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CLIMATE CHANGE AND CHAGAS DISEASE IN THE AMERICAS: A QUALITATIVE SYSTEMATIC REVIEW

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CLIMATE CHANGE AND CHAGAS DISEASE IN THE AMERICAS: A QUALITATIVE SYSTEMATIC REVIEW

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While many studies have found associations between climate change and factors affecting Chagas disease transmission, the future impact of climate change on the global spread of Chagas disease remains debatable. A qualitative, systematic review was conducted to assess the impact of climate change on Chagas disease transmission in the Americas (Central America, South America, and North America). The literature search was performed in January 2019 using the keywords climate, Chagas, and "trypanosoma cruzi" and the electronic databases PubMed, Scopus, and Ovid. Searches retrieved records from 1982 through 2019. The initial electronic database search identified a total of 191 record documents and 23 additional records through other sources. After assessment for inclusion eligibility, seven articles fulfilled the selection criteria and were included in the review. Most studies under review showed that Chagas disease transmission is highly sensitive to climate factors, specifically temperature, relative humidity, and precipitation. The majority of reviewed studies conducted in Latin American predict stable or decreased vector distributions and *T. cruzi* transmission rates as future consequences of climate change in their study areas. Notably, Mexico was the only geographical area studied in the Americas where

Chagas disease is currently endemic and also predicted to be at increased transmission risk under future climate change scenarios. Similarly, an expansion of areas in the United States at increased risk for Chagas disease transmission is also expected over the next several decades under climate change scenarios. Of particular interest is the predicted northern shift of triatomine species to central regions of the United States with historically unsuitable climates for *T. cruzi* vectors. The weight of evidence regarding the influences climate change may pose on *T. cruzi* vector species distributions demonstrates the sensitivity of Chagas disease transmission to future climate variability. In order to advance forecasts for the impact climate change may have on Chagas disease transmission in the Americas, it is imperative to further develop, utilize, and perhaps combine predictive species distribution modeling approaches that integrate accurate, long term data on climate variables, vector species distributions, Chagas disease incidence, as well as other socio-ecological variables.

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BACKGROUND

Epidemiology of Chagas Disease

Chagas disease, or American trypanosomiasis, is an emerging major public health concern for the growing world population and is currently a leading cause of chronic morbidity and mortality throughout Latin America (Bonney, 2014). Endemic to 21 Latin American countries (Schmunis, 2007), Chagas disease has been increasingly detected in non-endemic regions, such as the southern United States, over the last several decades. Recent data from the World Health Organization (WHO) estimates that over 25 million people are at risk of contracting Chagas disease worldwide, with approximately eight million people currently infected with *Trypansosoma cruzi* (*T. cruzi*), the intracellular protozoan parasite that causes Chagas disease (WHO, 2018). As one of the most prevalent, albeit neglected, infectious diseases of the Americas (Tapia-Garay et al., 2017), *T. cruzi* is "responsible for the third highest number of parasitic infections in the world, following malaria and schistosomiasis" (Diaz, 2008, p. 184), with 180,000 new *T. cruzi* infections occurring annually. Overall, Chagas disease is the deadliest parasitic disorder in Latin America, leading to more than 7,000 deaths per year (Alonso-Padilla et al., 2019).

Transmission of Chagas Disease

First described by Dr. Carlos Chagas in 1909 (Diaz, 2008), Chagas disease is a zoonosis caused by infection with the parasitic trypanosome, *T. cruzi* (Garza et al., 2014). Many mammals (e.g. dogs, cats, and rodents) are susceptible to *T. cruzi* infection, serving as reservoir hosts to the parasite once infected. *T. cruzi* parasites are transmitted between animals and to humans by blood-feeding triatomine bugs (also called reduviid bugs or

"kissing bugs") (Kumar, Abbas, Fausto, Robbins, & Cotran, 2005). After biting and subsequently feeding on the blood of mammalian hosts, infected triatomine bugs act as disease vectors, passing the *T. cruzi* parasites in their feces. Interestingly, *T. cruzi* is not directly introduced to hosts through triatomine bites, but rather hosts become infected when *T. cruzi* laden excreta comes into contact with damaged skin (e.g. scratching at bite sites) or mucosal surfaces (most frequently the eyes) (Klotz, Dorn, Mosbacher, & Schmidt, 2014). Infections can also occur through vertical transmission (from mother to fetus), blood transfusion, organ transplantation, by consumption of contaminated food or drinks, or laboratory accidents (Cordovez, Rendon, Gonzalez, & Guhl, 2014). Once *T. cruzi* is introduced into the bloodstream of a mammalian host, a variety of cell types within the body become vulnerable to infection (Bonney, 2014).

Clinical Manifestations of Chagas Disease

Chagas disease consists of two distinct clinical phases: the acute phase and the chronic phase. The acute phase occurs in the initial 8 weeks of infection, is usually asymptomatic, and thus, often goes undiagnosed. If symptoms do present during this phase, they are generally mild and are not unique to Chagas disease, including malaise, fatigue, body aches, headache, rash, loss of appetite, fever, vomiting and/or diarrhea (CDC, 2017). Physical examination may reveal swollen lymph nodes, mild enlargement of the liver or spleen, and/or a chagoma (localized swelling at the infection site). Present in ~ 1% of cases, Romana's sign is a rare, yet most recognizable marker of acute Chagas disease; characterized by unilateral swelling of the eyelids near the bite wound or site where infected feces was deposited into the eye. Parasitemia, the presence of parasites in the blood, is often high

during this phase, making diagnosis possible via microscopic blood examination (Bonney, 2014). Symptoms experienced during the acute phase usually abate after weeks to months, even without treatment. However, if left untreated, the infection will persist into the chronic phase (CDC, 2017) following a period of 5-40 years. The chronic phase includes two forms: an asymptomatic form ("indeterminant" or "latent") and a symptomatic form. Although the majority of people in the chronic phase will remain asymptomatic, approximately 20-30% of individuals will go on to develop serious, potentially life threatening, cardiac and/or intestinal complications (e.g., cardiomyopathy, heart failure, cardiac arrest, megaesophagus, and megacolon) (Garza et al., 2014).

The Ecology of Chagas Disease and Vectors

The epidemiological triangle of Chagas disease includes host, pathogen, and triatomine vectors as they interact together within the environment. Distributed widely throughout the Americas, from the southern United States to Argentina, *T. cruzi* triatomine vectors "have a wide range of climatic and ecological tolerability because they inhabit diverse ecosystems" (p. 1). Due to their high vagility and ability to survive at varying altitudes, triatomines are suited for sundry habitats and capable of exploiting diverse food sources. Thus, distribution of these vectors is strongly influenced by environmental factors, with variances in temperature, humidity, and precipitation having the ability to significantly alter the risk of vector transmitted *T. cruzi* infections (Parra-Henao, Suarez-Escudero, & Gonzalez-Caro, 2016).

Chagas Disease and Climate Change

The broad impacts of climate on health are well established and substantiated throughout the literature, with many assessments forecasting an increased future incidence of infectious diseases due to climate change factors (Medone, Ceccarelli, Parham, Figuera, & Rabinovich, 2015). Projected impacts of global climate change on temperature and rainfall conditions have the potential to influence the geographic distribution of disease vectors, conceivably altering the vulnerability of human populations to vector-borne diseases, including Chagas disease (Garza et al., 2014). There is evidence indicating that climate change has facilitated a northern shift of *T. cruzi* triatomine vectors, and thus Chagas disease risk, from endemic countries of Latin America to non-endemic areas of North America, including the southern United States. By allowing more habitats to become suitable for vectors and reservoir host species of Chagas disease, climate change threatens to transform the disease from a Latin American problem to a global one (Carmona-Castro, Moo-Llanes, & Ramsey, 2018).

Vector Distribution Modeling of *T. cruzi* vectors and Climate Change

Triatomine vectors are the main route of *T. cruzi* infection in humans. Thus, one of the most important concerns regarding future Chagas disease transmission risk to human populations is the degree to which triatomine vector species may alter their geographic distributions over time. Climate change is one factor that may play a significant role in altering the geographic distributions of triatomine vector species, and hence, it is necessary to employ tools that enable prediction of future triatomine geographic distributions in response to climate change. Ecologic niche modeling (ENM) is one of those valuable tools, “available

for the exploration of geographical and ecological phenomena based on known species occurrences," which enables the identification of future trends of human "potential vulnerability" to Chagas disease in relation to projected geographic range alterations of triatomine species in response to changes in climate factors (Ceccarelli & Rabinovich, 2015, p. 1334).

Public Health Significance

As global climate change is predicted to accelerate over the coming decades, an increased frequency, intensity and duration of extreme climatic events are expected to occur and anticipated to affect Chagas disease transmission. This is a global public health priority. A better understanding of the relationship between climate and Chagas disease is an important step towards finding ways to mitigate the future impact of this disease on communities. Successful management of Chagas disease requires an understanding of the expected dynamics of the parasite, host, vectors, and environmental factors in the context of a changing climate.

Research Question and Objectives

While many studies have found associations between climate change and factors affecting Chagas transmission, the future impact of climate change on the global spread of Chagas disease remains debatable:

Research question:

What are the projected impacts of climate change on the transmission and spread of Chagas disease in the Americas?

Objectives:

1. Assess the influence of climate on the future distributions of *T. cruzi* vectors and, by extension, transmission and spread of Chagas disease in the Americas.

2. Identify the most important gaps in our current knowledge of the relationship between climate change and transmission/spread of Chagas disease in the Americas.

3. Suggest approaches for identifying, managing, and controlling the potential effects of climate change on the occurrence of Chagas disease worldwide.

