temperature’ had great publications number in the past years (as also shown in Fig. 2b), but after 2016, these keywords were less used. Other keywords such as ‘mosquito’, ‘*Aedes albopictus*’ and ‘arbovirus’ have also received a lot of attention recently studies (Fig. 3).

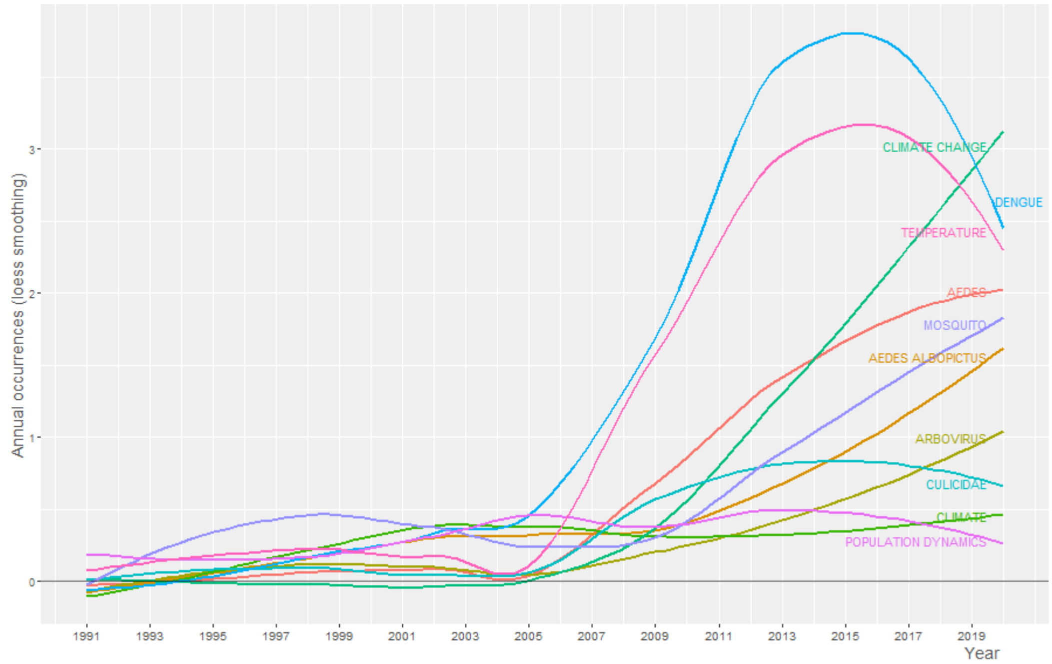


Figure 3. Temporal dynamic of the 10 most used keywords from 1991 to 2020.

Global scientific production and international collaborations

We found 63 countries that published and collaborated in the area. The first author countries that dominated the publications were USA (n = 91 papers), Brazil (n = 38 papers), Australia (n = 32 papers), Argentina (n = 21 papers), and UK (n = 13 papers) (Fig. 4). These five countries were responsible for 61.5% of the total publications in this area. The publication in the USA almost corresponds to 30% of the total.

A collaboration network showing partnerships between countries of all authors was formed by 20 clusters, 7 of them are formed by only 1 country, indicating that the collaboration is restricted among compatriots. These seven countries are Bangladesh, Chile, Denmark, Panama, Philippines, Portugal, and Sri Lanka. Portugal was the only one of seven countries with two publications, the other six countries had only one publication.

We also observed that countries with the largest publications number do not necessarily have the largest collaboration network, except for USA and UK. USA is the country that had the most international collaborations, publishing articles with 32 other countries and UK with 29 countries. However, some countries had fewer publications but had many collaborations, for example France published in partnership with 19 countries, followed by Belgium (n = 18 international collaborations), South Africa (n = 14), Sweden (n = 13), China (n = 11), Egypt and Switzerland (both n = 10). Brazil and Australia, which are countries with high numbers of publications, had partnerships with 16 and 13 countries, respectively, while Argentina had international collaboration with 5 countries.

The UK is the only one among the five countries with the most publications, where the majority of publications (77%) were with multiple countries. The same occurred with other countries with less publication, such as France, which has 6 publications and 5 of them are with international collaboration, other examples are Sweden (n = 4) and Nepal (n = 3) where none of the publications occurs only among compatriots. On the other hand, most publications of USA, Brazil, and Australia were made by compatriot researchers (87% for Brazil, 71% for USA, and 69% for Australia).

The correlation between countries publications number, dengue cases ($r = 0.077$; $P = 0.692$) and socioeconomic index (HDI: $r = 0.1765$; $P = 0.356$; Gini coefficient: $r = 0.2666$; $P = 0.162$; GDP per capita: $r = 0.3011$; $P = 0.112$) was not significant.

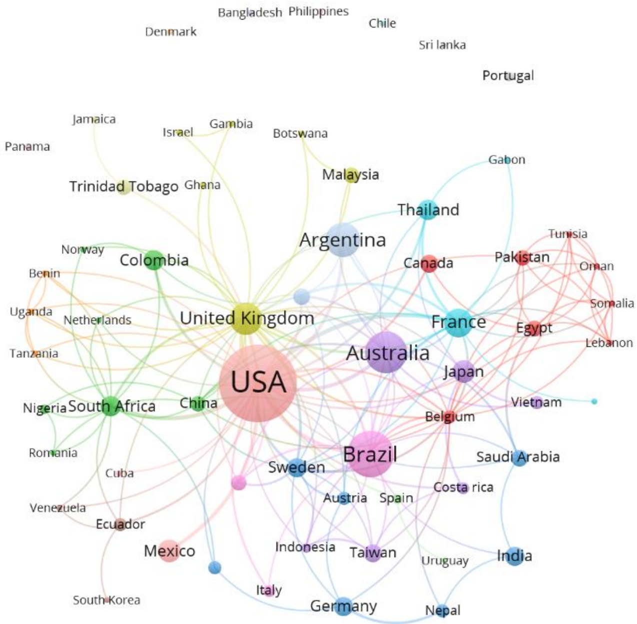


Figure 4. Collaboration networks between 63 countries in studies regarding temperature or climate change effects on *Aedes aegypti*. The nodes size representing the number of publication in the country, and the links indicate co-authorship between countries.

Discussion

The number of studies on climate change has been increasing over the years, and currently, this topic has received more attention from studies than the temperature effect on *Ae. aegypti*. The number of publications by countries followed a general pattern of science, in which countries from the Global North stand out, with two important exceptions in South America (Brazil and Argentina), which are among the top five countries in number of studies. Our results indicate the need to intensify international collaborations, especially between countries from the Global South. We show some mechanisms that have worked and can serve as an example to increase international collaborations.

Publications and keywords trends over the time

Although studies with the term ‘temperature’ has increased exponentially from 2005 to 2012, since 2017 the number has been decreasing, while studies on ‘climate change’ has increased exponentially in recent decades (1991 to 2014) (Haunschild et al. 2016). We observed an increase in studies using 'climate change' in keywords from 2006 to 2020. The topic climate change came into the spotlight worldwide in the late 1980s (Gupta 2010). Since 1990, Intergovernmental Panel on Climate Change (IPCC) released Assessment Reports (AR), which provide information on the hazards of climate change to human health, such as the increase in diseases or greater exposure to disease vectors, in addition to update the climate scenarios predicted for 2100. Thus, new studies are developed considering the climate change effects on species vectors based on the current IPCC-AR. The number of publications citing the IPCC-AR increases after the release of an IPCC-AR (Vasileiadou et al. 2011), and we observed this trend, with a growing number of publications in 2009, which may be a result of the publication of IPCC-AR4 in 2007.

In the keywords network, although the terms ‘temperature’ and ‘climate change’ are highlighted, the most frequently cited term was ‘dengue’. This does not mean that studies evaluated dengue virus, because, frequently, authors use the term dengue vector to refer to *Ae. aegypti*. Zika and chikungunya, other viruses transmitted by *Ae. aegypti*, had low frequency. Commonly, studies relating temperature or climate change effects to these viruses investigate the vectorial capacity of *Ae. aegypti* (Chepkorir et al. 2014, Liu-Helmersson et al. 2014), or the extrinsic incubation period of the virus (Mbaika et al. 2016, Winokur et al. 2020). However, viruses transmitted by the species are one of the few terms in the keywords network related to human health. Most terms in the keywords network are associated to vector biology (e.g., development, oviposition, population dynamic).

The use of terms related to modeling studies increased in recent years (from 2014 onwards), and most of them are associated with 'climate change'. Modeling studies use future climate change scenarios predicted by IPCC, generally to investigate the geographic expansion of *Ae. aegypti* in some countries, continents (Liu-Helmersson et al. 2016, Liu et al. 2019), or even its global expansion (Kamal et al. 2018, Ryan et al. 2019). These results are extremely important for decision-makers to plan measures to control species expansion in future climate change scenarios. Unfortunately, due to the lack of commitment from the governments of some key countries in global climate agreements (Zhang et al. 2017), and the consequences of possible climate tipping elements (Lenton et al. 2008), the geographic expansion of *Ae. aegypti* in the future is a likely scenario.

Asymmetries among countries with more publications

The three countries of the Global North, which are among the five countries with the most publications in the area, are also on the list of countries with the highest scientific production considering global studies on climate change, they are the USA, United Kingdom, Germany, Canada, China and Australia (Haunschild et al. 2016). However, we found a different pattern because two South American countries also appear in the top five (Brazil and Argentina). The large number of publications from developing countries shows that although these countries have lower investments for science and technology, their scientific contribution is high and fast growing (UNESCO 2015; Gui et al 2019), reinforcing that the global balance of research is changing (Adams 2012). Three factors may explain the high number of publication in these three developed countries. USA and Australia are among the 10 countries on their continents with the highest occurrence of *Ae. aegypti* (Kraemer et al. 2015) and they (including UK) have economical resources for research development, in addition to universities and research centers references in this area (e.g. University of Florida and Centers for Disease Control and Prevention in the USA; The University of Melbourne and James Cook University in Australia; The London School of Hygiene & Tropical Medicine in UK).

Among the developing countries with the most publications in the area, Brazil is one of the countries in the world that suffers most health consequences due to viruses transmitted by *Ae. aegypti*. According to Pan America Health Organization (PAHO), in 2019 the total of dengue cases in the country was 2.248,570, almost two million more compared to the previous year. Over a twenty years period (1995-2015), the cases of dengue reported in Brazil was more than half the total cases reported in the Americas (Nunes et al. 2019). In Argentina, the number of dengue cases has increased markedly in recent years, from 557 cases registered in 2017 to 59.358 in 2020 (PAHO). Although there is no correlation between dengue cases and the number of countries publication, the high number of dengue cases in these developing countries may be one of the reasons why they are among the most productive in the area. Associated to this, they have consolidated research groups and large research centers on this theme (Brazil: Fiocruz, Universidade de São Paulo, and Universidade Federal de Minas Gerais; Argentina: Universidad de Buenos Aires, and Universidad Nacional de Córdoba).

Falling behind

The research scenario is different in other countries with high number of people infected by the dengue virus. Some countries in Asia and South America has few publications, despite they have great number of dengue cases, which can explain the non-significant correlation between the number of publications and dengue cases. For example, India, Sri Lanka and Vietnam, had more than 150.000 dengue cases registered in 2017 and Colombia had 78.298 dengue cases in 2020. Other countries had no publication in the area, including Paraguay, Bolivia and Myanmar, totaling, respectively, 223.082 (2020), 85130 (2020) and 7729 (2017) records of dengue cases. Some of these countries are located in regions that are currently most suitable for the development of *Ae. aegypti*, such as Southeast Asia, South America, and West and Central Africa. These areas are also predicted to have the greatest expansion of *Ae. aegypti* distribution in future climate change scenarios (Iwamura et al. 2020).

International collaboration is essential to increase the visibility of countries with few or no publications (Boekholt et al. 2009), mainly due to the research funding (Chetwood et al. 2015), and the language. The USA and UK as well as other countries with high collaborations are English-speaking countries. English is the universal language of science (Gordin 2015) and English-speaking countries are more likely to collaborate internationally (Zeng et al. 2011, Ramírez-Castañeda 2020). Although the majority of international collaborations in this area occur in the USA and UK, we observed that at least one country on each continent (Australia, China, UK, South Africa, Brazil and USA) has a high number of international partnerships, reinforcing that developing countries have been increasing research networks. These countries can serve as a hub for boosting research on the own continent.

