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Ciguatera fish poisoning and climate change: analysis of national poison center data
in the United States 2001-2011

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Abstract

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By Daniel Gingold

Ciguatera fish poisoning (CFP) is the world's most common seafood-toxin disease. CFP occurs when humans consume fish that have fed on ciguatera toxin-producing organisms, and is characterized by acute gastrointestinal upset followed by neurological symptoms such as numbness, weakness, and disruption of temperature sensation. Recent studies have demonstrated a relationship between CFP incidence and warmer sea surface temperatures (SST). Also, increased severe storm frequency may create more suitable habitat for ciguatoxic organisms. Climate change is expected to affect SST and storm frequency in the Caribbean, and may cause an increase in CFP prevalence and expansion beyond its current tropical range.

The purpose of this hypothesis-generating ecological time-series study was to determine if CFP incidence is associated with periods of warmer SST and increased storm frequency in the Caribbean over the last decade to inform predictions regarding climate change and CFP.

1,272 CFP-related calls to US poison control centers between 2001-2011 were identified from the National Poison Data System and analyzed using descriptive analysis and Poisson regression. Results showed an independent association between monthly CFP calls and warmer SST and tropical storm frequency, using fishing yields as an offset. The optimal lag period for SST was between 5 and 16 months; the variable selected links current monthly CFP calls to the peak August SST of the previous year. The optimal lag period for storms was 18 months. The rate ratio for an increase in storms by one per month was 1.113 (95% CI [1.03, 1.234]), and the rate ratio of a one-degree increase in SST temperature was 1.612 (95% CI [1.167, 2.243]).

These estimates imply that if the maximum Caribbean SST increases by 2.5°C as projected, and storm frequency increases by 10% from 2001-2011 levels, approximately 239 additional calls per year can be expected (95% CI [49.5, 665.9]), a two- to four-fold increase.

Using CFP calls as a marker of CFP incidence, these results support the hypothesis that CFP incidence is positively associated with warming SST and increased tropical storm frequency, and should inform adaptation measures to limit the potential public health impacts of unmitigated climate change.

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CHAPTER 1: LITERATURE REVIEW

Climate Change and Public Health

The Intergovernmental Panel on Climate Change (IPCC) has determined with “very high confidence” (at least 9 out of 10 chance) that humans have played a role in the warming of the Earth’s climate. This “unequivocal” warming of the earth’s climate system is “very likely” (greater than 90% probability) due to anthropogenic increases in atmospheric greenhouse gases that trap the sun’s energy to warm the planet. Carbon dioxide emissions from fossil fuel use is the primary driver of this trend, although methane and agricultural nitrous oxide emissions likely contribute as well (1).

Warming of the earth’s climate over the last century is evident from observations in global mean air and sea temperature, increased snow and ice melting, and rising average sea level. These trends are projected to continue as greenhouse gas emissions rise, and would continue for years even if emissions are reduced or level off. Regional changes in long-term climate have also been observed, including changes in arctic temperatures in ice, precipitation amounts, ocean salinity, and wind patterns (2).

Changes in frequency and intensity of extreme weather events such as droughts, heavy precipitation, and heat waves have also been observed. While lack of historical data complicates calculation of long-term trends in tropical cyclones, there is observational evidence for an increase in intense tropical cyclone activity in the Atlantic since 1970, associated with increasing tropical sea surface temperatures (SST). While study results are mixed as to whether storm frequency

will increase, decrease, or remain constant, it is “likely” (greater than 66% probability) that tropical cyclones will also become more intense as climate change progresses, with higher wind speeds and heavier rainfall (3, 4). Storm frequency has been linked to SST, which is expected to increase in the North Atlantic Basin, although some models have predicted stabilization or decrease in global cyclone frequency (5, 6).

Changes in air and water temperature due to climate change are likely to affect environmental drivers of human health (7). Heat related illness will increase with more frequent and more severe heat waves, and rising seas and intense rainfalls will cause injuries related to floods and landslides. More frequent floods and storms also increase the risk of waterborne diseases, and more frequent and severe droughts put more people at risk of famine and starvation (7). These events will increase demand on public health and health care systems. Due to its role as a safety net with a broad clinical mission that includes pre-hospital and disaster medicine, emergency medicine will be one of the medical specialties most significantly burdened by climate change (8).