METHODS

Study Design

A qualitative, systematic review was conducted to assess the impact of climate change on Chagas disease transmission in the Americas (Central America, South America (e.g. Brazil, Argentina, Venezuela, and Chile) and North America (e.g. Mexico and the United States)).

Search Strategy and Key Words

A literature search was conducted in 2019 using the electronic databases PubMed, Scopus, and Ovid to obtain information on the impact of climate change on Chagas disease transmission. The following keywords were utilized in the database searches: **climate, Chagas, and "trypanosoma cruzi"**. Searches retrieved records from 1982 through 2019. References and citations of the articles identified were analyzed to ensure the inclusion of all relevant literature.

Selection Criteria

Several selection criteria were utilized to select articles from the database search results for detailed consideration in the review. The inclusion criteria included:

1. Peer-reviewed journal articles
2. English language articles
3. Full text/pdf articles
4. Ecologic study design
5. Articles that include geographical areas located within Central America, South America and/or North America
6. Articles that include *T. cruzi* vector species occurrence data
7. Articles with climate data, including at least one climate based projection of future Chagas disease transmission

No exclusion criteria were utilized in conducting the systematic literature review.

Coding and Evidence Table

Eligible studies were coded to gather data on the following fields:

1. Geographical study area (projection periods)
2. Vector species data
3. Chagas disease data
4. Covariate data
5. Climate change models/scenarios
6. Vector species distribution models
7. Model evaluation

8. Key Findings
9. Comments
10. Future considerations
11. Limitations
12. Quality assessment score

Quality Assessment

There is currently no validated tool for assessing the methodological quality of ecologic studies. Thus, we employed an adapted version of the checklist proposed by Betran et al. (2015) to evaluate aspects related to study design, statistical methodology and reporting quality of ecologic studies. The quality of each study was assessed based on 15 items with a maximum score of 21 points; 12 points for study design, 6 for statistical methodology and 3 for quality of reporting.

Table 1 Quality assessment criteria for ecologic studies

Study design (max = 12)	
Design	Multiple-group vs. Time-trend vs. Mixed
Sample size	Number of ecologic units included in the analysis as proportion of the total number of units, e.g. 100 countries of a total of 180 worldwide would be 55%.
Unbiased inclusion of units	Were the units included representative of the group for which inferences are being drawn?
Level of data aggregation	Population to which the units refer to.
Level of inference	Use of the results of the analysis of the study's sample data to draw inferences for individuals or groups (ecologic).
Pre-specification of ecologic units	Were the ecologic units selected to suit the hypothesis? (as opposed to selection motivated by convenience or necessity)
Outcomes of interest included	Inclusion of all relevant outcomes or only of some outcomes.
Source of data	Validity of the sources of data to represent the level that it refers to.
Statistical methodology (max = 6)	
Analytic methodology	All statistical methods are acceptable as long as they are used appropriately. Score is assigned based on the sophistication and flexibility of the method.
Validity of regression	Did the adjustments have at least 10 units per covariate?
Use of covariates	Did authors adjust analysis for desirable variables?
Proper adjustment for covariates	Are the outcomes standardized or adjusted for certain factors before model adjustment? For standardized or adjusted outcomes, the standardized or adjusted factors should be included in the adjustment model. If standardized/adjusted outcomes are not used, this criterion is considered to have been met.
Quality of reporting (max = 3)	
Statement of study design	Did the authors present key elements of study design in this paper?
Justification of study design	Did the authors justify the ecologic analysis, the rationale and the specific objectives, including any pre-specified hypothesis?
Discussion of cross-level bias and limitations	Did the authors caution readers about the limitations of the ecologic design, the ecologic fallacy, the impossibility of extrapolating to a different level?

RESULTS

The initial electronic database search identified a total of 191 record documents and 23 additional records through other sources. After the exclusion of duplicates, 135 unique records were screened. 20 full-text articles were assessed for inclusion eligibility, of which seven fulfilled the selection criteria and were included in the review (Carmona-Castro, et al., 2018; Ceccarelli & Rabinovich, 2015; Costa, Dornak, Almeida, & Peterson, 2014; Garza et al., 2014; Lambert, Kolivras, Resler, Brewster, & Paulson, 2008; Medone et al., 2015; Tapia-Garay et al., 2018).

Figure 1 PRISMA flow diagram of study selection

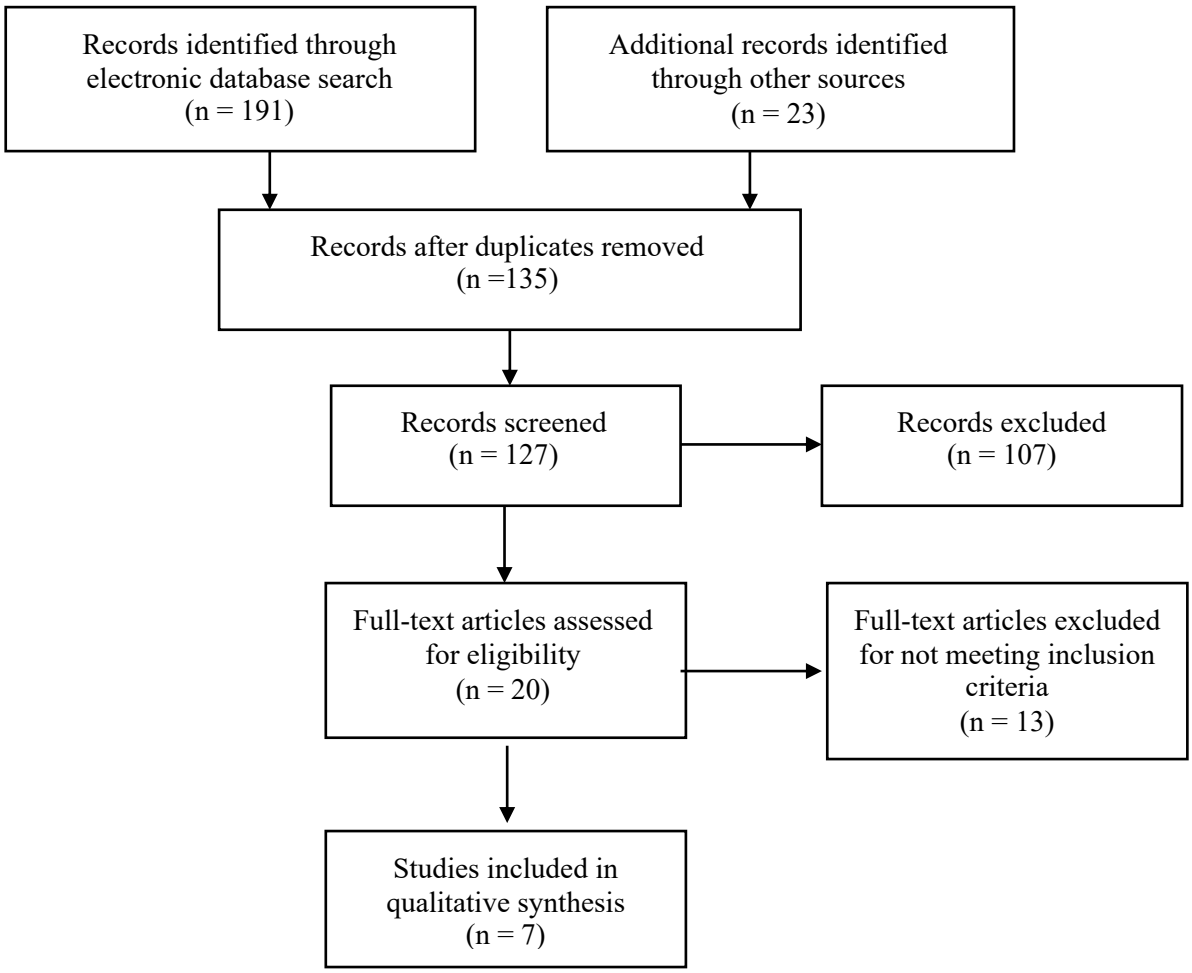

Table 2 summarizes the main characteristics of the seven studies that addressed climate change and the risk of Chagas disease transmission in the Americas under future climate change scenarios.

Table 2 Studies included in the review of climate impact on Chagas disease

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Carmona-Castro et al. 2018	North America (2050, 2070)	20 species modelled; *Eratyrus* (1), *Paratriatoma* (1), *Triatoma* (18) (Atlas of Mexican Triatominae compiled by Ramsey et al.)	Chagas specific entomological parameters (distribution of *T. cruzi* vector species)	U.S. Geological Survey's HYDRO1k 4 Topographical variables: elevation, aspect, topographical index and slope WorldClim 9 bioclimatic variables: annual mean temperature, temperature seasonality, max. temperature of warmest month, min. temperature of coldest month, temperature annual range, annual precipitation, precipitation of wettest month, precipitation of driest month, precipitation seasonality CONAPO Population growth	ECHAM6/IPCC RCP 4.5, 8.5	GARP, Maxent (ENMs)	pAUC	Significant alterations in risk of vector-borne *T. cruzi* transmission to North American populations are projected for both future time periods; specifically, in Mexico an exposure threat increase of 1.48% and 1.76% for urban and rural populations (respectively) is expected by the year 2050. Mean elevation was found to be the only important contributing variable to alterations in ENM range areas Size of current distribution range was found to be the best predictor of future distribution shifts. GARP models proved more accurate than MaxEnt models.	Impacts of climate change are expected to be specific to *T. cruzi* vector species and their geographical locations	Effective vector surveillance that incorporates trans-border perspectives is needed in North America to aid in future Chagas disease prevention and control. The current and future ENMs can be used in consideration with other factors to project the *T. cruzi* transmission threat, as both vector distribution shifts and human practices are expected to exacerbate vector presence and abundance in modified habitats.	No limitations noted within the study.	15