Central American countries had few collaborations and all of them were made with co-authors from other Central American countries or from the USA. However, Central America has a typical tropical climate, area where will may face problems with *Ae. aegypti* expansion. Therefore, it is important that international partnerships be made between countries with similar climates. Countries in Asia do not appear among those with the highest number of publications in the area. However, Taiwan has the highest occurrence of *Ae. aegypti* in the world, twice the number of occurrences compared to the second place (Brazil) (Kraemer et al. 2015). Despite the number is low, Taiwan (n=7), Indonesia (n=6), Thailand (n=6), and China (n=11) had international collaborations. Southeast China is one of the most populous regions in the country and this region is projected to expand the occurrence of *Ae. aegypti* in climate change scenarios for 2050 (Iwamura et al. 2020). China has a great potential of scientific publications. For example, the emerging of COVID-19 pandemic doubled the number of publications on this topic by Chinese authors in early 2020 compared to the previous two years. Thus, China can invest in studies with *Ae. aegypti* in advance to predict or even prevent the expansion of this species in future climate change scenarios.

Despite the UK is among the five countries with the largest number of publications and have great international collaborations, as well as France and Belgium, the *Aedes albopictus* occur more frequently than *Ae. aegypti* in Europe (Kraemer et al. 2015, Messina et al. 2019). However, in future climate change scenarios, the expansion of *Ae. aegypti* is projected mainly to Iberian Peninsula, Greece, and Italy (Iwamura et al. 2020). Few studies on the effect of temperature or climate change in *Ae. aegypti* were developed in these countries. We did not find study record for Greece, and Portugal is one of the countries that has publications only with compatriots. Other countries also published only with compatriots, including Sri Lanka, Bangladesh, and Philippines. Under the RCP 6.0 climate scenario, a scenario where the radiative forcing is stabilized after the year 2100, an expansion on distribution of *Ae. aegypti* is predicted by 2050 (Messina et al. 2019). Therefore, these countries deserve more attention.

Suggestions

Five inclusive mechanisms can be used to boost the international collaborations and increase visibility to Global South. First, research network should be expanded. For example, TReNDS (Thematic Research Network on Data and Statistics) is a United Nations initiative to Sustainable Development that seeks solutions to improve data usage to ensure sustainable development; and LABMAN (Latin American Brain Mapping Network) is a training and exchange programs to promote the improvement in neuroimaging and neuroscience systems in Latin America (Uludağ et al. 2009). Second, internationalization programs and governmental agencies should fund the exchange of researches and boost international collaboration (e.g. PrInt a program from Capes, a Brazilian governmental agency). Third, the academic mobility programs, mobility of academics seeking partnerships, exchange of information and ideas with researchers from different countries (Horta & Yonezawa 2013), should be stimulated. Fourth, editorial board of journals should increase the presence with authors representing the Global South (Pettorelli et al. 2021). Finally, data sharing and opening up data, in addition to generating new collaborations (Popkin 2019), it can lead to the development of large public databases.

In addition to research collaborations, it is important that countries commit to the global climate agreements. Some efforts to minimize GHG emissions, such as, restoration and combat to deforestation, are also useful for reducing the occurrence of *Ae. aegypti* and other insect vectors (Husnina et al. 2019, Mayi et al. 2019). These actions can help to minimize the invasion of anthropophilic mosquitoes, decreasing the incidence of infectious diseases (Bauch et al. 2014, Santos & Almeida 2018).

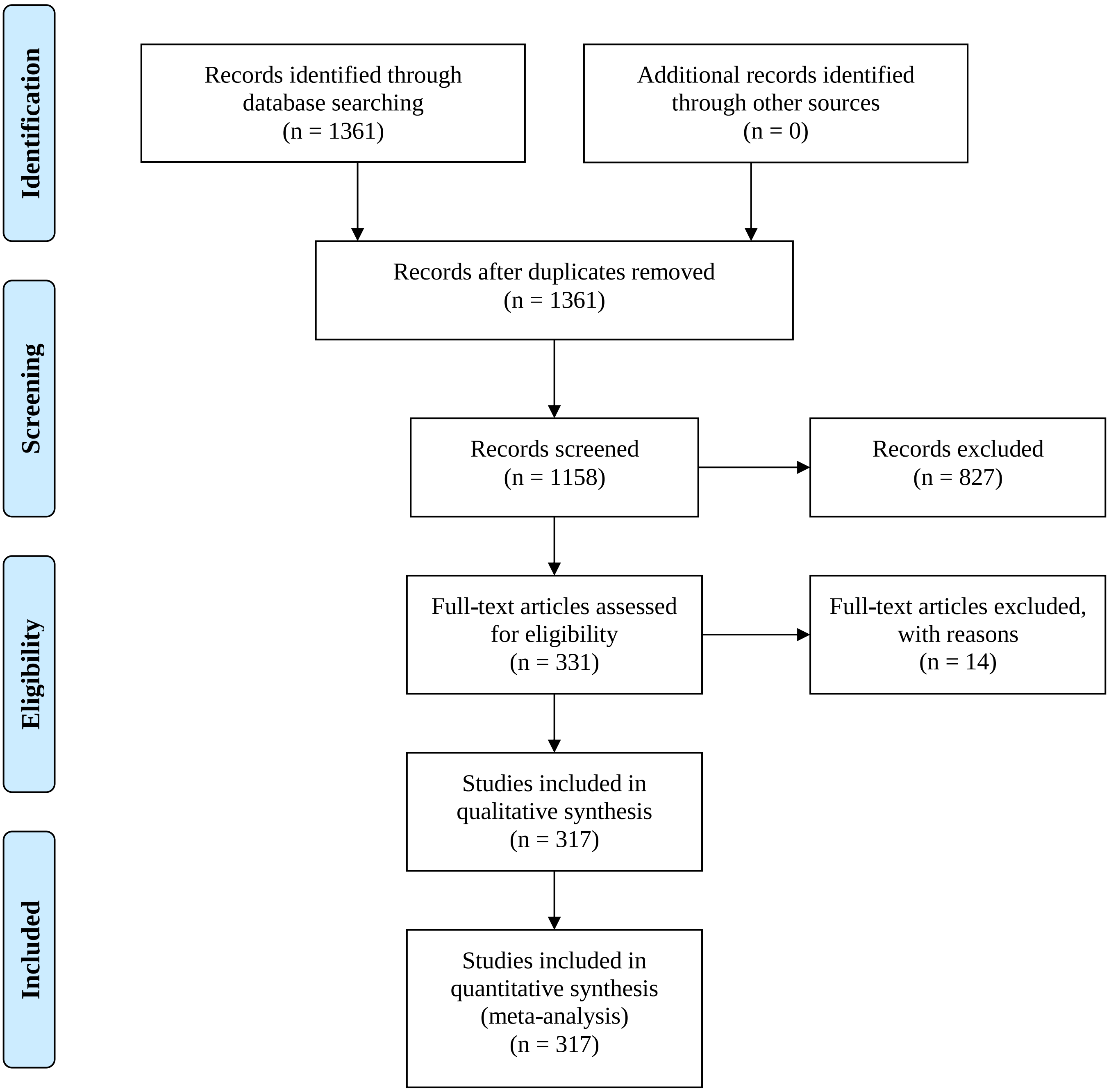
Conclusion

In general, studies evaluating the temperature or climate change effects on *Ae. aegypti* have attracted more attention from the scientific community in the last 30 years. Currently, more studies are investigating the effect of climate change on *Ae. aegypti*, while the number of studies assessing temperature effects has been decreasing. Two countries from South America are in the top 5 most productive countries and have many international collaborations in this area. They can act as hubs for other countries in the Global South, boosting research in the region. Many countries in Southeast Asia, South

America, and West and Central Africa, critical regions for the occurrence of *Ae. aegypti*, still have few publications in this area, so in future works, researchers should consider increasing international collaborations with these countries. The expansion in collaboration will ensure the knowledge required for these countries to arrange management actions in future climate change scenarios.

Supplementary material

SM1. PRISMA flow diagram



SM2. Bibliometric analysis methods using *VOSviewer* version 1.6.15

i) Keywords network

- we used keywords that were cited at least 2 twice
- trivial keywords and similar were removed, as follow: '*ae. aegypti*' a*edes-aegypti*' and '*aedes aegypti*'
- a merge term was performed, using thesaurus. We kept the term that appears more times. The following terms have been replaced:

  '*ae. albopictus*' replaced to '*Aedes albopictus*'
  'albopictus' replaced to '*Aedes albopictus*'
  'dengue virus' replaced to 'dengue'
  'matemathical modelling' replaced to 'mathematical model'
  'mosquitoes' replaced to 'mosquito'
  'mosquito-borne diseases' replaced to 'mosquito-borne disease'
  'ovitrap' replaced to 'ovitraps'
  'zika' replaced to 'zika vírus'

  The total keywords was 632, after application the filters 111 were used in keywords network.

- type of analysis: *co-occurrence*
- unit of analysis: *author keywords*
- counting method: *full counting*

SM3. The number of publications, number of dengue cases, and the socio-economic indices of each country.

Country	Number of publications	Dengue cases*	HDI**	Gini coefficient**	Per capita GDP***
Argentina	21	557	0.845	41.4	9912
Australia	32	1030	0.944	34.4	55060
Austria	2	85	0.922	29.7	50138
Bangladesh	1	29258	0.632	32.4	1856
Belgium	1	0	0.931	27.4	46421
Brazil	38	251663	0.765	53.9	8717
Canada	7	0	0.929	33.8	46195
Chile	1	10	0.851	44.4	14896
China	8	904	0.761	38.5	10262
Colombia	7	25993	0.767	50.4	6429
France	6	264	0.901	31.6	40494
Germany	4	629	0.947	31.9	46445
India	7	188401	0.645	37.8	2100
Italy	1	95	0.892	35.9	33228
Malaysia	4	82840	0.81	41	11414
Mexico	5	89518	0.779	45.4	9946
Nepal	3	2111	0.602	32.8	1071
Netherlands	2	0	0.944	28.5	52331
Norway	1	35	0.957	27	75420
Panama	1	9204	0.815	49.2	15731
Philippines	1	131827	0.718	44.4	3485
Portugal	2	11	0.864	33.8	23252
Romania	1	7	0.828	36	12919
Singapore	2	2689	0.938	NA	65233
Sri Lanka	1	185688	0.782	39.8	3853
Sweden	4	106	0.945	28.8	51615
Thailand	3	53190	0.777	36.4	7807
United Kingdom	13	465	0.932	34.8	42330
Uruguay	1	0	0.817	39.7	16190
USA	91	348	0.926	41.4	65297

* Dengue data were gathered from WHO (World Health Organization) of 2017.
** Human Development Index (HDI) data of 2019, and Gini coefficient of 2010-2018 (data of most recent year available during this period) were obtained from Human Development Report (United Nations Development Program 2020).
*** Gross domestic production (GDP) per capita data of 2019 was extracted from World Bank.

Chapter 2

Simulated climate change, but not predation risk, accelerates *Aedes aegypti* emergence in a microcosm experiment in western Amazonia

This chapter was published in volume 15(10): e0241070 of the PLoS ONE in 2020. doi: 10.1371/journal.pone.0241070.

Abstract

Climate change affects individual life-history characteristics and species interactions, including predator-prey interactions. While effects of warming on *Aedes aegypti* adults are well known, clarity the interactive effects of climate change (temperature and CO_2 concentration) and predation risk on the larval stage remains unexplored. In this study, we performed a microcosm experiment simulating temperature and CO_2 changes in Manaus, Amazonas, Brazil, for the year 2100. Simulated climate change scenarios (SCCS) were in accordance with the Fourth Assessment Report of Intergovernmental Panel on Climate Change (IPCC). Used SCCS were: Control (real-time current conditions in Manaus: average temperature is ~25.76ºC ± 0.71ºC and ~477.26 ± 9.38 parts per million by volume (ppmv) CO2); Light: increase of ~1,7ºC and ~218 ppmv CO2; Intermediate: increase of ~2.4°C and ~446 ppmv CO2; and Extreme: increase of ~4.5°C and ~861 ppmv CO2, all increases were relative to a Control SCCS. Light, Intermediate and Extreme SCCS reproduced, respectively, the B1, A1B, and A2 climatic scenarios predicted by IPCC (2007). We analyzed *Aedes aegypti* larval

survivorship and adult emergence pattern with a factorial design combining predation risk (control and predator presence – *Toxorhynchites haemorrhoidalis* larvae) and SCCS. Neither SCCS nor predation risk affected *Aedes aegypti* larval survivorship, but adult emergence pattern was affected by SCCS. Accordingly, our results did not indicate interactive effects of SCCS and predation risk on larval survivorship and emergence pattern of *Aedes aegypti* reared in SCCS in western Amazonia. *Aedes aegypti* is resistant to SCCS conditions tested, mainly due to high larval survivorship, even under Extreme SCCS, and warmer scenarios increase adult *Aedes aegypti* emergence. Considering that *Aedes aegypti* is a health problem in western Amazonia, an implication of our findings is that the use of predation cues as biocontrol strategies will not provide a viable means of controlling the accelerated adult emergence expected under the IPCC climatic scenarios.