However, the effect of changing climate on human health is not limited to these direct mechanisms. Derangements in regional climate systems will have profound effects on local and regional ecosystems, which in turn will affect human disease. Changes in distribution and population of vertebrate host species may change the range and frequency of vector-borne and zoonotic diseases. Increased sea temperatures along with carbon dioxide emissions acidify ocean waters and disrupt shell formation in many marine invertebrates. This will create more suitable

habitat for harmful algal blooms, especially in areas with increased nutrients from agricultural runoff. Algal blooms have been known to produce powerful liver toxins that can contaminate drinking water. Increased seawater temperatures have also been implicated in coral bleaching events in which stressed corals expel their symbiotic dinoflagellates that give the coral their color (9). These events severely damage these delicate ecosystems, decreasing available habitat for many fish and other reef dwelling organisms and possibly increasing habitat for harmful algae and dinoflagellates that produce ciguatera toxin which, when ingested by humans, can cause ciguatera fish poisoning (CFP).

Ciguatera Toxin Production

Ciguatera toxin is produced by benthic dinoflagellate plankton, which live as epiphytes on bottom-dwelling algae and on dead coral. Classically *Gambierdiscus toxicus* is implicated in producing ciguatera toxin, although other species of dinoflagellates may play a role in producing toxins as well. Toxicity of *G. toxicus* can vary significantly by strain; non-toxic strains have been identified, as have a number of strains producing toxins of varied potency. Generally, ciguatoxins from the Pacific (P-CTX) are generally more toxic to humans than those generated in the Caribbean (C-CTX) (10). The ecological advantage of toxin production for the dinoflagellate is unknown, although it is possible that a toxic environment kills competing dinoflagellates.

Water temperature, pH, and salinity are likely important factors in the growth and proliferation of ciguatoxic dinoflagellates (11). Nutrient-rich

agricultural runoff can also increase plankton growth (12). Reef disturbance from storms, dredging, or warm-water bleaching events may increase the habitat available for toxic dinoflagellates. Once a reef becomes ciguatoxic it can remain that way for many years (11). CFP events are often reported on windward sides of islands where wave and storm energy is most severe (11). Some studies show that environmental factors like temperature or salinity can affect the toxicity of dinoflagellate toxin, but other studies showed these environmental factors had little or no effect on toxicity (13). Modeling of *Gambierdiscus* growth from nutrient and physio-chemical data in Hawai'i showed that increased water temperature and dissolved nitrogen and phosphates such as those from river runoff increase the growth rates of *Gambierdiscus*. However, there may be threshold above which water temperatures would be too warm and would inhibit *Gambierdiscus* growth (13).

Ciguatoxin in Fish

Herbivorous fish consume algae and accompanying ciguatoxic dinoflagellates, and the toxin accumulates in fish tissues (14). Larger predatory fish are more likely to contain higher concentration of the toxin as it bioaccumulates up the food chain. Hundreds of fish species have been implicated in CFP, and most are fish that live in and around coral reefs. Species that are commonly associated with CFP in the US and the Caribbean include the moray eel, grouper, amberjack, snapper, mackerel, and barracuda. Indeed, it is illegal to sell barracuda for human consumption in Miami, FL, due to concerns of CFP (15).

Toxicity can fluctuate significantly among species, individual fish, seasons, and location. Once fish become toxic it can take a long time to excrete the ciguatoxin. The half-life of ciguatoxin excretion has been estimated to be around 260 days (15).

Ciguatoxic fish in the field that are poisonous to humans are usually unaffected by the toxin and indistinguishable in taste, smell, appearance, and behavior from non-toxic fish (10). However, laboratory studies have shown ciguatoxin can be lethal to freshwater and marine fish at high levels (15). Some laboratory results indicate that higher levels of toxin can cause behavioral changes, which may cause fish with high toxin loads to be preferentially preyed upon (15). The viscera, and in particular the liver, of affected fish are often implicated in more severe poisonings as these organs can contain 50 to 100 times more toxin than muscle flesh (11). The toxin is heat-stable, so cooking or freezing fish does not alter toxicity. The risk of CFP is often mediated in endemic areas by only eating the flesh of fish known to be at risk of being ciguatoxic (10).

Ecology of Ciguatera

CFP classically has been limited to the tropical regions, between 35 degrees latitude north and south (16). This is likely because water temperatures in this region are warm enough to support toxic dinoflagellates, and because reef habitats for these organisms are common in these regions. CFP is most prevalent in regions where sea surface temperature (measured by ships, buoys, and satellites at in the top few meters of the ocean surface) does not go below 24 °C. In a study of the

Caribbean basin all CFP cases during 2002-2007 occurred where annual average temperatures were above 25°C (17, 18).