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Ceccarelli and Rabinovich 2015	Venezuela (2020, 2060, 2080)	5 species modelled; *Panstrongylus geniculatus, Rhodnius prolixus, Eratyrus mucronatus, Rhodnius robustus, Triatoma maculata* (Carcavallo et al. Triatomine atlas)	Population Vulnerability Index	WorldClim (current)/CCAF-Climate (future) 19 bioclimatic variables: incl. temperature seasonality, isothermality, temperature annual range, min. temperature of coldest month, precipitation of wettest quarter, max. temperature of warmest month, annual precipitation Vector competence Population growth	CSIRO Mark 3.0/IPCC A1B, B1	Maxent (ENM)	AUC	Global climate change is predicted to slightly decrease the overall future vulnerability of the Venezuelan population to *T. cruzi* vector species. Only 3 bioclimatic variables made significant contributions to vector suitability model projections (temperature seasonality, isothermality, and temperature annual range).	Fewer Venezuelan citizens will be exposed *to T. cruzi* vectors over the next 50-70 years.	Predictions can enhance ability to prevent and control Chagas disease transmission in Venezuela in the future.	Several factors that may affect Venezuela's vulnerability to T. cruzi transmission via triatomine vectors were not included in the analysis. There is a debate on the optimal spatial resolution to be used in ENM studies, depending on the source of data. Data in this study was derived from a geographic range map based on occurrence points, and thus may not accurately reflect areas where the species are absent. Over estimation of species distributions may have resulted, leading to false positives in the distribution data.	16

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Costa et al. 2014	Brazil (2020, 2050)	5 species modelled; *T. b. brasiliensis, T. b. macromelasoma, T. juazeirensis, T. sherlocki, T. melanica* (entomological collections of Fundacao Oswaldo Cruz, state health departments, and field collections conducted by the Laboratorio de Biodiversidade Entomologica)	Chagas specific entomological parameters (distribution of *T. cruzi* vector species)	WorldClim 7 bioclimatic variables (Annual mean temperature, mean diurnal temperature range, max. temperature of the warmest month, min. temperature of the coldest month, annual precipitation, precipitation of the wettest and driest months)		GARP, Maxent (ENMs)	pAUC and the Jackknife approach	An increase in mean temperature of 1.72°C and a decrease in mean precipitation of 55.6 mm are predicted for 2050. Models project little change in species' distributions under future climate change scenarios. *T. b. brasiliensis* has the greatest distributional potential to colonize new areas.	Predict a relatively stable future distribution of studied triatomine species.	Conclusions may help guide proactive surveillance and control activities to reduce risk of future Chagas disease transmission in Brazil.	Some environmental/ vector distribution data may be inaccurate or biased due to passive human transport, outdated surveys, misidentification, poor geo-referencing, and hybrid phenotypes.	17

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Garza et al. 2014	North America (2050)	2 species modelled; *T. gerstaeckeri, T. sanguisuga* (museum collection and voluntary collectors' databases, and fieldwork conducted by study team members)	Human population *T. cruzi* vector exposure risk	WorldClim 15 bioclimatic variables (Annual mean temperature, mean diurnal range, isothermality, temperature seasonality, ma. temperature of warmest month, min. temperature of coldest month, temperature annual range, annual precipitation, precipitation of wettest month, precipitation of driest month, precipitation seasonality, precipitation of wettest quarter, precipitation of driest quarter, precipitation of warmest quarter, precipitation of coldest quarter)	CCCMA, CSIRO, HADCM3/ IPCC A2A, B2A	MaxEnt (ENM)	AUC	A potential northern distributional shift of *T. gerstaeckeri* and a northern and southern shift in the distribution of *T. sanguisuga* from their current range are predicted due to climate change, indicating an increase in *T. cruzi* transmission risk for North American populations by the year 2050 Annual mean temperature proved to be the biggest contributing climate variable to both vector species' distributions.	Predicted northward shift of Chagas disease risk due to climate change.	More studies are needed to produce a comprehensive list of confirmed hosts for *T. cruzi.*	The potential distribution of most hosts should be included in the ENMs. However, little is known about confirmed *T. cruzi* mammalian hosts, so they were not included in the models.	17

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Lambert et al. 2008	United States (2030)	3 species modelled; *T. lecticularia, T. protracta, T. sanguisuga* (entomological literature)	Human population *T. cruzi* vector exposure risk	PRISM Climate Group Monthly minimum temperature data SEDAC population density data	IPCC report, 2001 Prediction of a 1°C (1.8°F) temperature increase by 2030	ArcGIS	Compared resulting model to: 1) findings of a GARP model 2) location of 6 known autochthonous cases of Chagas disease in U.S.	Much of the southern United States is currently at risk for Chagas disease transmission. The future increase in temperature predicted by the IPCC is expected to promote expansion of the current vector range into the central United States by the year 2030.	Potential for Chagas disease to emerge in the United States.	Interdisciplinary collaboration between epidemiologists, entomologists, veterinarians, ecologists, geographers and infectious disease specialists is necessary to increase accuracy of future disease risk predictions. Comprehensive fine-scale studies of higher risk areas may be informed by study results.	Classification of triatomine species, selection of the utilized threshold data, and use of 2000 census data in predictive mapping.	14

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Medone et al. 2015	Venezuela, Argentina (2050)	2 species modelled; *Rhodnius prolixus, Triatoma infestans*	Force of Infection (FOI)	WorldClim 19 bioclimatic variables (Temperature seasonality, isothermality, temperature annual range, min. temperature of coldest month, precipitation of wettest quarter, max. temperature of warmest month, annual precipitation)	HadGEM2-ES/ IPCC RCP 6.0	Maxent (ENM)	pAUC	Climate change projections are estimated to have a differential impact on both species' climatic niches. Forecasts reveal increased expansion of *R. prolixus* to new areas, whereas a future decrease in its current geographical range is expected for *T. infestans*. Overall study conclusions reflect a future decrease of suitability in areas of Venezuela and Argentina currently at moderate-to-high risk of *T. cruzi* transmission, with a lower incidence of Chagas disease infections expected in these regions by 2050. Minimum temperature of the coldest month and mean temperature of the coldest quarter were found to be the biggest contributing	Climate change is predicted to have varying influences on the FOI for Chagas disease in Argentina and Venezuela.	Future research needed to assess the robustness and generality of conclusions about future T. cruzi transmission risk in Argentina and Venezuela.	Failed to include socio-environmental variables and adequate criterion of spatial and temporal scale selection to ENMs. Limited climate data due to fewer weather stations in Latin America, compared to other parts of the world.	18

References	Study area (projection periods)	Vector species data (source)	Chagas disease data	Covariate data	Climate change models/ scenarios	Vector Species Distribution Model	Model Evaluation	Key Findings	Comments	Future Considerations	Limitations	Quality assessment score (max=21)
Tapia-Garay et al. 2018	Chile (2070)	1 species modelled; *T. infestans* (National Museum of Natural History, Health Ministry of Chile, Public Health Institute, Entomology Institute of Metropolitan University of Educational Services, and literature reports)	Number of confirmed Chagas disease cases from 1939-1965 (Parasitology Laboratory of the Medicine Faculty of the University of Chile)	WorldClim 7 bioclimatic variables (mean annual temperature, temperature seasonality, max. temperature in the warmest month, annual precipitation, precipitation during the driest month)	INPE, IPCC RCP 2.6 and RCP 8.5	MaxEnt (ENM)	AUC	The distribution of *T. infestans,* under two global climate change scenarios, showed low variation with a minimal reduction tendency in suitable areas. Maximum temperature in the warmest month and precipitation in the driest month contributed considerably to the future distributions of both *T. infestans* and Chagas disease. Annual precipitation, temperature seasonality, and the average temperature were also shown to be relevant to the Chagas disease model. Climate change predictions in Chile include an increase of temperature over the entire country. A decrease in precipitation is expected in Chile between 2011-2070.	Climate change appears to play a major role in the reemergence of Chagas' disease and *T. infestans* in Chile.	The impact of temperature and precipitation on the distribution of *T. infestans* indicates the need for aggressive vector control efforts in Chile.	Possible sample bias in occurrence data.	16

Vector species occurrence data

Each study utilized varying sources to obtain prevalence occurrence data on *T. cruzi* vector species important to their geographic study area. Ceccarelli & Rabinovich (2015) obtained data on the occurrence of five triatomine species endemic to Venezuela (*Eratyrus mucronatus, Panstrongylus geniculatus, Rhodnius prolixus, Rhodnius robustus, and Triatoma maculata*) from an atlas on triatomines produced by Carcavallo et al. (1999). The Carcavallo et al. (1999) atlas was also the source of *Rhodnius prolixus* and *Triatoma infestans* species distribution data in Venezuela and Argentina utilized by Medone et al. (2015). Occurrence data of *Triatoma infestans* in Chile were compiled from multiple sources including the National Museum of Natural History, Health Ministry of Chile, Public Health Institute, Entomology Institute of Metropolitan University of Educational Services, and literature reports (Tapia-Garay et al., 2018). Data obtained from the entomological collections of Fundacao Oswaldo Cruz, state health departments, and field collections conducted by the Laboratorio de Biodiversidade Entomologica were assembled to provide occurrence points for five triatomine species (*Triatoma b. brasiliensis, T. b. macromelasoma, T. juazeirensis, T. melanica, and T. sherlocki*) widespread in Brazil (Costa et al., 2014). The Atlas of Mexican Triatominae, compiled by Ramsey et al. (2015), was utilized to obtain occurrence records for 20 epidemiologically important species in North America including *Eratyrus* (one species), *Paratriatoma* (one species) and *Triatoma* (18 species) (Carmona-Castro et al., 2018). Another study gathered occurrence data for two common North American vector species, *T. gerstaeckeri* and *T. sanguisuga*, from museum collections and voluntary collectors' databases, and through fieldwork conducted by their study team

members (Garza et al., 2014). Finally, the occurrence data for three vector species common in the United States, including *T. lecticularia*, *T. protracta*, and T. *sanguisuga*, was sourced from entomological literature (Lambert et al., 2008).