Resumo

As mudanças climáticas afetam as características individuais de história de vida e a interação entre as espécies, incluindo a interação predador-presa. Embora os efeitos do aquecimento em *Aedes aegypti* adultos sejam bem conhecidos, os efeitos interativos entre as mudanças climáticas (temperatura e concentração de CO_2) e o risco de predação no estágio larval permanecem inexplorados. Nesse estudo, nós realizamos um experimento em um microcosmo que simula mudanças na temperatura e no CO_2 para o ano 2100 na cidade de Manaus, Amazonas, Brasil. Os cenários simulados de mudanças climáticas (SCCS) foram desenhados de acordo com o Quarto Relatório de Avaliação do Painel Intergovernamental sobre Mudanças Climáticas (da sigla em inglês IPCC). Os (SCCS) utilizados foram: Controle (condições climáticas atuais e em tempo real de Manaus, com temperatura média de ~25,76ºC ± 0,71ºC e ~477,26 ± 9,38 partes por milhão por volume (ppmv) de CO_2); Brando: aumento de ~1,7ºC e ~218 ppmv de CO_2; Intermediário: aumento de ~2,4°C e ~446 ppmv de CO_2; e Extremo: aumento de ~4,5°C e ~861 ppmv de CO_2, todos os aumentos foram relativos ao SCCS Controle. Os SCCS Brando, Intermediário e Extremo reproduzem, respectivamente, os cenários climáticos B1, A1B e A2 previstos pelo IPCC (2007). Nós analisamos a sobrevivência larval e o padrão de emergência de adultos de *Aedes aegypti* utilizando um desenho fatorial que combina o risco de predação (controle e presença do predador – larva de *Toxorhynchites haemorrhoidalis*) e os SCCS. Os SCCS ou o risco de predação não afetaram a sobrevivência larval de *Aedes aegypti*, mas o padrão de emergência dos adultos foi afetado pelos SCCS. Dessa forma, os nossos resultados não indicaram efeitos interativos dos SCCS e do risco de predação na sobrevivência larval e no padrão de emergência de *Aedes aegypti* criados em SCCS na Amazônia ocidental. *Aedes aegypti* é

resistente as condições testadas nos SCCS, principalmente devido a alta sobrevivência mesmo no SCCS Extremo, e cenários mais quentes aumentaram a emergência de adultos de *Aedes aegypti*. Considerando que o mosquito *Aedes aegypti* é um problema de saúde na Amazônia ocidental, uma implicação dos nossos resultados é que o uso de pistas de predação como uma estratégia de biocontrole de *Aedes aegypti* não é um meio viável para controlar a aceleração na emergência de adultos dessa espécie, essa emergência mais rápida é esperada de acordo com os cenários climáticos do IPCC.

Introduction

Climate change is among the main environmental concerns of this century (IPCC 2014a). Its effects on arthropod vectors have been stimulating intense research, due to the risks that such vectors may pose to human health. Mosquitoes are one of the main vectors of human diseases, globally causing more than 17% of all infectious diseases (WHO 2017). Worldwide, the geographic range of mosquitoes is expanding (Ryan et al. 2019), and the number of vector-borne diseases has also increased in recent years (Watts et al. 2018). The main mosquito-borne diseases, such as dengue and malaria cause some 700,000 deaths annually, and the large numbers of people infected often overloads health systems (WHO 2017). *Aedes aegypti* (*Ae. aegypti*) mosquitoes are one of the main disease vectors, being responsible for the transmission of dengue, yellow fever, Zika, and chikungunya viruses. Around the world, some 390 million people are infected with dengue virus each year (Bhatt et al. 2013). The effects of climate change on adult disease vectors are well known (Campbell-Lendrum et al. 2015, Franklinos et al. 2019), because the virus is transmitted during this stage. However, few studies focus on larval life-history, despite it being well known that changes that occur in the environment of the larval stage, such as climate change, may shape the development and behavior of adults (this being known as a carry-over effect) (O’Connor et al. 2014).

Climate change affects biodiversity at multiple levels. It may cause shifts on biomass (Dossena et al. 2012), metabolism and behavior (Laws 2017), at the individual level and, at population level, it can alter species distribution via changes in local conditions. Consequently, community composition can be altered by climate change (Gruner et al. 2017), changing ecosystems and food webs (Vucic-Pestic et al. 2011, Bellard et al. 2012, Boukal et al. 2019). There are two ways in which predator-prey interactions are influenced by climate change. First, it can increase the metabolic rates of individuals, as a consequence of higher temperatures (Vucic-Pestic et al. 2011), affecting the ability of predators to forage, capture and handle prey. In this way, climate change may modify prey density (density-mediated interactions) (Preisser et al. 2005); Second, besides direct predation, climate change alter predator-prey interactions via production, transmission, and reception of chemical cues. Under such circumstances, both predator and prey may suffer reduction in their abilities to detect each other (Draper & Weissburg 2019). In predation risk situations, releases of chemical cues is common, and the detection of predator by prey through them can modify feeding behavior and/or development rates (trait-mediated interactions) (Preisser et al. 2005).

Temperature increases can influence the metabolism, behavior and life-history traits of adult mosquitoes (Mordecai et al. 2017, Ezeakacha & Yee 2019), including speeding up development (Carrington et al. 2013, Couret et al. 2014, Leonel et al. 2015). This may result in enhanced offspring production and, consequently, increase the number of people infected by etiologic agents transmitted by mosquitoes. For example, Ryan et al. (Ryan et al. 2019) showed that warming increases the transmission risk of diseases caused by *Ae. aegypti* and *Aedes albopictus*. Meanwhile, predation risk can cause different responses in mosquitoes; adult female *Culex pipiens* increase dispersal distance in the presence of predators (Alcalay et al. 2018), while predation risk does not alter *Ae. aegypti* survivorship (Chandrasegaran & Juliano 2019), even though it decreases adults lifespan (Bellamy & Alto 2018). In natural systems, individuals, populations and community dynamics are all affected by both abiotic and biotic factors (Huston & McBride 2002). Thus, it is essential to better understand the unexplored interactive effects of simulated climate change scenarios (SCCS) and predation risk on

Ae. aegypti larval stage. Understanding the efficacy of predation risk in the development of a disease vector species under different SCCS can provide information on carry-over effects, and a perspective into the efficacy of using predation cues as biocontrol strategies.

Our overall goal was to understand the single and interactive outcomes of SCCS and predation risk on larval survivorship and adult emergence pattern of *Ae. aegypti*. It is important to consider this interaction in an environment that favors the development of this species, such as western Amazonia, where the climate is hot and humid throughout the year. Accordingly, we conducted an experiment in a microcosm simulating real-time climatic condition in Manaus (Control) and gradual increase in temperature and CO_2 in other three SCCS for this city in the year 2100. We used as a predator *Toxorhynchites haemorrhoidalis* (*T. haemorrhoidalis* Diptera: Culicidae) larvae to investigate the effect of predation risk on *Ae. aegypti*. This microcosm simulates four climate change scenarios predicted by the Fourth Assessment Report (AR4) of Intergovernmental Panel on Climate Change (IPCC) (IPCC 2007).

It is widely known that temperature increases, within thermal tolerance, affects development and behavior of *Ae. aegypti* (Reinhold et al. 2018). Predation risk alone would not affect directly prey survivorship, but might lead to changes in prey development and behavior, as well as phenotypic alterations (Preisser et al. 2005, Stoks et al. 2005). Although, effects of predation risk under climate change are uncertain, they can either accelerate, decrease or cause no change in prey behavior and life-history characteristics (Draper & Weissburg 2019). Accordingly, we hypothesized that the single or interaction effects of both ecological factors, SCCS and predation risk, would not affect *Ae. aegypti* larval survivorship, mainly since SCCS lie within the thermal tolerance of *Ae. aegypti* (Reinhold et al. 2018). Our second hypothesis was that increase in climatic variables (temperature and CO_2) under SCCS would accelerate adult emergence of *Ae. aegypti*, and interactive effects of SCCS and predation risk would lead to earlier emergence. In this context, we discuss implications of our findings concerning the impact of predation risk on *Ae. aegypti* larvae reared under different SCCS to western Amazonia.

Methods

Simulated climate change scenarios (SCCS)

The SCCS (microcosm) comprised of four chambers (4.05m x 2.94m), designed in accordance with the AR4-IPCC (2007) recommendations to simulate temperature and CO_2 concentrations for the year 2100 in Manaus. The microcosm is located in the Center for Studies of Adaptations of Aquatic Biota of the Amazon (long-term project ADAPTA), installed in the Laboratory of Ecophysiology and Molecular Evolution at the National Institute for Amazon Research (LEEM/INPA), Manaus, Amazonas, Brazil.

The SCCS include: i) Control: real-time current conditions in Manaus, Amazonas, Brazil, the average temperature is 25.76 ± 0.71ºC and the CO_2 concentration is 477.26 ± 9.38 parts per million by volume (ppmv). The other three scenarios reproducing respectively B1, A1B and A2 climatic conditions predicted by AR4-IPCC (2007) are: ii) Light: increase of ~1.7°C and ~218 ppmv CO_2, iii) Intermediate: increase of ~2.4°C and ~446 ppmv CO_2, and iv) Extreme: increase of ~4.5°C and ~861 ppmv CO_2. Temperature and CO_2 concentration of the Control SCCS varied instantaneously according to external values to capture real-time daily variation in Manaus. Values of temperature and CO_2 concentration for the Control SCCS were used to estimate values for Light, Intermediate and Extreme SCCS (S1 and S2 Figs). The SCCS was monitored automatically every 2 min to maintain temperature and CO_2 concentration values. Photoperiod was 12h light:12h dark, and humidity was approximately 80% in all chambers.

Predator and prey

To study the effect of predation risk on *Ae. aegypti* larval survivorship and adult emergence pattern, we designed two treatments: control (without predation) and predation risk using *T. haemorrhoidalis* larvae as the predator. This species frequently coexists in natural and artificial environments with *Ae. aegypti* (Steffan & Evenhuis 1981). *Aedes aegypti* larvae use different strategies to avoid predators, such as seeking shelter in macrophytes roots (Ofulla et al. 2010). In such habitats, they are under predation risk effects, which can lead prey to decrease the search for food resources and allocate energy in defense instead of development (Lima 1998, Werner & Peacor 2003). Larvae of *T. haemorrhoidalis* were collected in Manaus and, prior to the experiment, were housed individually in cups with water and fed daily with *Ae. aegypti* larvae until reaching the 3rd instar. Based on a pilot study, we estimated that each predator consumes one *Ae. aegypti* larva per day, and set this as the number to feed to the predators during the experiment. Predators were acclimatized in each SCCS for two days prior to the beginning of the experiment. We also acclimatized an additional two individuals for replacement purposes (in case a predator died).

Eggs of *Ae. aegypti* were obtained from colonies held by the Malaria and Dengue Laboratory at INPA. These colonies were established with wild-caught eggs collected in Manaus, using oviposition traps. *Aedes aegypti* eggs were collected with authorization and approval of the Brazilian Biodiversity Authorization and Information System (SISBIO; Permit 61563). We install multiple traps to obtain eggs in different private properties. Each owner gave us permission to install the traps. Fieldwork did not involve endangered or protected species. We placed filter paper to collect eggs of 4th and 5th generation adults from these colonies, and used these in the experiment. In each SCCS, the filter paper containing the eggs were placed in plastic containers until hatching occurred (± 17 hours). Following hatching, 60 first instar larvae were placed in each replication (see below).