Natural and anthropogenic disturbances of coral reefs have long been recognized to increase toxic dinoflagellate growth and CFP (15, 19). Coral bleaching is a worldwide problem and occurs in response to increased water temperature, pollution, sedimentation, or salinity change. Stress on the coral polyps causes them to expel colorful symbiotic algae, causing the coral to lose its color. Coral bleaching has been associated with temperature changes of as little as 1°C increase in average summer sea-surface temperature (15). Increased coral bleaching from higher sea temperatures and more frequent storms, as well as man-made structures in the ocean may also increase habitat for macroalgae and associated toxic dinoflagellates (20). Recent reports also suggest that CFP is associated with oil rigs and other artificial reefs that provide habitat for toxic dinoflagellates (10). It is also possible that increased carbon dioxide in the atmosphere will create more acidic seawater, decreasing the level of carbonate in the water used by coral to maintain its skeletal structure. This may make coral more susceptible to damage by storms, earthquakes, or tourism, further damaging the reef and allowing for more growth of toxic dinoflagellates (15). Storm may also increase macroalgae and *Gambierdiscus* growth by increasing nutrients in the water from agricultural runoff, as well as purging substances that inhibit growth during low rainfall periods (15).

The time period between increased dinoflagellate production and human CFP is not known. Early studies indicated that reef fish can become toxic very rapidly in the presence of a *Gambierdiscus* bloom, and the lag period between the peak

dinoflagellate abundance and CFP is on the order of one month (15). However, more recent studies have indicated that the lag period can be longer than this, up to 11 months or more (13).

Epidemiology of CFP

Ciguatera fish poisoning is the most common non-bacterial illness associated with fish consumption (17). Worldwide it affects between 50,000 and 200,000 people annually (21). Indigenous inhabitants of endemic areas have recognized it for centuries, and neurological effects of CFP were first described in detail by a British naval doctor in 1786 (22). It is most prevalent in tropical and sub-tropical regions of the Pacific and Indian Oceans, as well as the tropical Caribbean. Although traditionally CFP has been found between latitudes 35°N and 35°S, incidence among areas in this region vary significantly across the globe (Figure 1) (15). However, due to worldwide exportation of fish caught in endemic areas as well as tourism, cases can occur almost anywhere worldwide, including inland in the US and Europe. The number of cases reported in the literature has increased in the last 30 years, likely because of tourism expansion into endemic areas, but also because of natural and anthropogenic environmental changes. Detection bias, resulting from better recognition of the clinical syndrome and better reporting systems, may also have played a role (23).

There are few epidemiological studies of ciguatera in the United States. Ninety percent of cases reported to the Centers for Disease Control and Prevention (CDC) in the US are from Florida and Hawaii, although the disease is also endemic in

Puerto Rico and reports from local fish have been observed in Texas and the Carolinas (15, 24). Most US epidemiological studies have been performed in southern Florida, where the disease is relatively common and healthcare providers are required to report cases to local health departments. Risk estimates in Dade County, FL were at least 5 cases per 10,000 persons per year, compared to 73/10,000 in the US Virgin Islands (15, 25). In comparison, the incidence rate from 1992-2001 in French Polynesia was 363 per 100,000 person-years. This study also supported previous reports that have found that incidence rates increase with age, likely due to locals avoiding feeding fish that have a high risk of causing ciguatera poisoning to children (23).

CFP is underreported to surveillance and medical professionals since its symptoms can mimic gastroenteritis and be non-specific. This is true around the world and in the US and other Caribbean countries. Reporting rates in the Caribbean may be 20-40%, and as low as 2-10% in the US (25). Studies in Miami estimate risk of CFP could be as high as 50 cases per 10,000 per year, taking into account estimated reporting rates (25). Reporting and case confirmation may also be sensitive to outbreak bias (26). These studies were performed with local health departments, and though one did use the local poison control center to examine reporting rates to the local public health department, no studies are available using National Poison Data System (NPDS) as a surveillance or epidemiological tool to monitor ciguatera poisoning in the United States.

The seasonality of CFP in endemic areas has been suggested but is controversial. Consumption of ciguatoxic fish during holidays may mimic a seasonal

pattern in CFP incidence, and traditional fishermen of island areas may avoid fish known to be ciguatoxic during certain periods, potentially masking seasonal patterns of the toxin. Small studies have shown some seasonality, however. For example, CFP peaked in spring and fall in a study in Puerto Rico from 1985-1987 (27). Seasonality therefore appears to be a local phenomenon and no generalization can be made about global seasonality, as many other studies have reported that CFP is not seasonal (15).