Covariate data

For current climate conditions, most studies utilized varying combinations of 19 available bioclimatic variables downloaded from WorldClim (Carmona-Castro et al., 2018; Ceccarelli & Rabinovich, 2015; Costa et al., 2014; Garza et al., 2014; Medone et al., 2015; Tapia-Garay et al., 2018). WorldClim variables are derived from aggregated monthly climate data of global weather stations (Medone et al., 2015). One study acquired monthly minimum temperature data from the PRISM Climate Group dataset (Lambert et al., 2008).

Among the selected studies, five also applied WorldClim bioclimatic predictor variables for periods of future projection (Carmona-Castro et al., 2018; Costa et al., 2014; Garza et al., 2014; Medone et al., 2015; Tapia-Garay et al., 2018). Two studies utilized different sources for future climate variable data, including CCAF-Climate datasets (Ceccarelli & Rabinovich, 2015) and the 2001 Intergovernmental Panel on Climate Change (IPCC) report (Lambert et al., 2008).

Data on population density, population growth, climate diversity (e.g. tropical and subtropical), and topographical variables (e.g. elevation, aspect, and slope) were described in individual studies.

Global change models/scenarios

The majority of reviewed studies used varying climate models and climate change scenarios for the future climate projections utilized in their distribution modeling approaches.

All climate change scenarios were derived from the Intergovernmental Panel on Climate Change (IPCC) Special Report on Emissions Scenarios (IPCC, 2001). Models and scenarios were selected as study authors deemed appropriate for their geographic study area.

One study chose the general circulation model, European Hamburg global climate model version 6 (ECHAM6), for 2050 and 2070 projections, wherein they analyzed two climate change scenarios: representative concentration pathway (RCP) 4.5 (current emissions change trends) and RCP 8.5 (accelerated emissions trends with inadequate control policies) (Carmona-Castro et al., 2018). A second study utilized the CSIRO Mark 3.0 model for 2020, 2060, and 2080 projections under two climate change scenarios, including A1B (maximum energy requirements with a balanced emphasis on all energy sources) and B1 (minimum energy requirements and emissions) (Ceccarelli & Rabinovich, 2015). Medone et al. (2015) used the HadGEM2-ES model and climate change scenarios RCP 6.0 (accelerated trends) and RCP 8.5 (accelerated emissions trends with inadequate control policies) for 2050 projections. Another study employed three climate models, including the Canadian Centre for Climate Modelling and Analysis (CCCMA), the Hadley Center for Climate Change (HADCM3), and the CSIRO Mark 3.0, for its 2050 climate projections. Two climate change scenarios were used in these models: A2A (increased population and regional economic development) and B2A (increased population and local environmental sustainability) (Garza et al., 2014). Lastly, Tapia-Garay et al. (2018) used the Instituto Nacional de Pesquisas Espaciais (INPE) climate model in two global change scenarios, RCP 2.6 (decreasing emissions trends) and RCP 8.5 (accelerated emissions trends with inadequate control policies), for their 2070 projections.

Two studies, Costa et al. (2014) and Lambert et al. (2008), did not utilize climate change models/scenarios prior to constructing their vector species distribution models.

Vector species distribution models: Spatial Analyses

All studies included in this review make use of spatial analysis, which is based on the idea of stacking layers containing different kinds of data (e.g. species occurrence data, climate data, population data, topographical data) and comparing them with each other on the basis of their geographical locations (Costa & Peterson, 2011). Among the selected studies, six used ecological niche modeling programs, including a maximum entropy approach to modeling species' distributions (Maxent), the Genetic Algorithm for Rule Set Prediction (GARP), or both (Carmona-Castro et al., 2018; Ceccarelli & Rabinovich, 2015; Costa et al., 2014; Garza et al., 2014; Medone et al., 2015; Tapia-Garay et al., 2018), and one utilized the ArcGIS modeling program (Lambert et al., 2008) towards projections of future *T. cruzi* vector species distributions in their geographic study areas. The details of these models are explained below.

Ecological Niche Modeling: Maxent and GARP

A couple of modeling approaches were utilized by studies to approximate species' ecological niches. Ecological niche modeling (ENM) "applies machine learning techniques to predict vector species' geographic distributions by relating species occurrence data to eco-geographical variables" (Peterson, 2006, p. 1823). Most studies included in this review utilized ENMs to better understand facets of Chagas disease transmission, specifically the predicted suitability of their geographic study area for the vector species (i.e. ecological niches) under current and future climate conditions.

Maxent and GARP are two ENM software programs used extensively in terms of their application to infectious disease systems (Costa, Almeida, & Peterson, 2014). Both programs relate environmental conditions (e.g. climate data) to known *T. cruzi* vector species' occurrence records. These relationships are then compared to the geographical landscape over which observations were obtained (Costa et al., 2014).

Maxent is an inductive modeling program that utilizes presence only vector species' occurrence data along with environmental variables to derive a probability of "potential" suitable habitat. This program is most useful when occurrence records are available, but limited data exists for range or habitat of a species of interest. Environmental layers, such as climate and topographical data, are stacked upon each other within the model. Occurrence data is subsequently added to the model, whereby Maxent can then look for relationships within the stacks of environmental layers. Maxent focuses on fitting a probability distribution for occurrence of the species in question to a set of pixels across the study region, "based on the idea that the best explanation of unknown phenomena will maximize the entropy of the probability distribution, subject to constraints" (Peterson, Papes, & Eaton, 2007, p. 69). With regard to ENMs, these constraints consist of the values of pixels where the species has been detected (Phillips, Anderson, & Schapire, 2006). Running a Maxent model results in values ranging from 0 to 1, with values closer to 0 indicating less habitat suitability for vector species and values closer to 1 designating higher habitat suitability potential (Carmona-Castro et al., 2018).

The GARP computer program is based on a genetic algorithm, which divides occurrence data into subsets for model calibration (rule training and intrinsic testing) and

model evaluation (extrinsic testing). Through an iterative process, GARP develops a set of rules based on calibration data. Each rule is considered a gene. The resulting set of genes are subsequently combined randomly to further generate many possible models which describe the potential of the species to occur under varied environmental conditions (e.g. precipitation levels, temperatures, elevation, ect.) (Stockwell, 1999).

Four studies exclusively used Maxent to model their ecologic niches under current and future climate conditions (Ceccarelli & Rabinovich, 2015; Garza et al., 2014; Medone et al., 2015; Tapia-Garay et al., 2018). A couple of studies utilized both GARP and Maxent programs to produce their ENMs, albeit for different research purposes. Carmona-Castro et al. (2018) aimed to compare GARP and Maxent modeling approaches in order to ascertain the program with greater predictive potential, whereas Costa et al. (2014) sought to combine models derived from both GARP and Maxent programs to develop a single, comprehensive ENM.

ArcGIS

Lambert et al. (2008) used a more simplified program, ArcGIS, for both their vector species distribution modeling and Chagas disease risk assessments. ArcGIS is a geographic information system (GIS) designed to produce detailed maps, build spatial models, and manage/analyze spatial data (Hanafi-Bojd, Sofizadeh, & Shoraka, 2018).

Model Validation

Receiver operating characteristic (ROC) analysis is widely used to evaluate the statistical accuracy of species distribution model predictions (DeLong, DeLong, & Clarke-Pearson, 1988). Spatial model predictions can "present errors of omission (false negatives,

leaving out known distributional area) and errors of commission (false positives, including unsuitable areas in the prediction)" (p. 63). ROC analysis involves plotting sensitivity (i.e. proportion of known species' presences predicted present or 1 – false negative rate) against 1 – specificity (i.e. proportion of known species' absences predicted present or false positive rate). Subsequent comparisons are made between the area under the ROC curve (AUC) and null expectations, either probabilistically or through bootstrap manipulations (Peterson, Papes, & Soberon, 2007). Theoretically, AUC = 1 indicates a perfect result; whereas a test performing no better than random yields AUC = 0.5 (Garza et al., 2014). Three studies under review utilized AUC to assess the predictive accuracy of their ENMs (Ceccarelli & Rabinovich, 2015; Garza et al., 2014; Tapia-Garay et al., 2018).

Recently, the use of AUC as the standard measurement of accuracy for species' distribution models has come under criticism. In light of these concerns, the partial AUC (pAUC) was proposed as an alternative summary measure to the full AUC. When using the pAUC, only regions of the ROC space where data have been observed are considered (Lobo, Jimenez-Valverde, & Real, 2008). As such, pAUC was chosen by three studies to evaluate their ENMs (Carmona-Castro et al., 2018; Costa et al., 2014; Medone et al., 2015).

Alternatively, Lambert et al. (2008) utilized two alternative model validation methods; first comparing their results with an ENM generated with GARP, and secondly, comparing their results to the location of the six known autochthonous cases of Chagas disease in the United States.