Experimental design

We designed a factorial experiment to test the effect of predation risk and SCCS on *Ae. aegypti* larval survivorship and adult emergence pattern (Fig 1). Survivorship was defined as larvae that survived until the adult stage, to calculate this we used the number of emerged adults divided by the initial number of larvae in each replicate. Adult emergence pattern was estimated via counting the number of adults emerged in each replicate on a daily basis, time to adult emergence was considered from hatching to adult emergence. We included four replicates for each combination of factors (predation risk and SCCS). The experimental units were plastic containers (20x30x6 cm) with distilled water and fish food TetraMin™ to provide *Ae. aegypti* feed.

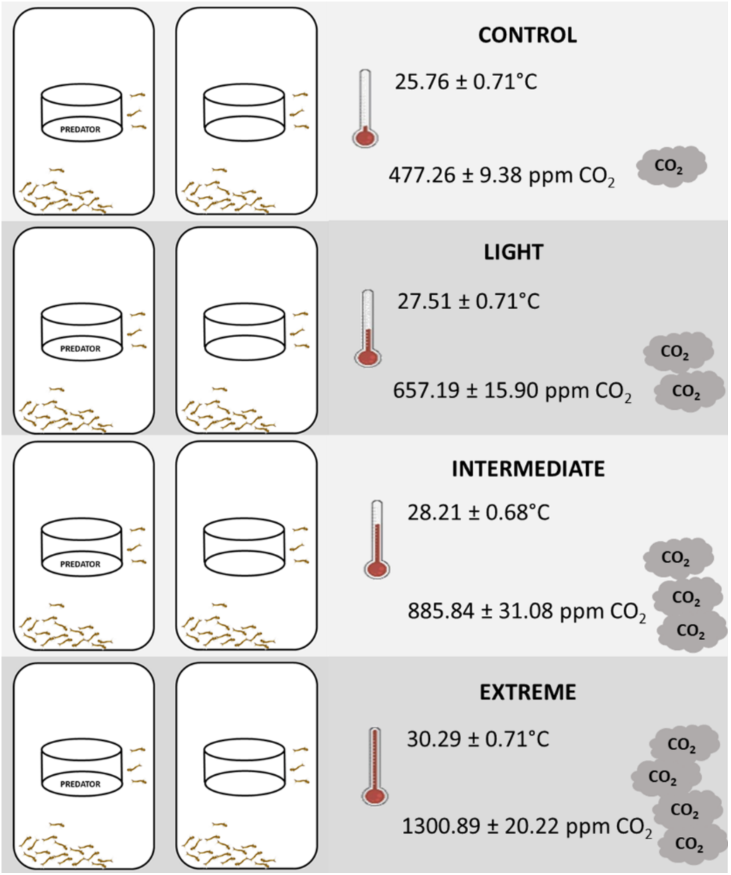


Fig 1. Experimental design. Experiment with two predation risk levels (predation risk – first column; and control – second column) in the four SCCS (Control, Light, Intermediate and Extreme - rows). Four replicates were used in the experiment. For each SCCS, the mean temperature and CO_2 concentration are shown. Humidity was 83.91 ± 2.10% in all scenarios.

At the beginning of the experiment, we filled the plastic containers with 600 mL of distilled water and placed the predator cage in the center of each container. The predator cage was a circular plastic container, 10.1 cm in diameter, sealed with nylon mesh to ensure water circulation, but still prevent entrance of *Ae. aegypti* into the predator enclosure (see Fig 1). The predator cage was placed in all experimental replicates (predation risk or control) to avoid any effect caused by the presence of the cage itself.

Then, to each replicate, we added one predator and 60 randomly selected *Ae. aegypti* first instar larvae. Each replicate received 0.0264g of food every two days. The density 0.1 larvae/mL and the amount of food were calculated to avoid effects related to intraspecific competition (Roberts & Kokkinn 2010). If evaporation occurred, water was added to the plastic containers to maintain the original water level. The 3rd instar *T. haemorrhoidalis* larvae were fed daily with one 4th instar *Ae. aegypti* larva, other than those used in the experiment. Predation of *Ae. aegypti* larva by *T. haemorrhoidalis* larva releases chemical cues that could be perceived by the other larvae in the container (Chandrasegaran & Juliano 2019).

Aedes aegypti were maintained in the replicates until adult emergence, we recorded the daily adult emergence and total survivorship in each replicate.

Statistical analysis

To evaluate whether the SCCS (Control, Light, Intermediate and Extreme), predation risk (predator and control), and their interaction, affected *Ae. aegypti* larval survivorship and adult emergence pattern, we performed a two-way ANOVA, while a *post hoc* least square means test was carried out if any of the tested factors tested were significant.

Adult emergence pattern was evaluated using two complementary approaches. We used linear mixed model considering the replicates as a random factor, an autocorrelation function to control repetition across days, and SCCS and predation risk as fixed factors. This model is equivalent to a two-way ANOVA with repeated measures, and was used to detect if SCCS, predation and their interaction affected the response variable, i.e. number of emergences, controlling the repeated measures and time autocorrelation. Second, to better understand the effect of these predictors on emergence patterns without including time in our models as fixed factor (keeping enough degrees of freedom), we evaluated the distribution of emergence time through the estimation of skewness and kurtosis of the adult emergence per day for each replicate. Skewness measures horizontal asymmetry in data distribution relative to normal curve. A symmetrical distribution is indicated by a skewness coefficient of zero; positive and negative skewness values indicate the data are right-skewed and have a longer right tail, and left-skewed with a longer left tail, respectively. For example, a right-skewed would indicate an early emergence of *Ae. aegypti*, whereas a left-skewed would indicate a late emergence. Kurtosis measures vertical asymmetry in data distribution relative to a normal curve. Zero values indicate a normal curve (mesokurtic); positive values (leptokurtic) indicate that the shape of the curve is more peaked than the normal distribution; negative values (platykurtic) indicate that the shape of the curve is flatter than the normal curve. A positive kurtosis would indicate that most larvae emerge at the same time, whereas a negative kurtosis would indicate a more evenly emergence distribution. Then, we applied a two-way ANOVA and a *post hoc* least square means test using skewness and kurtosis as response variables and SCCS and predation risk as predictors. Finally, we plotted emergence patterns per day. All analyses were carried out in the R environment (R Core Team 2020).

Results

Survivorship

Mean *Ae. aegypti* larval survivorship was higher than 78% for all SCCS. Larval survivorship was not affected by SCCS (F = 2.77, *P* = 0.0638), predation risk (F = 1.14, *P* = 0.2957), or by interaction between them (F = 1.45, *P* = 0.2517) (Fig 2).

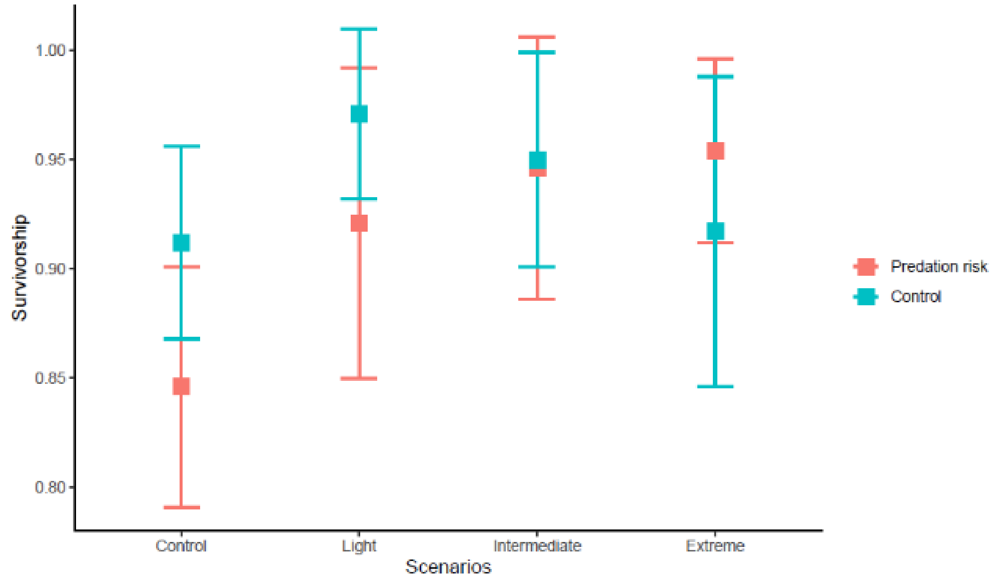


Fig 2. *Aedes aegypti* larval survivorship. Mean (confidence interval of 95%) of total larval survivorship of *Aedes aegypti* larvae after 14 days in four SCCS (Control; Light- increase of ~1.7°C; Intermediate- increase of ~2.4°C; and Extreme- increase of ~4.5°C) in the presence (predation risk) and absence (control) of *Toxorhynchites haemorrhoidalis* predatory larva.

Emergence patterns

The first *Ae. aegypti* adult emergence was on day seven in the Extreme SCCS (n = 3 individuals), on day eight in the Intermediate SCCS (n = 11 individuals), while in the Light and Control SCCS the first adult emerged on day nine (n = 39 individuals; n = 3 individuals, respectively), with higher emergence rate in the Light SCCS. Adult *Ae. aegypti* emergence was not influenced by fixed factors SCCS ($F = 0.0536$; $P = 0.9836$), predation risk ($F = 0.0221$; $P = 0.8819$), or their interaction ($F = 0.0282$; $P = 0.9936$). However, adult emergence pattern measured by skewness and kurtosis revealed interesting results. SCCS significantly affected both skewness ($F = 4.287$; $P = 0.0147$) and kurtosis ($F = 4.905$; $P = 0.0085$). Emergence pattern in the Intermediate SCCS was not significantly different from the Control SCCS (df = 24; $P = 0.0584$), but was significantly higher (right skewness) than the Light (df = 24; $P = 0.0269$) and Extreme (df = 24; $P = 0.0291$) SCCS (Fig 3). This indicates that most individuals emerged earlier in the Intermediate SCCS. Furthermore, emergence pattern estimated by kurtosis in the Intermediate SCCS was different from the other three SCCS (Control: df = 24, $P = 0.0449$; Light: df = 24, $P = 0.0286$; and Extreme: df = 24, $P = 0.0107$) (Fig 4). The Intermediate SCCS was the only one with positive kurtosis (peak of frequency distribution), indicating that most individuals emerged on day ten, while in the other SCCS the adult emergence was more evenly distributed across several days (Fig 5).

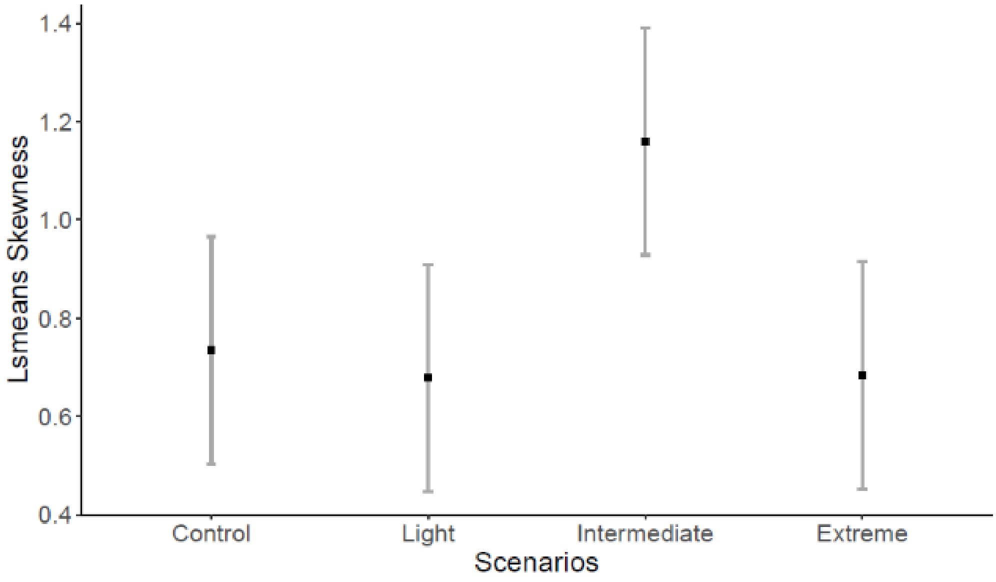


Fig 3. Least squares mean (confidence interval of 95%) for skewness. Emergence pattern estimated by skewness of *Aedes aegypti* between four SCCS (Control; Light- increase of ~1.7°C; Intermediate- increase of ~2.4°C; and Extreme- increase of ~4.5°C).

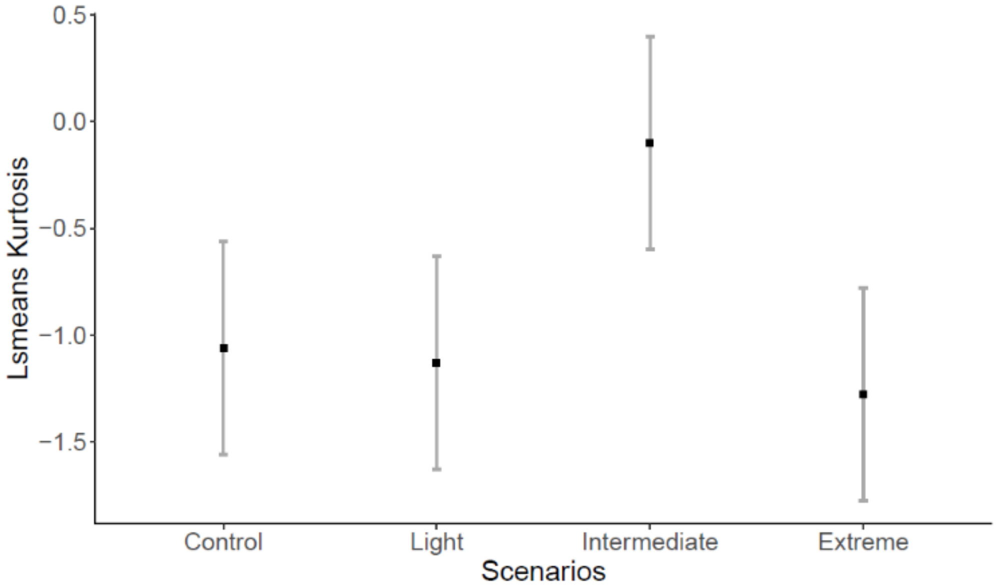


Fig 4. Least squares mean (confidence interval of 95%) for kurtosis. Emergence pattern estimated by kurtosis of *Aedes aegypti* between four SCCS (Control; Light- increase of ~1.7°C; Intermediate- increase of ~2.4°C; and Extreme- increase of ~4.5°C).

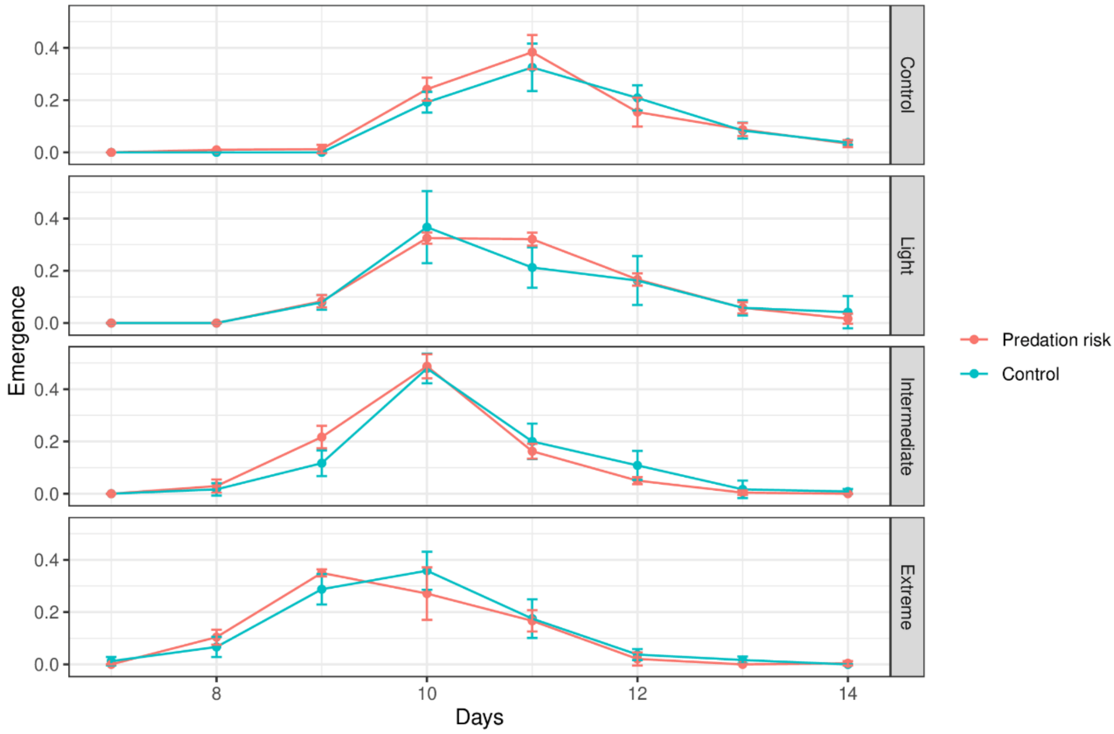


Fig 5. Mean (±SE) adult emergence of *Aedes aegypti*. Mean adult emergence in four SCCS (Control; Light- increase of ~1.7°C; Intermediate- increase of ~2.4°C; and Extreme- increase of ~4.5°C), and in two predation treatments: control and under predation risk (predator: *Toxorhynchites haemorrhoidalis* larva), from the first (day 7) until the last day (day 14) when all individuals reached adulthood.

Discussion

We showed that simulated climate change scenarios accelerate development time of *Ae. aegypti* larvae, which agrees with previous studies in western Amazonia (Leonel et al. 2015), with a emergence peak on a single day in Intermediate SCCS. We also found that *Ae. aegypti* larval survivorship was not affected by SCCS and predation risk, with larval survivorship rates being greater than 78% in all replicates, indicating the resilience of this species. We observed only SCCS did affect adult emergence pattern of *Ae. aegypti*, indicating that, in this study, climatic variables effects (temperature and CO_2 concentration) are stronger ecological driver than predation risk, particularly those related to chemical and visual cues.

Other studies have also reported that predation risk did not affect development time or survivorship *Ae. aegypti* larvae (Chandrasegaran et al. 2018, Chandrasegaran & Juliano 2019), although, in some cases, an effect was perceived in the adult stage. For example, blood feeding success was higher in *Ae. aegypti* females exposed to predator risk during the larval stage (Chandrasegaran & Juliano 2019). Similarly, Chandrasegaran et al. (Chandrasegaran et al. 2018) found interactive effects of predation risk, competition and food availability on teneral reserves in *Ae. aegypti* males. Also, interaction between predation risk and high intraspecific competition reduced the egg production of *Ae. aegypti* females (Chandrasegaran & Juliano 2019). In our study, we did not find any effect of predation risk on *Ae. aegypti* larval survivorship or adult emergence pattern, even in interaction with SCCS. These findings have implications for human health, as the impact of predation risk may not keep pace with the accelerated development of *Ae. aegypti* larvae under SCCS. Consequently, a warmer world will have more mosquitoes and an increase in vector-borne diseases (Iwamura et al. 2020).

Toxorhynchites haemorroidalis larvae, here used as predation risk, is a natural predator of other immature culicids and share the same oviposition habitats as *Ae. aegypti*. Accordingly, *Toxorhynchites* larvae have the potential to be used as a biocontrol agent, especially against disease vector species (Focks 2007). The presence of *T. haemorrhoidalis* larvae in our experiment could broadcast to chemical cues that, if detected by the *Ae. aegypti* larvae, could change the adult emergence pattern. Many studies on pest control use predation cues to manage pests. For example, beetle larvae consumed fewer leaves when these leaves were previously exposed to predators (Hermann & Thaler 2014). Chemical trails of ladybird on plants repel aphids that are cereal pest (Ninkovic et al. 2013). However, our finding suggests that biocontrol strategies based on predation cues are not effective in the control of *Ae. aegypti* larvae. However, it is important to highlight that it does not mean the direct predation of *Toxorhynchites* is not efficient as a biocontrol agent.

Some non-exclusive explanations can account for the absence of the interaction effect between SCCS and predation risk on *Ae. aegypti* larvae survivorship and adult emergence pattern. This absence may be due to an alteration caused by climatic variables in the release of chemical cues or decreasing prey sensitivity to chemical signals of predator presence (Harley 2011, Draper & Weissburg 2019). In addition, the presence of *Toxorhynchites* does not seem to be a real threat to some mosquito species. For example, species of *Aedes* select sites for oviposition based on levels of available organic matter, and they do not avoid areas where predators are present. As a result, females prioritize sites with abundant resources for their progeny, regardless of predator presence (Juliano et al. 2010, Vonesh & Blaustein 2010). Although the ability to detect predation risk varies among Diptera, Romero et al. (Romero et al. 2011) observed that predation risk did not affect Diptera flower visitation rates, contrary to many other insect orders assessed by them. Thus, as with other dipterous insects, *Ae. aegypti* larvae may not be able to detect predation risk.

Our results revealed that predation risk does not modify *Ae. aegypti* adult emergence patterns, but also showed that an increase in climatic variables (temperature and CO_2 concentration) caused distinct effects on emergence distribution of *Ae. aegypti*. We observed that the Intermediate and not the Extreme SCCS sped up the emergence of adult *Ae. aegypti*, agreeing with previous studies showing that warmer environments increase development (Carrington et al. 2013, Couret et al. 2014, Leonel et al. 2015). Typically, the relationship between temperature and life history traits is non-linear (Mordecai et al. 2019), and species have a thermal optimum to complete their development. Temperatures above the thermal optimum decrease species performance (e.g. immature survival). Although emergencies started earlier in the Extreme SCCS, the Intermediate SCCS revealed a pronounced emergence on a single day (10^{th} day). This suggests that the larval response to predation risk does not change the phenological patterns of *Ae. aegypti* larval development, but reveals that individual SCCS can alter patterns of emergence, a result with consequences and implications for human health.

Considering that *Ae. aegypti* is the vector of several diseases, and that the Intermediate SCCS is not so far from becoming a reality given the nature of mitigation measures taking place and the speed of their implementation, it is important to carry out this species might behave in the face of SCCS. As the climate change patterns across Amazonia will not be homogeneous (Marengo et al. 2009), it is important to carried out such experiments in ways that incorporate the nature of regional differences. There are many uncertainties in how combined effects of biotic and abiotic factors may influence *Ae. aegypti* larval life-history characteristics; our results add new pieces to this puzzle. Western Amazonia and regions with similar climatic conditions, will probably suffer increases in mosquito populations, partly as a result of the intensive urbanization process (the main driver to their establishment), and partly as a result of climate change, since, as we showed here, *Ae. aegypti* larvae develops faster under SCCS. Our study showed that biocontrol methods simulating predation risk using *T. haemorrhoidalis* larvae are unlikely to be effective for *Ae. aegypti* control, because these signals have no effect on this species. Though the use of *T. haemorrhoidalis* in direct biological control should not be discounted. Therefore, in the near future, shorter life cycles will result in high numbers of mosquitoes, with potential increase in cases of diseases caused by this vector.