Projections of Climate Change Impacts on T. Cruzi Transmission

Carmona-Castro et al. (2018) examined the projected impact of climate change on *T. cruzi* vector transmission in North America. Current and future distributions of 20 epidemiologically important North American triatomine species were modeled, comparing predictive outcomes of both Maxent and GARP programs, with the inclusion of nine temperature/precipitation variables and the inclusion/exclusion of topographical variables. The climatic niche suitability for *T. cruzi* vectors was analyzed for 2050 and 2070 in both RCP 4.5 and RCP 8.5, resulting in significant distribution shifts predicted for the majority of species, with little difference found in ecological niche breadth projections made in RCP 4.5 compared to RCP 8.5. No significant range differences were detected between Maxent and GARP models; however, GARP models were shown to perform better overall (pAUC > 1). In addition, mean elevation was found to be the only important contributing variable to alterations in ENM range areas. All in all, size of current distribution range was found to be the best predictor of future distribution shifts, revealing the expected impacts of climate change to be specific to *T. cruzi* vector species and their geographical locations. Finally, significant alterations in risk of vector-borne *T. cruzi* transmission to North American populations are projected for both future time periods; specifically, in Mexico an exposure threat increase of 1.48% and 1.76% for urban and rural populations (respectively) is expected by the year 2050.

Cecarrelli & Rabinovich (2015) analyzed the potential consequences of future alterations in climate factors on the geographic distribution of five triatomine species in Venezuela. The future climatic niche suitability for each species were modeled with Maxent

software, under two IPCC future emissions scenarios of global climate change (A1B and B1), the Global Climate model CSIRO Mark 3.0, and three future projection periods (2020, 2060, and 2080). A series of vulnerability indexes were also calculated at the county, state, and country level for Venezuela, measured to reflect the "human population potentially exposed to a change (intensity and direction) in the geographic distribution" of the five triatomine species analyzed (p. 1335). The AUC procedure was used to evaluate the goodness-of fit of the niche models' predictions. Out of the 19 bioclimatic variables included in the Maxent models of suitability predictions for each vector species, only three made significant contributions to those projections (temperature seasonality, isothermality, and temperature annual range), trending generally toward a more variable and extreme climate as compared to current conditions. However, according to their models, global climate change is predicted to slightly decrease the overall future vulnerability of the Venezuelan population to *T. cruzi* vector species, even when accounting for future population growth. Thus, over the next 50-70 years, fewer areas in Venezuela are expected to have populations vulnerable to triatomine vector exposure.

Costa et al. (2014) examined the distribution potential, and by extension, *T. cruzi* transmission risk, of the *Triatoma brasiliensis* species complex (*T. b. brasiliensis, T. b. macromelasoma, T. juazeirensis, T. sherlocki, T. melanica*) under present and projected future climate conditions in Brazil. ENMs were constructed using both Maxent and GARP programs to estimate prospective distributions of all five triatomine vector species. Each model incorporated seven bioclimatic variables, under global climate change scenarios for 2020 and 2050. The resulting models were combined and then evaluated to determine the

potential for climate change-mediated distributional shifts of vector species. In light of emerging concerns regarding the use of the AUC approach for model evaluation, the alternative pAUC method was used to assess ENMs for *T. b. brasiliensis, T. b. macromelasoma*, and *T. juazeirensis*. However, due to small sample sizes (N = 7) of *T. melanica* and *T. sherlocki* species, the pAUC method was deemed inappropriate for their model evaluations. Thus, a jackknife approach, designed for models based on limited occurrence data, was used instead. Distributional predictions of ENMs for *T. b. brasiliensis, T. b. macromelasoma*, and *T. juazeirensis* were found to be statistically significant ($P < 0.0001$). Models for *T. sherlocki* and *T. melanica,* however, failed to yield predictions that were better than random. Although this study found *T. b. brasiliensis* to be the member of the complex with the greatest future distributional potential, the overall distribution of the complex, and thus *T. cruzi* transmission risk, appears relatively stable in Brazil through the year 2050.

Garza et al. (2014) sought to forecast the future distributions of two common vector species epidemiologically important to North America, *T. gerstaeckeri* and *T. sanguisuga*, under predicted climate change conditions for the year 2050. The future climatic niche suitability for each species was modeled with Maxent software, incorporating 15 bioclimatic variables, two IPCC global climate change scenarios (A2 and B2), and three different general circulation models (CCCMA, CSIRO, and HADCM3) for the future projection period of 2050. All models were evaluated and found to be statistically robust (AUC > 0.90). Annual mean temperature proved to be the biggest contributing climate variable to both vector species' distribution models. Overall, a potential northern distributional shift of *T.*

gerstaeckeri and a northern and southern shift in the distribution of *T. sanguisuga* from their current range are predicted due to climate change, indicating an increase in *T. cruzi* transmission risk for North American populations by the year 2050.

Tapia-Garay et al. (2018) aimed to determine the future risk of Chagas disease vector transmission in Chile due to climate change by modeling the distribution potential of the *T. infestans* vector species, as well as that of Chagas disease. Using the Maxent program, both distribution potential models were constructed with the incorporation of seven bioclimatic variables and under two IPCC global change scenarios, RCP 2.6 and 8.5, for the future projection period of 2070. Goodness-of-fit of the models was evaluated using the AUC, with both *T. infestans* and Chagas disease distribution models proving to be adequate (AUC > .95). Climate change appears to play a major role in the reemergence of Chagas' disease and *T. infestans* in Chile, with two climate variables, including the maximum temperature in the warmest month and precipitation in the driest month, contributing considerably to the distributions of both *T. infestans* and Chagas disease. Annual precipitation, temperature seasonality, and the average temperature were also shown to be relevant to the Chagas disease model. Although a high degree of overlap between Chagas disease and *T. infestans* distribution areas is predicted, the overall future distribution of *T. infestans* under the impact of projected climate changes showed a minimal reduction tendency in suitable areas of Chile by the year 2070.

Medone et al. (2015) assessed the impact of climate change on the geographical distribution of two *T. cruzi* vector species (*R. prolixus* and *T. infestans*) epidemiologically important to Venezuela and Argentina. ENMs were constructed using the Maxent program to

estimate prospective distributions of both triatomine vector species. Each model incorporated 15 bioclimatic variables and the bioclimatic projections of the HadGEM2-ES model under the IPCC global climate change scenario RCP 6.0 for current and 2050 conditions. The pAUC was used to evaluate the goodness-of-fit of the models' predictions. The Maxent models showed pAUC values of 1.001 for *R. prolixus* and 1.055 for *T. infestans*, indicating the robustness of the models. The epidemiological implications of current to future transitions in the climatic niche were estimated in terms of variations in the force of infection (FOI) on the populations of Venezuela and Argentina. FOI, defined as "the rate at which susceptible individuals acquire an infectious disease," was assessed through conversion of climatic suitability to *T. cruzi* transmission risk. The pAUC procedure was used to evaluate the goodness-of-fit of the models' predictions, with both species' climatic niche models proving to be adequate (mean pAUC > 1.0). Minimum temperature of the coldest month and mean temperature of the coldest quarter were found to be the biggest contributing variables to climatic niche models for *R. prolixus* and *T. infestans*, respectively. Climate change projections are estimated to have a differential impact on both species' climatic niches, and thus, varying influences on the FOI for Chagas disease in Argentina and Venezuela. Forecasts reveal increased expansion of *R. prolixus* to new areas, whereas a future decrease in its current geographical range is expected for *T. infestans*. Despite the heterogeneous results, overall study conclusions reflect a future decrease of suitability in areas of Venezuela and Argentina currently at moderate-to-high risk for *T. cruzi* transmission, with a lower incidence of Chagas disease infections expected in these regions by 2050.

Lambert et al. (2008) investigated the effects of projected climate change factors on the potential for emergence of Chagas disease in the United States by the year 2030. They also sought to determine the optimal climate conditions for triatomine vector species effectiveness, as well as the regions of the U.S. most at risk for future vector *T. cruzi* transmission. Current minimum temperature data was acquired through PRISM, whereas future temperature data was based upon IPCC predictions of a 1º C (1.8º F) increase in temperature by the year 2030 (IPCC, 2001). Using overlay analysis, the current and future climate data, occurrence data for three vector species (*T. lecticularia, T. protracta, T. sanguisuga*), and SEDAC population density data were incorporated into the ArcGIS distribution modeling program. The populations at highest risk for future *T. cruzi* transmission due to increased vector species activity were established with the spatial analyst zonal statistics tool in ArcGIS. The current population at increased Chagas disease transmission risk was delineated through analysis of the minimum threshold temperature for increased triatomine vector activity. Further incorporation of temperature predictions for 2030 allowed for the identification of at-risk populations under the future climate change scenario. The accuracy and utility of the resulting species distribution model was evaluated with two forms of model validation. First, the resulting model was compared to a GARP ENM. Species distribution range overlap between the study and GARP models occurred through the southeastern tip of New Mexico and southwestern Texas. However, variation in the models occurs where the GARP range expands further north into the Texas panhandle and southeastern New Mexico; a difference likely due to the study's use of an increased vector activity threshold in the ArcGIS models, whereas the GARP model is only based on

the vector's distribution. Second, a comparison was made between model results and known locations of the six autochthonous cases of Chagas disease in the United States, with five out of the six autochthonous cases having occurred within the area of the model delineated as currently at higher risk for disease transmission. Altogether, the model shows much of the southern United States is currently at risk for Chagas disease transmission, and the future increase in temperature predicted by the IPCC is expected to promote expansion of this range into the central United States by the year 2030 (Lambert et al., 2008).

This section presents the results of the research described in the methods section. The results are not interpreted in this section. Only write about results from your study, not those from other studies or from a 'parent study' of your research project. Use tables and graphs to display quantitative or qualitative data as needed. Tables and graphs may be inserted in the body of the text or may be placed together at the close of the text prior to the REFERENCES section. If tables or graphs are inserted in the text, make efforts to minimize splitting them across pages. If tables or graphs are split across pages, include headings on continuation pages as needed to facilitate understanding results.