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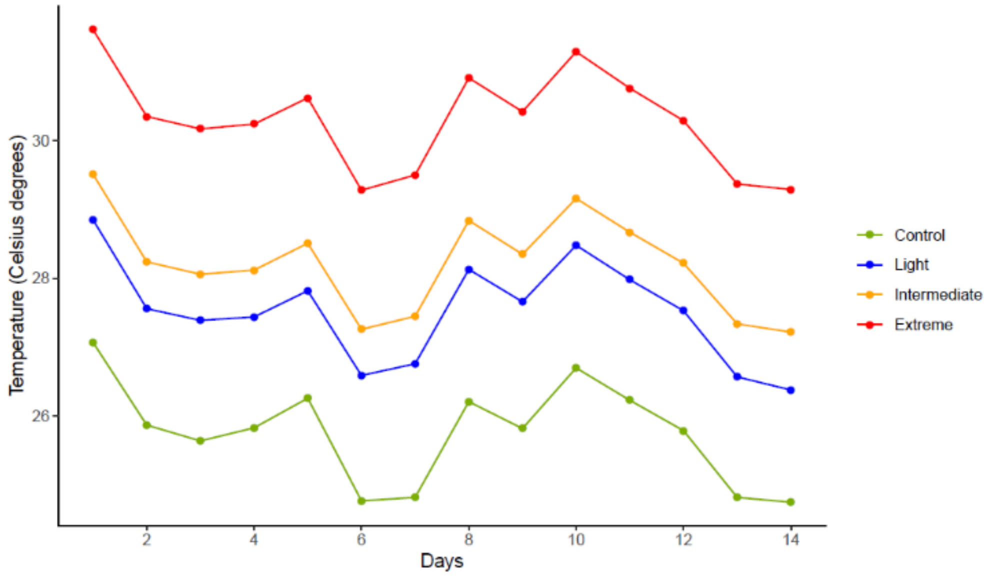
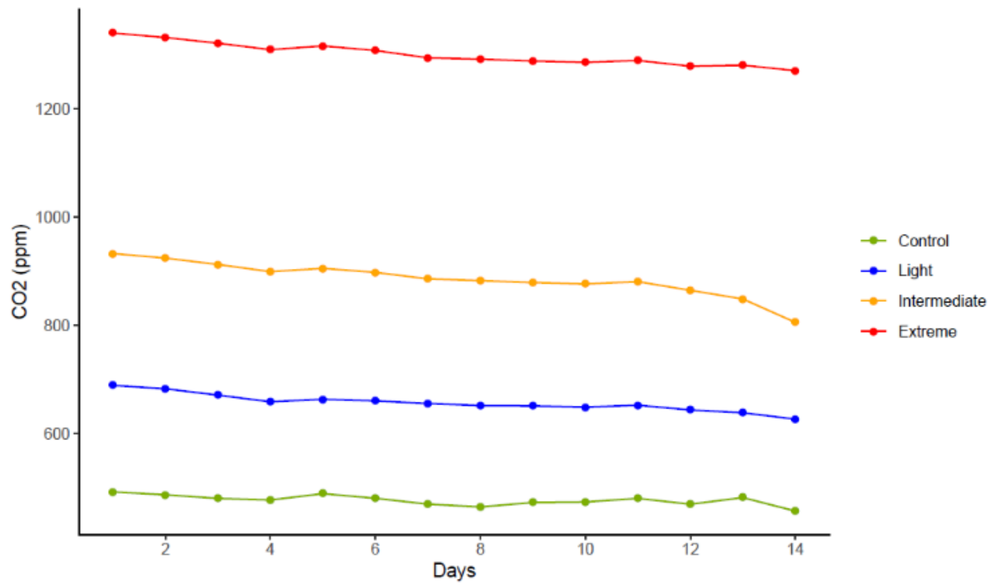
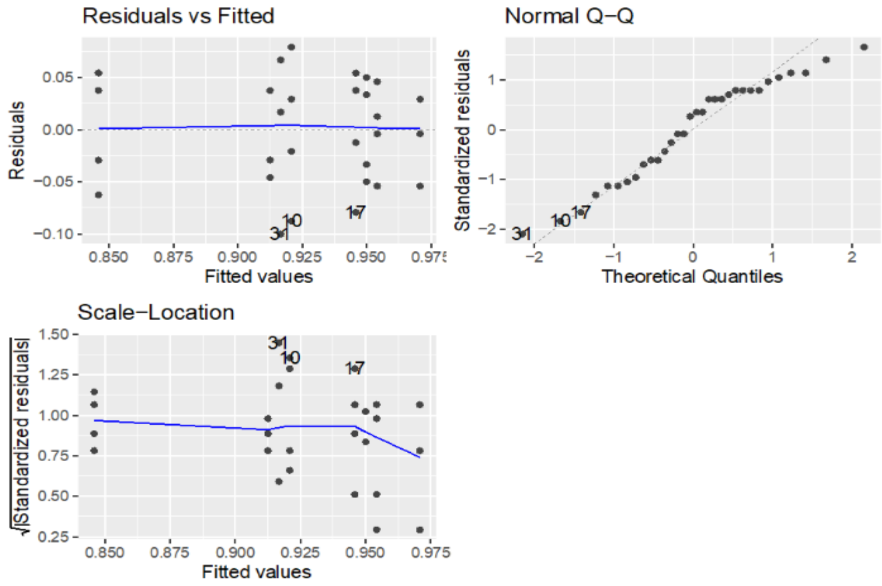
Supporting information



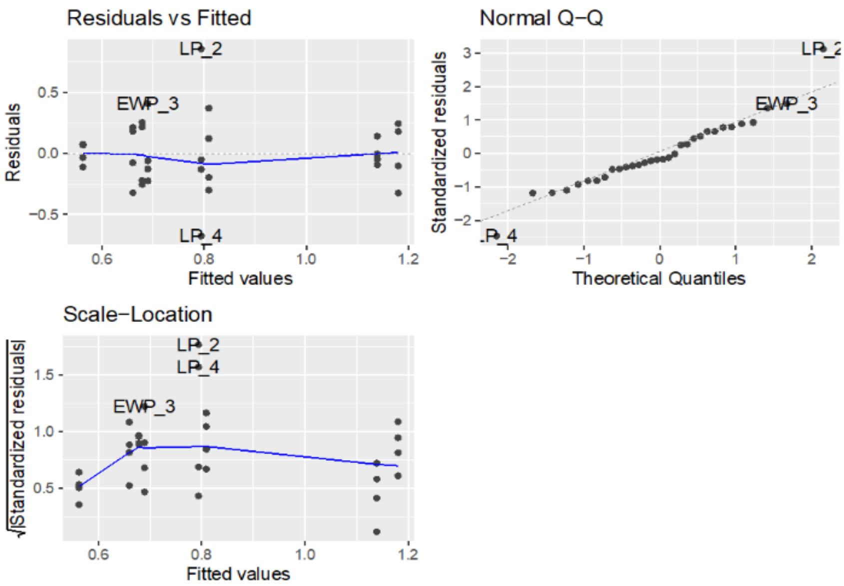
S1 Fig. Mean of daily temperature in each of the four simulated climate change scenarios during fourteen days of the experiment.



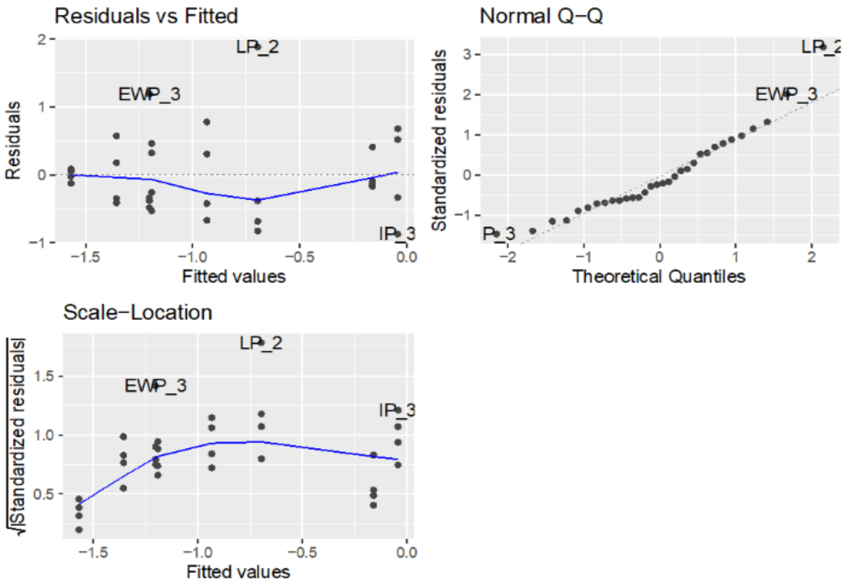
S2 Fig. Mean of daily CO_2 concentration in each of the four simulated climate change scenarios during fourteen days of the experiment.



S3 Fig. Diagnostic plots for the ANOVA model of survival as a function of predator (presence and absence) and SCCS (Control, Light, Intermediate and Extreme).



S4 Fig. Diagnostic plots for the ANOVA model of emergence skewness as a function of predator (presence and absence) and SCCS (Control, Light, Intermediate and Extreme).



S5 Fig. Diagnostic plots for the ANOVA model of emergence kurtosis as a function of predator (presence and absence) and SCCS (Control, Light, Intermediate and Extreme).

Chapter 3

Simulated climate change scenarios reveal distinct responses in antioxidant defense system of *Aedes aegypti* larvae and adult

Abstract

Climate change can affect species physiology, particularly ectotherms such as insects. Understanding how climatic change affect physiological responses at a cellular level of vectors of pathogens is important, because they affect the occurrence of diseases. We assess the effect of simulated climate change scenarios (SCCS) in the antioxidant defense system (ADS) of *Aedes aegypti* larvae and adults. *Aedes aegypti* is an interesting organism model because it has a complex and short life cycle, and is vector of several arboviruses that cause diseases, including dengue, Zika, chikungunya, and yellow fever. We performed a microcosm experiment in western Amazonia (Manaus, Amazonas, Brazil) simulating climate change scenarios by increasing temperature and CO_2 concentration simultaneously, according to predicted scenarios in the Fourth Assessment Report (AR4) of Intergovernmental Panel on Climate Change (IPCC) for the year 2100. *Aedes aegypti* larvae and adults were reared in this microcosm, composed of four SCCS, including the Control (current conditions in Manaus), and the other three scenarios correspond, respectively, to B1, A1B, and A2 climatic scenarios predicted by AR4-IPCC (Light: increase ~ 1.8ºC and 167 ppmv CO_2; Intermediate: increase ~ 2.5ºC and 315 ppmv CO_2 and Extreme: increase ~ 4.6ºC and 776 ppmv CO_2). We evaluated two main enzymes of ADS, superoxide dismutase (SOD), and catalase

(CAT) in *Aedes aegypti* larvae and adult females and males. We observed that ADS responses in *Aedes aegypti* larvae and adult females were similar, there was no difference in SOD activity neither in CAT activity among SCCS for larvae or females. However, SCCS affected enzyme activities in adult males. All SCCS differed in SOD activity in males, the highest activity of this enzyme was in the Extreme SCCS. Control and Light SCCS differed for CAT activity in males, the highest level was found in the Control SCCS. These results suggest that carry-over effects, when the experience lived during the larval stage can lead to changes in adult performance, can be sex-dependent for ADS and *Aedes aegypti* males have greater sensitiveness to climatic change than females. Our study sheds a new light on the effects of future SCCS in antioxidant defense system of *Aedes aegypti*, showing that ADS ability to respond to climate change was different in *Aedes aegypti* larvae and adults.

Resumo

As mudanças climáticas podem afetar a fisiologia das espécies, principalmente ectotérmicos como os insetos. Assim, é importante entender como variáveis climáticas podem afetar respostas fisiológicas a nível celular de uma espécie que é vetor de patógenos, pois isso pode afetar a ocorrência de epidemias causadas por arbovírus. O objetivo desse estudo foi avaliar os efeitos de cenários simulados de mudanças climáticas (SCCS) no sistema de defesa antioxidante (ADS) de *Aedes aegypti* larvas e adultos. *Aedes aegypti* é um modelo de estudo interessante, porque tem um ciclo de vida curto e complexo, e é vetor de várias arboviroses que causam doenças, como dengue, Zika, chikungunya e febre amarela. Nós desenvolvemos um experimento em um microcosmo na Amazônia ocidental (Manaus, Amazonas, Brasil), que simula cenários de mudanças climáticas nos quais a temperatura e a concentração de CO_2 aumentam simultaneamente, esse microcosmo foi construído de acordo com os cenários previstos no Quarto Relatório de Avaliação (AR4) do Painel Intergovernamental sobre Mudanças Climáticas (IPCC) para o ano 2100. Larvas e adultos de *Aedes aegypti* foram criados nesse microcosmo, que é composto por quatro SCCS: Controle (condições climáticas atuais em Manaus), onde a temperatura média é 28,48 ± 1,14ºC e a concentração de CO_2 é 462,79 ± 14,80 ppmv. Os outros três cenários correspondem respectivamente aos cenários climáticos B1, A1B e A2 previstos pelo AR4-IPCC, são eles: Brando: aumento ~ de 1,8ºC e 167 ppmv de CO_2; Intermediário: aumento ~ de 2,5ºC e 315 ppmv de CO_2 e Extremo: aumento ~ de 4,6ºC and 776 ppmv CO_2. Nós avaliamos as duas principais enzimas do ADS, superóxido dismutase (SOD) e catalase (CAT) em larvas e adultos machos e fêmas de *Aedes aegypti*. Nós observamos que as respostas do ADS de larvas e fêmeas de *Aedes aegypti* foram similares, não houve diferença na atividade da SOD

nem da CAT entre os SCCS para larvas ou para fêmeas. No entanto, a atividade das enzimas foi distinta entre machos adultos em resposta aos SCCS. A atividade da SOD em machos foi significativamente diferente entre todos os SCCS, a maior atividade desta enzima foi no SCCS Extremo. A atividade da CAT em machos foi diferente entre os SCCS Controle e Brando, o nível mais alto dessa enzima foi encontrado no SCCS Controle. Esses resultados sugerem que efeitos "carry-over", o qual ocorre quando a experiência vivida durante o estágio larval pode levar a mudanças na performance do adulto, pode ser dependente do sexo para o ADS, e que machos adultos de *Aedes aegypti* tem uma maior sensibilidade as variáveis climáticas do que as fêmeas. Nosso estudo traz novas informações sobre os efeitos de SCCS futuros no sistema de defesa antioxidante de *Aedes aegypti*, mostrando que a capacidade de resposta do ADS frente aos SCCS foi diferente em larvas e adultos da espécie.