DISCUSSION

Climate change is an escalating threat as its potential ramifications continue to be identified. While direct consequences of climate change, such as the development of extreme weather events or alterations in precipitation and temperature, are more apparent, indirect consequences are less discernable (Coumou & Rahmstorf, 2012). For instance, increases in temperature and modified weather patterns owing to climate change may indirectly alter

spatial patterns of disease vectors (Genchi et al., 2011). Arthropod vectors, including *T. cruzi* transmitting triatomines, are cold-blooded insects; thus, their internal temperature and, by extension, their ability to thrive are greatly affected by environmental temperatures. As such, a northern expansion of many arthropod vector species is anticipated in response to projected climate change. Furthermore, some vector-borne pathogens are particularly sensitive to variations in climate, so climate change may increase their incidence and/or intensity, thereby altering their current patterns of disease transmission. Ultimately, by modifying the global environment, climate change may enhance the transmission of infectious diseases, particularly those transmitted by vectors (Coumou & Rahmstorf, 2012), including Chagas disease.

Triatomines, their biology, their potential as *T. cruzi* vectors, and their overall role in Chagas disease transmission cycles, are significantly impacted by climate factors. Possessing the ability to populate diverse ecosystems, from in and around domestic residences to a variety of outdoor settings, supplies them with an expansive range of climatic and ecologic tolerability. "Temporal and spatial changes in temperature, precipitation, and humidity affect their biology and ecology, which can alter the risk of transmitting *T. cruzi*" (Parra-Henao, Suárez-Escudero, & González-Caro, 2016, p. 1). In addition, triatomine species are highly vagile and can thrive in diverse altitudes, allowing them to exploit sundry food sources and terrains. Accordingly, environmental factors strongly influence habitat preferences of triatomine species, and thus, motivate their distributions and their ability to transmit Chagas disease (Bustamante, Monroy, Rodas, Juarez, & Malone, 2007).

Evidence suggests temperature plays an important role in triatomine behavior, *T. cruzi* development, and by extension, Chagas disease transmission. For one, development and life cycles of triatomine species are greatly impacted by temperature, as higher temperatures have been linked to accelerated development and increased species' generations. A study conducted by Hack (1955) found one triatomine species, *T. infestans*, to have double the generations per year in hotter climates when compared to more temperate areas. Another study discovered the life cycles of triatomine species are impacted by temperature as well, finding "a significant correlation between shortened development time and increased rearing temperature" (Carcavallo, 1999). Temperatures exceeding 30º C also increase the feeding rate of triatomines, enabling them to avoid dehydration (Carcavallo & Curto de Casas, 1996). Excessive temperatures can speed up *T. cruzi* development in vectors as well (Asin & Catala, 1995). Furthermore, conclusions of reviewed studies strengthen the link between temperature and the future global distributions of triatomine species, as temperature variables (e.g. temperature seasonality, isothermality, temperature annual range, minimum temperature of coldest months, annual mean temperature, and maximum temperature) were consistently found to be the major bioclimatic contributors to vector suitability model predictions (Ceccarelli & Rabinovich, 2015; Medone et al., 2015; Garza et al., 2014; Tapia-Garay et al., 2018; Lambert et al., 2008). These studies used a range of modeling approaches (e.g. ArcGIS, Maxent, and/or GARP), validated by varying analytical methods, and the results are generally consistent, indicating that the epidemics of Chagas disease are driven by temperature to some extent.

Relative humidity is another key factor that influences varying stages of the triatomine vector's life cycle. Combined effects of temperature and humidity act to regulate vector feeding frequency, survival rate, and likelihood of *T. cruzi* infection and transmission (Carcavallo, 1999). Burgos et al. (1994) determined that high temperatures speed up vector metabolism, while low relative humidity increases feeding frequency in an effort to enhance water intake and avoid dehydration.

Precipitation is another contributor to Chagas disease transmission. First, as a determinant of relative humidity (along with temperature and atmospheric pressure), levels of precipitation may influence the life cycle of triatomine vectors (Carcavallo, 1999). Additionally, Tapia-Garay et al. (2018) and Medone et al. (2015) found precipitation variables to be important contributors to their current and future vector distribution models, and thus, they are a decisive factor of the geographic limits within which Chagas disease transmission can be expected to continue.

Many studies addressing the question of climate change impacts on vector-borne diseases have suggested that environmental change is likely to strengthen transmission potential and expand the geographical range of disease vectors into, for example, higher latitudes (Lafferty, 2009). However, recent studies suggest a shift (rather than expansion) in the geographical distribution of species and vector-borne diseases in the context of global warming (Lafferty, 2009; Rolandi & Schilman, 2012), consistent with results from several studies included in this review (Medone et al., 2015; Costa et al., 2014; Garza et al., 2014). For example, Garza et al. (2014) predicted a northern shift in the distribution of *T. gerstaeckeri* and a northern and southern distributional shift of *T. sanguisuga* from their

current ranges due to climate change. In contrast, vector species movements anticipated by Costa et al. (2014) models are almost negligible, suggesting the *T. brasiliensis* species complex in Brazil is unlikely to show large-scale distributional shifts in response to changing climates. Additional evidence suggests "insects adapted to higher latitudes may present a broader thermal-tolerance range than those adapted to lower latitudes," leading some researchers to postulate that tropical insect vectors will exhibit increased sensitivity to temperature changes (Chown & Nicolson, 2004), and thus, differential impacts of climate change will occur across latitudes and species (Deutsch et al., 2008). In agreement with these considerations, Medone et al. (2015) observed a differential impact of climate change on two vector species: *R. prolixus* (tropical species) shows a future expansion to new areas, whereas *T. infestans* (sub-tropical species) shows a decrease in its future geographical range compared with current conditions.

Tropical and subtropical regions are often burdened with parasitic diseases such as Chagas because those climates promote species richness (Dunn, Davies, Harris, & Gavin, 2010), and therefore can offer a legion of potential vectors and hosts to support their life cycles. "Complex host interactions are key to survivability and sustainability of parasites, and these complex interactions can be altered by a changing climate to promote infectious diseases" (Daszak, 2000, p. 444). In accordance, climate change has the potential to alter or extend the natural ranges of these organisms and make regions of our globe that were previously uninhabitable for parasites habitable.

Historically, vector-borne Chagas disease transmission has occurred primarily in parts of Mexico, Central, and South America, where triatomine species are adapted to domiciliary

and peri-domiciliary settings (Montgomery, Parise, Dotson, & Bialek, 2016). We would expect these regions of Latin America where Chagas disease is currently endemic to be most affected by future climate change; however, projections do not support this hypothesis. In fact, the majority of reviewed studies conducted in Latin American predict stable or decreased vector distributions and *T. cruzi* transmission rates as future consequences of climate change in their study areas (Ceccarelli & Rabinovich, 2015; Medone et al., 2015; Costa et al., 2014; Tapia-Garay et al., 2018). Two studies conducted in Venezuela anticipate a decreasing trend in the vulnerability of the Venezuelan population to *T. cruzi* infection between current and future climate conditions (Ceccarelli & Rabinovich, 2015; Medone et al., 2015). Medone et al. (2015) predicted similar impacts of climate change in Argentina, with the number of new cases of human *T. cruzi* infections per year expected to decrease by 2050. The distribution of the *T. cruzi* vector, *T. infestans,* also showed low variation, with a minimal reduction tendency under two global change scenarios in Chile, indicating a decreased future Chagas disease transmission risk in another endemic area of South America (Tapia-Garay et al., 2018). Similarly, ecological models for regions of Brazil predict little likely change in future *T. cruzi* vector species' distributions due to changing climates (Costa et al., 2014). Notably, Mexico was the only geographical area studied in the Americas where Chagas disease is currently endemic and also predicted to be at increased transmission risk under future climate change scenarios (Carmona-Castro et al., 2018; Garza et al., 2014). For example, all species distribution models under future climate change scenarios conducted by Garza et al. (2014) predict a shift in the suitable habitat, and thus distribution, of the *T. sanguisuga* vector species towards northern and eastern regions of Mexico, supporting the

conclusion that an increase in temperature predicted by future climate estimations is correlated with a potential increase of Chagas disease risk in these regions of Mexico. Additionally, Carmona-Castro et al. (2018) noted a total of 88.9% of the current Mexican population reside in areas with potential exposure to at least one vector species. They predict consistent increases of 1.48% for urban populations and 1.76% for rural populations in the proportion of Mexico residents potentially exposed to *T. cruzi* vectors by the year 2050.