Introduction

Climate change will cause numerous changes in ecological community structure and ecosystem function (Gillooly et al. 2002, Brown et al. 2004), altering species distribution (Chen et al. 2011) and inducing phenological changes (Cohen et al. 2018). However, many ecosystem-level consequences of environmental changes emerge from changes in individual physiological processes (Brown et al. 2004, Savage et al. 2004, Lemoine & Burkepile 2012). In this context, understanding the physiological response to climate change is critical for predicting the consequences of climate change on communities and ecosystems (Lemoine 2017). In addition, climate changes can be particularly challenging for organisms dependent of environmental temperature to regulate their physiological functions, such as insects (González-Tokman et al. 2020). Physiological alterations can cause changes in insect life-history traits, such as development and reproduction (Monaghan et al. 2009, Costantini et al. 2016). This assessment is highly relevant for vector-borne pathogens, which consequences go beyond ecosystem functioning and affect the occurrence of epidemics caused by arboviruses and, consequently, can impact public health (Patz et al. 2003).

Temperature increase, one of the main consequences of climate change, stimulates metabolic processes, which can cause an unbalance in oxygen rates within tissues, generating reactive oxygen species (ROS) (Lushchak 2011). ROS formation and accumulation may damage biomolecules, such as DNA, lipids, and proteins. In order to self-protect against ROS, organisms have a non-enzymatic (e.g. tocopherol and ascorbic acid) and enzymatic (e.g. superoxide dismutase, catalase, and peroxidases) antioxidant defense system (ADS). Oxidative stress occurs when ROS production is higher than its neutralization by the ADS (Halliwell & Gutteridge 2015). Accordingly, the response of individuals to oxidative stress can lead to consequences in their life-history, such as reproductive decisions (Costantini et al. 2016) and longevity (Beaulieu et al. 2015), generating trade-offs in resources allocation. For example, female butterflies reared at high temperature increased their antioxidant capacity and longevity, but laid fewer eggs compared to control temperature (Beaulieu et al. 2015).

Most studies on the impact of climate change are based on the effect of changing temperature, because it is a key variable in metabolism (Johnston & Bennett 2008). Despite that, evidences suggest impacts on the metabolism and physiology due to the simultaneous effects between temperature and CO_2 on ADS. For example, Li et al. (2017) detected differences in ADS enzymes of whitefly *Bemisia tabaci* adults exposed to high temperature and CO_2. They detected and increase of superoxide dismutase (SOD) and peroxidases (POD) activities under high temperature and CO_2, whereas catalase (CAT) activity was lower compared to control. Considering that temperature rise are associated with increasing atmospheric CO_2 concentrations (IPCC 2014c), and both variables are hardly dissociated in a long term scenario, it is important to understanding the responses of ADS of insects, especially those vector of diseases.

Most aquatic insects have complex life cycle, undergoing different environments during their life stages. Larvae and pupae inhabit aquatic systems, while adults are terrestrial (Wilbur 1980). In this way, the efficiency in enzymes activity of ADS can be different during these life stages, to avoid possible damage caused by metamorphosis (e.g. increase in free radicals production) (Jovanović-Galović et al. 2004) or by stressors in the environment (Chen et al. 2018, Yousef et al. 2019). In addition, the experience lived during the larval stage can change adult performance, known as carry-over effect (O'Connor et al. 2014).

In this way, our goal in this study was to evaluate the effects of climate change on ADS of *Aedes aegypti* (*Ae. aegypti*) larvae and adults reared in simulated climate change scenarios (SCCS). The SCCS is a microcosm composed of four rooms that simulate a simultaneous increase in temperature and CO_2 concentration, ranging from a Control SCCS to an Extreme SCCS. The SCCS are based on climatic conditions predicted by Fourth Assessment Report (AR4) of Intergovernmental Panel on Climate Change (IPCC, 2007). We evaluated CAT and SOD, two main enzymes of ADS, across *Ae. aegypti* life stages (larvae and adults from both sexes). *Aedes aegypti* is a vector of viruses that causes diseases, including dengue, Zika, chikungunya, and yellow fever, and has a short and complex life cycle, rendering an interesting organism model of study.

Considering that *Ae. aegypti* larvae were exposed to different climatic conditions in each SCCS and that temperature increase may stimulate metabolic processes, our first hypothesis is that enzymatic activity of *Ae. aegypti* fourth instar larvae, as well as adults, will be crescent with increasing in climate variables. Considering that in many situations, males are more sensitive than females (Gupta et al. 2007, Blanckenhorn et al. 2014, Dmochowska-Ślęzak et al. 2015), possibly due to their differences in metabolic rates (Rogowitz & Chappell 2000), our second hypothesis is that ADS males responses to climate change would be more pronounced than females.

Material and Methods

Simulated Climate Change Scenarios (SCCS)

In order to understand the effects of climatic variables on *Ae. aegypti* larvae and adults, we reared individuals in a microcosm that simulate climate change scenarios (increase in temperature and CO_2 concentration). The microcosm is located in the Center for Studies of Adaptations of Aquatic Biota of the Amazon (long-term project ADAPTA), installed in the Laboratory of Ecophysiology and Molecular Evolution at the Instituto Nacional de Pesquisas da Amazônia (LEEM/INPA), Manaus, Amazonas, Brazil. The microcosm was constructed according to the Fourth Assessment Report (AR4) of the IPCC (2007), and simulated current climatic conditions in Manaus and three future climatic conditions predicted for the year 2100. The microcosm is composed by four rooms and each one simulate a climate change scenarios, including: i) Control (current conditions in Manaus), average temperature 28.48 ± 1.14ºC and CO_2 concentration 462.79 ± 14.80 ppmv; ii) Light: increase ~ 1.8ºC and 167 ppmv CO_2; Intermediate: increase ~ 2.5ºC and 315 ppmv CO_2; Extreme: increase ~ 4.6ºC and 776 ppmv CO_2. The Light, Intermediate and Extreme SCCS simulated respectively B1, A1B and A2 climatic conditions predicted by AR4-IPCC (2007). The reference for the increase in temperature and CO_2 is the Control SCCS. The humidity was about 73% in all rooms. To ensure the system accuracy, temperature and CO_2 was measured every two minutes in all rooms.

Aedes aegypti larvae and adults

All *Ae. aegypti* eggs used in the experiments were obtained from Malaria and Dengue laboratory, localized at the INPA. Fourth instar larvae and adult mosquitoes (males and females) were used in these experiments. These organisms were entirely reared in the microcosm (from egg to adult). In each SCCS, we added plastic containers (replicates) filled with distilled water (1000 ml). Previous to the beginning of the experiment, we placed only the containers with water in each SCCS during 24 hours for water acclimation. After this period, *Ae. aegypti* eggs were added in all SCCS and after their hatching (after ± 17 hours) first instar larvae were randomly chosen and put into the replicates. We used six replicates per SCCS and placed 100 larvae per replicate. Larvae were fed every two days with 0.044g fish food Tetramin™, resulting in a ratio of 0.1 larva/ml of food. This ratio avoids intraspecific competition (Alto et al. 2005, 2008). If water evaporated, the plastic containers were refilled with distilled water to maintain the initial water volume. We carried out independent set of experiments for each life stage, one set for larvae and another set for adult mosquitoes. For the first set of experiments, we followed the egg development up to the fourth larval instar, the 4^{th} instar larvae were used for the analysis of the antioxidant defense system. For the second set of experiments, we followed the egg development until the adults emergence, right after emergence the adults were removed from each replicate using an entomological aspirator and separated by sex for the analysis of the antioxidant defense system.

Antioxidant defense system

We define an independent pool of individuals, ranging from 25-30 living individuals from each replicate, for larvae, adult females, and adult males. Each pool was homogenized using a cold pestle and mortar in phosphate buffer solution (pH 7.2) containing 0.01 mM phenylmethylsulfonyl fluoride. The homogenate was centrifuged for 20 min at 4°C and 4.000 *g*. The supernatant was carefully collected and frozen at 20ºC for further analysis.

To estimate the protein content, we followed the Bradford method (1976), using albumin bovine serum as standard. We quantified superoxide dismutase (SOD) and catalase (CAT), two main enzymes of the insect antioxidant defense system (ADS)

(Felton & Summers 1995). SOD activity was quantified using SOD Assay Kit (Sigma-Aldrich), which monitors the formazan dye upon reduction of WST-1 (water-soluble tetrazolium salt) at 440 nm. SOD activity was expressed in Units (U) SOD/mg^{-1} protein. One unit of SOD is the amount of sample required to cause 50% inhibition of the colorimetric reaction. CAT activity was quantified following Aebi protocol (1984), which measured CAT activity by hydrogen peroxide (H_2O_2) degradation at 240 nm. One unit of CAT was defined as enzyme activity that catalyzed reduction of 1μMol H_2O_2/minute/mg protein. All tests were made at least in duplicate.

Statistical analyses

To evaluate if the activity of antioxidant enzymes (SOD and CAT – response variables) of *Ae. aegypti* larvae, females and males differ between in SCCS (predictor with four levels: Control, Light, Intermediate and Extreme), we performed a generalized linear model (GLM) with gamma distribution. Gamma distribution is ideal for positive and continuous response variable and diagnostic plots also indicate that gamma distribution was the best choice compared to Gaussian distribution. Analyses were separately run for each enzyme, life stage and sex. If we detected a significant effect of SCCS on enzyme activity, we carried out a *post hoc* least square means test to verify differences in enzyme activity for each comparison of SCCS. We reported pseudo R^2 estimated by Nagelkerke method (Nagelkerke 1991). All analyses were carried out in the R environment (R Core Team 2020).

Results

Antioxidant defense system responses, measured through SOD and CAT enzymes, were similar in *Ae. aegypti* larvae and females, while male responses were affected by SCCS. For larvae and females, SCCS did not affect SOD (larvae: P = 0.1224, pseudo R^2 = 0.278; females: P = 0.3540, pseudo R^2 = 0.231 – Fig.1 a, b) and CAT activity (larvae: P = 0.0553, pseudo R^2 = 0.383; females P = 0.8913, pseudo R^2 = 0.079 – Fig.2 a, b). For *Ae. aegypti* males, we detected significant differences in the activity of both enzymes (SOD: P<0.0001; pseudo R^2 = 0.903; CAT: P = 0.016; pseudo R^2 = 0.512). We also found that all SCCS differed in SOD activity (Control and Light: P = 0.0182; Control and Intermediate: P<0.0001; Control and Extreme: P<0.0001; Light and Intermediate: P = 0.070; Light and Extreme: P<0.0001; Intermediate and Extreme: P<0.0001 – Fig. 1c) and the Control and Light SCCS differed for CAT activity (P = 0.0166 – Fig. 2c).

Enzymatic activity of CAT and SOD for *Ae. aegypti* males showed a similar pattern in all SCCS, except in the Extreme SCCS. For both enzymes, we observed a high baseline level in the Control SCCS, and the activity decreases in Light and Intermediate SCCS. Among SCCS, the highest levels of SOD for males were found in the Extreme SCCS (twice as high as the baseline level), while for CAT the highest level was found in the Control SCCS.