While not currently considered endemic to Chagas disease, triatomines and *T. cruzi* infections are not foreign to the United States (Montgomery et al., 2016). *T. cruzi* transmission by blood transfusion in the United States has been reported for several decades (Leiby, Herron, Read, Lenes, & Stumpf, 2002), whereas house infestation by vectors and vector-borne *T. cruzi* transmission to human populations have been documented only recently in some areas of the southern U. S. (Beard et al., 2003), and are completely unknown in the other regions (Sarkar et al., 2010). In the United States, there are estimated to be at least 300,000 cases of Chagas disease, mostly among people originally from Latin American countries where Chagas disease is endemic (Montgomery et al., 2016). As of 2017, Chagas disease was reportable in only six U.S. states (Arizona, Arkansas, Louisiana, Mississippi, Tennessee, and Texas), and most cases identified were chronic cases and not the result of vector-borne transmission (Bennett et al., 2018). In fact, fewer than 30 cases of autochthonous (locally acquired) infection have been cited in the United States to date (Montgomery et al., 2016). Although 11 species of triatomine bugs have been documented in the United States, and all but one (*Triatoma incrassata*) have demonstrated infection with *T. cruzi*, the risk for autochthonous *T. cruzi* transmission in the United States is still currently

considered low because of better housing conditions (compared to much of Latin America), reduced exposure to triatomine vectors, and a lack of transmission associated with suspected domestic reservoirs (e.g. dogs) (Bennett et al., 2018). However, climate change threatens to disrupt the epidemiological patterns of Chagas disease in the United States. According to the consensus of several studies, expansion of areas at increased risk for Chagas disease transmission is expected under future climate scenarios (Carmona-Castro et al., 2018; Garza et al., 2014; Lambert et al., 2008). Of particular interest is the predicted northern shift of triatomine species to central regions of the United States with historically unsuitable climates for *T. cruzi* vectors (Garza et al., 2014; Lambert et al., 2008). These findings could indicate a trend in future *T. cruzi* vector distributions that may not be limited to the United States, warranting further investigation. At a minimum, these results stipulate that while the vulnerability to Chagas disease of some currently endemic regions of Latin America may decrease due to climate change, geographic regions with climates that are favorable for vector-borne Chagas disease transmission could fluctuate to include a number of currently Chagas-free regions of the United States.

Other factors associated with Chagas' disease transmission

Apart from variations in climate, additional factors not considered in vector species distribution models of studies included in this review may influence the distribution of triatomine vector species and *T. cruzi* transmission risk, under present and future conditions (Pulliam, 2000).

For instance, vegetation type is thought to be an important predictor of abundance for some triatomine species. Likewise, perturbed vegetation, in relation to agriculture and pasture, has been linked to increased triatomine abundance, suggesting that deforestation and habitat degradation are two important factors contributing to triatomine species' distributions (Parra-Henao, Suárez-Escudero, & González-Caro, 2016). Alterations in land use also bring people into contact with wild triatomine vectors that they otherwise would not likely encounter (Guhl, Pinto, & Aguilera, 2009), incidentally enhancing these vectors' primary role in *T. cruzi* transmission.

Human movement has played an important role in altering populations at risk for Chagas disease transmission. Although initially a disease predominantly affecting the rural poor of Latin America, increased urbanization since the 1940's has steered Chagas disease into cities (Coura & Vinas, 2010). The past several decades have also seen "a dramatic increase in human migration from endemic areas of Latin America to Europe, North America, and the Western Pacific," leading to the globalization of *T. cruzi* infections to non-endemic regions. Additional factors contributing to the expansion of *T. cruzi* vectors and infected persons throughout the world include diminished global trade barriers and increased international travel (Klein, Hurwitz, & Durvasula, 2012, p. 2).

Secondary (non-vectorial) *T. cruzi* infections can occur through vertical transmission (from mother to fetus), blood transfusion, organ transplantation, by consumption of contaminated food or drinks, or through laboratory accidents (Gascon, Bern, & Pinazo, 2010). While domestic vector transmission remains the main route of *T. cruzi* infection in disease-endemic areas, vertical transmission is the most important route of transmission in

both non-endemic countries and in urban areas of disease endemic countries, with an estimated 1,000 children born annually with congenital Chagas disease. To date, non-endemic areas with reported cases of congenital Chagas disease include North America, Europe and Asia (Cucunuba et al., 2012). Furthermore, orally acquired *T. cruzi* infections via consumption of contaminated food or drinks have been on the rise since 1965. South America, for example, has experienced Chagas disease outbreaks linked to ingestion of contaminated sugar cane, guava and acai juices (Pinto, Valente, & Valente, 2004).

Limited or absent screening programs in both endemic and at risk non-endemic regions is another major contributor to the global Chagas disease burden. Due to the mostly asymptomatic nature of Chagas disease, screening is fundamental to its diagnosis at every stage. Detection at early stages of the disease allows for curative anti-parasitic treatment, while chronic stage diagnosis enables integral disease management that may prevent life-threatening complications. Screening is also imperative to prevent person to person spread of Chagas disease, as may occur through vertical transmission, organ transplantation, and blood transfusion (Prat et al., 2019).

Moreover, lack of provider awareness of Chagas disease is pervasive in non-endemic areas, creating another barrier to controlling Chagas disease transmission in these regions (Montgomery et al., 2016). For instance, Lambert et al. (2008) found that most healthcare providers in the United States are not familiar with Chagas disease; a fact that is particularly concerning as *T. cruzi* transmission is projected to escalate here in coming decades due to climate change and other contributing factors, such as human migration from Latin America. Regardless of where the initial *T. cruzi* infection is acquired, increasing provider awareness

can lead to improved disease diagnosis and management for all patients, and ultimately aid in controlling the spread and severity of *T. cruzi* infections (Montgomery et al., 2016).

Finally, socioeconomic factors have historically, and will likely continue to play a primary role in *T. cruzi* vector exposure. Poor quality housing and unsanitary living conditions (e.g. thatched roofs, mud-stick walls, and dirt floors) encourage triatomine bugs to thrive and infest dwellings, thereby allowing for increased contact with human hosts (Starr, Rojas, Zeledon, Hird, & Carpenter, 1991). Substandard living conditions are more common in rural, endemic regions of Latin America, creating favorable habitats for triatomine vectors in these areas. Chagas' association with poor and marginalized populations has resulted in a social stigmatization of this disease in many endemic regions, discouraging those who may be infected to seek medical care, as a diagnosis could lead to embarrassment, or even exclusion from the labor market (Klein, Hurwitz, & Durvasula, 2012). As Chagas disease continues to spread to non-endemic areas of the world, such as North America, attention should be paid to existing conditions in these regions that promote the spread of *T. cruzi* infections. For instance, certain low-income areas in Texas, referred to as "colonias," are at an increased risk for triatomine species infestation. Characterized by loosely constructed residences and poor sanitation systems, these neighborhoods offer suitable conditions and accessible habitats for *T. cruzi* vector species to thrive within while in close proximity to their human hosts (Short, Caminade, & Thomas, 2017). Additionally, socioeconomic factors specific to immigrant populations in non-endemic regions, including "cultural and language barriers, lack of a regular healthcare provider, lack of access to affordable insurance or healthcare, lack of information, job constraints, lack of trust in government programs, and

fear," further limit the ability to provide these at-risk populations with culturally appropriate care (Klein, Hurwitz, & Durvasula, 2012, p. 9).

Ultimately, these additional factors affecting vector species spread and *T. cruzi* transmission must be considered in context with the anticipated effects changing climate variables are forecasted to have on the global spread of Chagas disease.

Limitations of studies

The limitations of all studies included in this review begin by the very nature of their ecologic design. Despite the many practical advantages of ecologic studies, including low cost and convenience, there are several inherent methodological issues that can hinder making causal inferences based on their conclusions. The most significant limitation of using ecologic associations to draw causal inferences is ecologic bias, "which is the failure of expected ecologic effect estimates to reflect the biologic effect at the individual level" (Morgenstern, 1995, p. 71). The heterogeneity of aggregate (ecologic) level exposure and covariate data underlies ecologic bias, as "aggregate data cannot characterize within-group variability in exposure and covariate variables." Consequently, supplementing aggregate data with individual-level data is necessary to remove ecologic bias (Wakefield & Haneuse, 2008, p. 908).

An additional factor that can limit the accuracy of reviewed studies' species distribution models is sampling bias, as it may lead to an over or under estimation of vector species occurrence data (Rocchini et al., 2017). For example, Tapia-Garay et al. (2018) found the presence probability of *T. infestans* to be most concentrated in the central zone of Chile, despite more northern regions of Chile offering better suited habitats for this vector species.

One possible explanation for this finding is a sample bias in their occurrence data, seeing as good climatic conditions in the central zone of Chile allow for better study of this area, as opposed to the northern desert, where high altitudes and extreme climates prevent adequate sampling of the region. Considering such uncertainties that potentially undermine the outputs of species distributions models is critical for interpreting results accurately and informing appropriate Chagas disease prevention and control efforts (Rocchini et al., 2017).

Furthermore, limitations due to the spatial resolution and interpolation process associated with the WorldClim dataset utilized by the majority of reviewed studies should be considered. In particular, limited weather stations in Latin America (relative to other parts of the world) necessitates interpolation of climate variables from larger distances in these regions, making the reliability of the resulting climate variables uncertain. Thus, the incorporation of additional environmental variables and/or socioeconomic factors is required to make inferences linking the climatic suitability of vector species to *T. cruzi* transmission risk (Medone et al., 2015).

The complexity of the *T. cruzi* transmission cycle presents another limitation to studies included in this review. As noted by Garza et al. (2014), *T. cruzi* transmission involves various insect vectors and mammalian hosts in domestic, peri-domestic, and sylvanic cycles. Although ideal modeling exercises would include the potential distribution of all hosts and vectors, relatively little is known about which mammalian species are confirmed hosts of *T. cruzi*; thus, including unconfirmed mammalian hosts in distribution models would only add confusion to our understanding of this biological interaction.