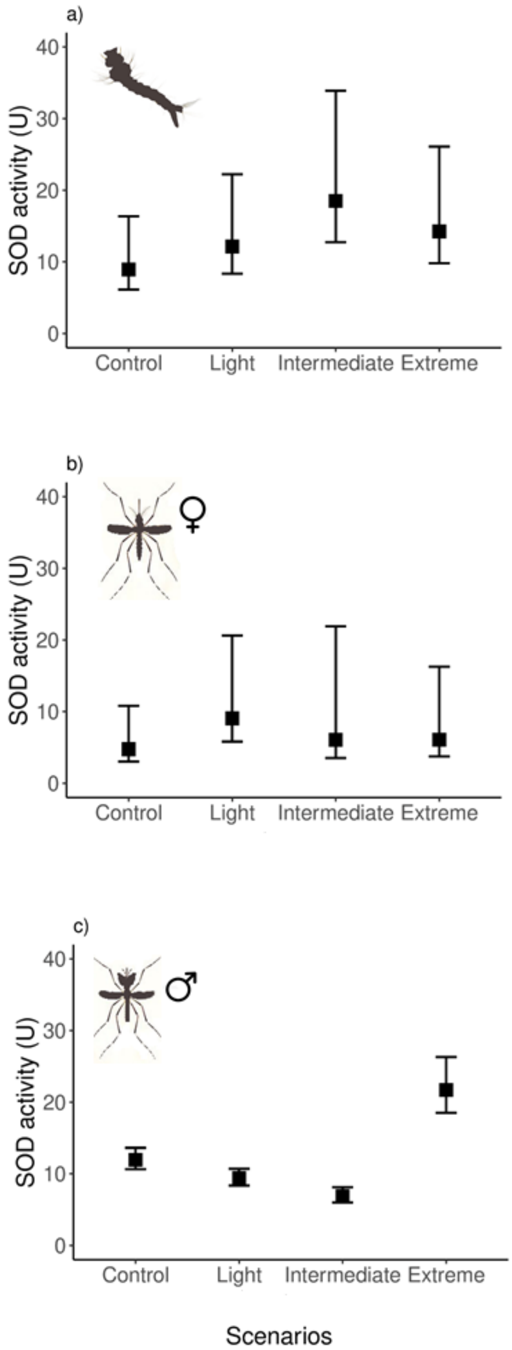


Fig. 1 – Mean and confidence interval (95%) of superoxide dismutase (SOD) activity in *Aedes aegypti* (a) larvae, (b) female, and (c) male reared in a microcosm that simulates four climate change scenarios: Control – current conditions in Manaus and Light, Intermediate and Extreme, simulated respectively B1, A1B and A2 climatic conditions predicted by AR4-IPCC (2007).

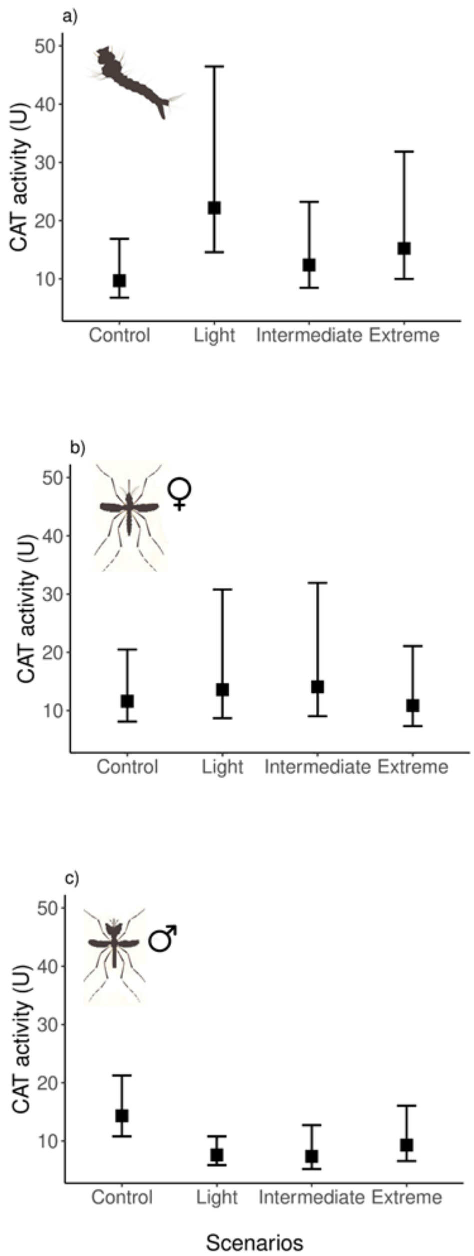


Fig. 2 – Mean and confidence interval (95%) of catalase (CAT) activity in *Aedes aegypti* (a) larvae, (b) female, and (c) male in reared in a microcosm that simulates four climate change scenarios: Control – current conditions in Manaus and Light, Intermediate and Extreme, simulated respectively B1, A1B and A2 climatic conditions predicted by AR4-IPCC (2007).

Discussion

Insect responses to stressors may be shaped by life stage (Blanckenhorn et al. 2014), sex (Gupta et al. 2007), physiology (Beaulieu et al. 2015) and may vary between population and individuals (Sinclair et al. 2012). Here, we observed that simulated climate change scenarios (SCCS) drove distinct responses in ADS of *Ae. aegypti* larvae, adult females and males. Larvae and females were not affected by SCSS, different from males. We did not detect differences in both SOD and CAT enzyme activity of *Ae. aegypti* larvae between SCCS, different from our hypothesis. Temperature ranges in SCCS were within the thermal range variation of *Ae. aegypti* development, ranging from 16ºC to 34ºC (Christophers 1960), and the individuals were exposed since egg to adults in all SCCS. These circumstances can facilitate larvae acclimation (Gray 2013).

Contrary to our first hypothesis, females maintained the same baseline level, using as reference the Control SCCS, for both enzymes in all SCCS, while males showed differences in both enzymes as a response to SCCS. Supporting our second hypothesis, ADS of *Ae. aegypti* males were more sensitive than females, which may indicate that *Ae. aegypti* females had a developmental acclimation to SCCS related to their phenotypic plasticity during early life stage (Angilletta 2009), possibly creating a carry-over effect that is sex-dependent.

Considering that insects sensitivity to environmental changes is distinct at each life stage (Kingsolver et al. 2011) and sex-specific (Blanckenhorn et al. 2014), the different responses of *Ae. aegypti* may be related to life-history trade-offs. Energy allocation in one aspect of life-history decreases the investment elsewhere (Monaghan et al. 2009), and larvae invest their energy on development. In a study using the same SCCS as we did here, Piovezan-Borges et al. (2020) observed about 78% of *Ae. aegypti* larval survivorship in all SCCS. Then, a large amount of energy available in an unlimited food environment may be allocated to development and less energy is displaced to ADS.

Females kept their antioxidant defense stable regardless SCCS, indicating greater acclimation to SCSS than males. In *Ae. aegypti* females, the energy that would be used on ADS can be allocated for investment in reproduction. Costantini et al. (2016) showed that for songbird females with reduced antioxidant defenses, the increase in oxidative stress has delayed egg laying and reduced clutches size compared to control, but the reproductive success was not affected. An investment in reproduction can be a good solution in a short-term period, however, it can generate consequences in long-term. Considering that low investment is applied on ADS, there is a great chance for damage on biomolecules caused by reactive oxygen species (ROS) accumulation, which can lead to accelerated senescence (Monaghan et al. 2009). Another possibility is that a large amount of ROS may have been formed, inhibiting the enzymatic activity of SOD and CAT (Ma et al. 2017), or even this inhibition may have been caused by the action of CO_2 (Mitsuda et al. 1958) which can cause damage to biomolecules. New studies should consider this trade-off of energy allocation between reproduction and ADS, which goes beyond this study.

Aedes aegypti males were more sensitive to SCCS than larvae and females. For males, we observed that Light and Intermediate SCCS decreased SOD activity compared to Control SCCS (basal level), but a large increase in the Extreme SCCS. Possibly, in the Extreme SCCS the ROS production was higher than the other SCCS, increasing SOD activity. One product resulting from SOD activity is H_2O_2, which may be degraded by CAT or POD. It is expected that in SCCS with increase in SOD activity, CAT activity would also be increase (Ighodaro & Akinloye 2018), but we did not observe this pattern in *Ae. aegypti* males. Two non-exclusive explanations can help to understand the pattern we found: i) CAT amount in organisms exposed to Extreme SCCS was not sufficient to degrade the H_2O_2 formed, and ii) H_2O_2 degradation was processed by another enzyme, such as POD (Felton & Summers 1995, Halliwell & Gutteridge 2015). The increase in SOD activity in newly emerged males in Extreme SCCS can decrease cellular damage, and may increase longevity, being a long-term investment (Metcalfe & Monaghan 2003). However, we highlighted that it is necessary to evaluate other factors, such as reproduction rates and adult longevity to better comprehend trade-offs of energy allocation.

Other studies using newly emerged insects also showed differences on physiological responses between males and females. Dmochowska-Ślęzak et al. (2015) evaluated variation in ADS in the different life stages of mason bee *Osmia bicornis,* and found that newly emerged males had higher SOD and CAT activity than females. Gupta et al. (2007) evaluated cellular damages by organophosphate compounds in reproductive tissue of *Drosophila* males and females, and they showed that males were affected and decrease their reproductive responses, generating a reduced offspring. They argue that these damages may reduce the reproductive performance of males. This difference between males and females may be due to differences in their metabolic rates (Rogowitz & Chappell 2000).

Evidences suggest that very large increase in temperature is necessary for CAT and SOD activation and increase activity. Zhang et al. (2015) detected increase in SOD activity in a ladybeetle species exposed to 39ºC, 14ºC higher than the temperature in the control, while a significant increase in CAT activity was detected at 35ºC. Cui et al.

(2011) observed an increase in SOD activity in the rice borer *Chilo suppressalis* larvae at 36ºC, while for CAT the enzyme activity increases from 33ºC to 39ºC. Here, the simultaneous effect of the increase in temperature and CO_2 on the Extreme SCCS (with an average temperature of 33ºC), activated the ADS of *Ae. aegypti* males in this SCCS, which further highlights its sensitiveness.

Overall, our study sheds new light on physiological responses of *Ae. aegypti*, an important pathogen vector, to SCCS. Our results illustrate that ADS ability to respond to SCCS differ in *Ae. aegypti* larvae and adults, due to higher sensitiveness of male s compared to larvae and females. When exposed to Extreme SCCS, the first antioxidant defense line, measured through SOD, was activated in *Ae. aegypti* males, revealing that this climatic condition can be challenging for males. In this context, part of males energy must be allocated to combat ROS formation as a consequence of an increase in temperature and CO_2 concentration. In contrast, climatic variables tested in all SCCS do not seem to be sufficient to activate the antioxidant defenses of *Ae. aegypti* larvae and females. Then, less energy is used to neutralize ROS formation by ADS, and larvae and females may invest energy into their development and reproduction, respectively.

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General conclusion and perspectives

In this thesis, I investigated the climate change effect on *Aedes aegypti* (*Ae. aegypti*) addressing different scales. In a global perspective, I evaluated patterns of studies related to the temperature and climate change effects on *Ae. aegypti*. Moreover, I evaluated how simulated climate change scenarios (SCCS) predict for the year 2100 affects the species development and their physiological characteristics.

In the global patterns of studies, I showed the research network in this area marginally includes countries that suffer from problems related to diseases caused by the species, an alarming result. Moreover, the results of the second chapter (species development) reinforce predictions regarding an increase in mosquito population in a close future, due to the high survivorship of *Ae. aegypti* even in Extreme SCCS, and the faster emergence in warmer climatic conditions, regardless of predation risk. The results of the chapter assessing the physiological scale evaluated through antioxidant defense system of *Ae. aegypti* showed a higher sensitivity of males to SCCS compared to females and larvae, indicating that energy allocation may differ between life stages and sexes.

Considering all these results, I suggest that future researches should:

i) Extend the international collaboration in this area, mainly with regions where *Aedes aegypti* is abundant, or would expand its distribution due to future climate change scenarios.

ii) Investigate the influence of direct predation in *Ae. aegypti* in SCCS, to evaluate the specie survivorship in these conditions, and the predator foraging behavior in SCCS.

iii) Test whether predation risk can affect the interspecific interaction of species vector of pathogens reared in SCCS.

iv) Investigate development and reproduction of *Ae. aegypti* adults reared in SCCS to understand the energetic costs of these processes for both sexes.

Climate change is a global challenge, and due to its consequences, the scientific community, and many governments are considering this phenomenon as a priority. The results of this thesis reinforce that is essential to strengthen research networks in this area and find new strategies for vector control. Besides that, vector control measures, mitigating greenhouse gases emissions, as well as reforestation and decreased deforestation is essential to avoid the increase in problems caused by *Ae. aegypti*.

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Appendix

List of 317 studies used in bibliometric analysis of Chapter 1.

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