Additional limitations of studies included in this review concern their use of the AUC or the pAUC to evaluate their vector species distribution or ecological niche models. The AUC has long been considered the standard method to estimate the predictive accuracy of distributional models derived from presence absence species data (Lobo et al., 2008), and thus, was utilized by several studies to evaluate their ecological niche models (Ceccarelli & Rabinovich, 2015; Garza et al., 2014; Tapia-Garay et al., 2018). However, there are several characteristics of the AUC that make its use as a measure of distribution model accuracy questionable. First, AUC scores disregard the predicted probability values and the goodness-of-fit of distribution models (Ferri, Flach, Hernandez-Orallo, Senad, 2005). "AUC is a discrimination index that represents the likelihood that a presence will have a higher predicted value than an absence, regardless of the goodness of fit of the predictions" (Lobo et al., 2008, p. 146). As such, a poorly fitted model (i.e. one that over/under estimates all predicted values) may have a good discrimination power. A well-fitted model with a poor discrimination power is also possible, if, for instance, probabilities for presences are only moderately higher than those for absences (Hosmer, Lemeshow & Sturdivant, 2013). Another weakness of ROC plots is that they "summarize model performance over all conditions a model could operate in" (Lobo et al., 2008, p. 146). However, researchers are typically interested in one or a few possible situations, rather than all of them. For example, extreme right and left areas of the ROC space correspond to high false-positive and high false-negative rates, and are thus, generally useless (Baker & Pinsky, 2001).

In an effort to mitigate the above concerns, the pAUC has been proposed as an alternative to the full AUC (Baker & Pinsky, 2001), and as such, three studies included in

this review chose to use the pAUC to validate their ENMs (Carmona-Castro et al., 2018; Medone et al., 2015; Costa et al., 2014). However, the pAUC fails to avoid all drawbacks associated with the full AUC (Lobo et al., 2008). First, both pAUC and AUC give equal weight to omission and commission errors, yet these errors do not share equal importance in many applications of species distribution modeling (Peterson, 2006). For instance, there is a higher degree of uncertainty associated with absences compared to presences when obtaining presence-absence species data. Recorded absences may indicate low detectability of the species or they may reflect non-sampled areas; thus, the likelihood of false absences is higher than false presences. Consequently, by assigning equal weight to commission errors (misclassification of absences) and omission errors, the results of the AUC and pAUC may be misleading (Elith et al., 2006). Finally, and most importantly, "species distribution data are referred to a concrete geographical extent, and increasing the geographical extent outside presence environmental domain entails obtaining higher AUC scores" (p. 147). Thus, simply enhancing the area of the territory modeled allows artificially high AUC scores to be obtained. Decisively, this feature prevents use of both the AUC and pAUC as accurate performance measures of predictive species distribution models (Lobo et al., 2008).

It is important to consider all of these study limitations and their potential influence on the relationships identified between changes in climate and future Chagas disease transmission.

Future recommendations

The following directions for future research are suggested to further our current understanding of the associations between climate change and the global distribution of Chagas disease.

First, predicting the biological effects of climate change on vector *T. cruzi* transmission requires a more thorough understanding of Chagas disease ecology. To this end, additional research is necessary to produce an exhaustive list of confirmed *T. cruzi* mammalian hosts. Development of innovative modeling techniques has enabled production of predictive lists of potential hosts for other emerging infectious diseases (e.g. leishmaniasis) (Stephens et al., 2009); these techniques may also be applied to Chagas disease.

Secondly, the application of novel, combined spatiotemporal modeling approaches in Chagas disease research is required to attain a more comprehensive understanding of the complex relationship between *T. cruzi* vectors, hosts, and anticipated changes in climate, and by extension, more accurate predictions of future Chagas transmission risk areas.

Furthermore, developing accurate global climate change scenarios based on projections of future population growth and socio-economic development necessitates the consideration of the potential confounding effects of urbanization, migration, tourism, and other human behaviors.

Additionally, the importance of environmental factors, insect vectors, and mammalian hosts to *T. cruzi* transmission suggests that interdisciplinary collaboration between epidemiologists, entomologists, veterinarians, ecologists, geographers and infectious disease

specialists is necessary to advance knowledge of this complex disease system, estimate the cost and effectiveness of control strategies, and ultimately address the current and future public health challenges Chagas disease poses to global populations.

Another area in need of special attention relates to quality control of Chagas disease incidence and vector species occurrence data from reporting agencies (e.g. laboratories, hospitals and clinics, health departments, and other governmental agencies). Addressing existing issues including lack of healthcare provider awareness, under-reporting and missed diagnosis, limited screening and diagnostic modalities, insufficient patient reporting and Chagas disease stage reporting, and vector species misidentification will vastly improve the accuracy of data gathered through *T. cruzi* surveillance activities. Improvement of disease and vector species surveillance in both endemic and non-endemic areas is essential for effective Chagas disease prevention and control programs.

Developing strategies to enhance patients' access to diagnosis and treatment is an essential component to reducing the global Chagas disease burden. Although two anti-parasitic drugs, benznidazole and nifurtimox, are currently available for the treatment of Chagas disease, various factors hinder their effective usage, including "lack of access to diagnosis, drug toxicity and absence of treatment algorithms to address adverse effects, failures in drug supply and distribution, and inconsistent drug efficacy against the symptomatic chronic stage." To address these barriers to effective Chagas disease treatment, future research and development should focus on expanding the clinical study of new anti-parasitic drugs, discovering improved biomarkers that enable monitoring of disease

progression, and developing inexpensive and accessible diagnostic tools (Alonso-Padilla et al., 2019, p. 145).

Finally, the successes and failures of current *T. cruzi* vector control and Chagas disease management programs in endemic countries can inform future control efforts in both endemic areas of Latin America and at risk non-endemic regions, including the United States. Several intergovernmental initiatives between endemic Latin American countries were developed in the 1990's, aimed at decreasing Chagas disease transmission to human hosts by focusing on domestic *T. cruzi* vector control. As a result of multifaceted campaigns involving "widespread insecticide use, improved housing conditions, and promotion of public education", annual mortality and morbidity rates due to Chagas disease have steadily fallen between 1990 and the present (p. 2). However, large sylvanic mammalian reservoirs of the parasite have persisted over time, resulting in new human infections and contributing to the failure of eradicating the disease entirely (Klein, Hurwitz, & Durvasula, 2012). In addition, persistent house re-infestation due to residual peri-domestic foci after insecticide application and the development of pyrethroid insecticide resistance casts doubt on the feasibility of eliminating Chagas disease through vector control methods alone (Gaspe et al., 2018).

Vector control efforts also do not address *T. cruzi* transmission through other routes (e.g. blood and organ donors, congenital transmission, oral transmission), socioeconomic and cultural aspects of Chagas disease transmission, or barriers to diagnosis and treatment; thus, *T. cruzi* continues to thrive in human hosts throughout both endemic and non-endemic regions (Klein, Hurwitz, & Durvasula, 2012).

Somewhat surprisingly, the overall wealth of a government does not appear to mitigate the socioeconomic factors associated with Chagas disease transmission. In fact, recent studies found that "90% of the people infected with *T. cruzi* now live in Latin America's three wealthiest economies: Argentina, Brazil, and Mexico" (p. 145) Further, in the United States of America, the richest country of the western hemisphere, there are "at least 300,000 immigrants from Latin America living with Chagas disease with limited or no access to treatment" (Alonso-Padilla et al., 2019, p. 145). These findings suggest that a lack of awareness or lack of interest, rather than lack of resources, on the part of governments of endemic and non-endemic countries are instrumental to the Chagas disease burden in these areas.

Given the biological, social, political and economic aspects of Chagas disease, creating sustainable, comprehensive disease control programs is a challenge. First, in order to complement existing vector control programs in endemic countries, the importance of peri-domestic and sylvanic areas as sources re-infestation must be emphasized, and as such, should be focal points of disease surveillance activities (Yoshioka, Provedor, & Manne-Goehler, 2018). Enhancing community-based vector control interventions that encourage regular residential insecticide spraying by householders is another sustainable, low cost, and highly effective method to prevent house infestation by triatomine vectors, especially in remote, resource poor endemic regions (Cecere, Rodriguez-Planes, Vazquez-Prokopec, Kitron, & Gurtler, 2019). Historically, endemic country-level Chagas disease control policies mainly emphasize prevention of vector-borne *T. cruzi* transmission, overlooking the importance of early diagnosis, treatment and education to the successful elimination of

Chagas disease (Yoshioka, Provedor, & Manne-Goehler, 2018). Community health interventions, specifically in situ screening interventions, are useful additions to current vector control strategies, as they increase access to diagnostic screening, enhance awareness and knowledge of Chagas disease, facilitate access to treatment, and prevent further spread of Chagas disease through secondary transmission routes (Prat et al., 2019). Non-endemic countries also have an important role to play in aiding in the global efforts to eliminate Chagas disease. "Most importantly, healthcare providers in non-endemic countries with large immigrant populations from Chagas disease endemic areas need to be educated about the existence of the disease, its clinical manifestations, and the appropriate mechanisms of diagnosis and treatment of infected patients" (p. 9). Facilitating at-risk populations' access to healthcare services and implementing systemic screening protocols for pregnant women and blood / organ / tissue donors from endemic countries are additional recommendations for the management of Chagas disease in non-endemic countries (Klein, Hurwitz, & Durvasula, 2012). Ultimately, coordination among regional, national, and international policymakers, researchers, healthcare providers, and public health professionals is essential to the success of future Chagas disease elimination efforts.

CONCLUSION

The weight of evidence regarding the influences climate change may pose on *T. cruzi* vector species distributions demonstrates the sensitivity of Chagas disease transmission to future climate variability. In order to advance forecasts for the impact climate change may have on Chagas disease transmission in the Americas, it is imperative to further develop, utilize, and perhaps combine predictive species distribution modeling approaches that

integrate accurate, long term data on climate variables, vector species distributions, Chagas disease incidence, as well as other socio-ecological variables. While the task at hand is considerable and will require a concerted effort to achieve, the insights it can contribute to future global health efforts may prove to be invaluable. Chagas disease has become more than a neglected disease that mainly affects the rural poor in Latin America: it is growing into a worldwide concern that can have severe consequences for human health over the long term. If it is not taken seriously now, it could become an insurmountable threat to global public health in the future.

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