Ciguatoxin Pharmacology

Ciguatoxin has a direct effect on voltage-sensitive sodium ion channels, increasing the permeability of the membrane to sodium ions. This alters the cell's ability to maintain optimal solute concentration in the cell and can alter its ability to generate and propagate action potentials. The toxin stimulates sodium ion entry into the cell through binding to the sodium channel. This increases cellular excitability, causing an increased sensitivity of action potentials followed by a decrease in sensitivity after the membrane depolarizes (15). Although little is known about the pharmacokinetics of ciguatoxins in mammals, this effect on neuron, muscle, and cardiac sodium channels is implicated in the neurophysiological toxidrome in human CFP (11). There is also evidence that ciguatoxins act on calcium channels in the nitric oxide synthase pathway, although the clinical manifestations of these mechanisms are not well described (28).

CFP in Humans

Humans eating contaminated fish are susceptible to the toxidrome caused by the ciguatera toxin, which causes gastrointestinal upset followed by neurologic symptoms (10). The toxin is lipid-soluble, so the gut absorbs it quickly after eating. Timing, duration, and severity of symptoms of CFP are highly variable. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and diarrhea typically begin within 12 hours of consuming the toxin, and usually last only one or two days (11).

Neurological symptoms usually begin after the gastrointestinal symptoms but still in the first few days of the illness, and while they usually resolve within a few weeks, some can persist for months or even years. Paresthesias in the extremities or oral pharynx are the most common neurological symptoms, and hot-cold reversal is not always present but is a classic characteristic of CFP (10). This symptom can also be caused by the brevetoxin in Neurotoxic Shellfish Poisoning (NSP), which must be considered if this symptom is present and there is a history of shellfish consumption. Other symptoms include arthralgia, myalgia, pruritus, headache, perspiration, sensation of loose teeth, and dysuria (11). Weakness, ataxia, insomnia, vertigo, and fatigue can also occur and can persist chronically (22). Cardiovascular autonomic dysregulation such as blood pressure variability, hypotension, and bradycardia can occur in 15% of patients and are more frequent after consuming carnivorous fishes (11, 22). These symptoms are generally limited to 5 days duration. Coma is the most feared neurological effect, although it is very rare and has only been described in the Pacific regions. The most common serious complication of CFP is dehydration from vomiting and diarrhea, which can be severe

especially in children and infants. Mortality rates have been reported as high as 5% but the true rate is likely closer to 0.1% (15). Usually deaths result from heart failure, respiratory failure, or shock and are associated with consumption of fish liver, roe, or other organs, all of which are known to contain high levels of toxin.

Sensitization of individuals to ciguatoxin has been reported, and patients with a history of CFP maybe more likely to experience the neurological symptoms than people eating the same fish that have not been previously exposed (10). There are also anecdotal reports of alcohol, fish, caffeine, other foods, or dehydration causing worsening or relapse of symptoms (10).

Ciguatoxin Detection

There is no reliable diagnostic test for CFP in humans. Diagnosis is typically made based on history of consuming a fish that could be ciguatoxic, description of symptoms consistent with CFP, and exclusion of alternative diagnoses (10).

There are many folk methods for detecting ciguatoxin in fish, which have not been validated, including cooking the fish with a silver coin, which should darken if the fish is toxic. Traditional communities have long avoided CFP by avoiding specific reefs or fish known to cause CFP, eating only the flesh of suspect fish, and eating only smaller or herbivorous fish during ciguatera outbreaks. Some traditional practices like rubbing liver on gums to produce a tingling sensation may work occasionally, but while soaking the fish in water before cooking may remove other water-soluble toxins it is unlikely to affect the lipid-soluble ciguatoxin (11, 19).

Bioassays that have been used to identify toxic fish by feeding organs to animals such as a cat, mongoose, or chick are effective but often cumbersome due to the time needed to observe the animal and the quantity necessary to make the animal sick (11). A mouse bioassay using intraperitoneal injection of purified fish extract is specific and reliable, but time consuming and resource-intensive (11, 15). Laboratory techniques such as liquid chromatography-mass spectrometry (LC-MS) and cell-based assays have been developed, although these methods can also be expensive and require laboratory infrastructure that is often not available in developing countries in which CFP is endemic (10, 15).

Recently, immunological test kits have been promising in reaching the goal of a cheap, effective, widely available test that can be used for screening individual fish, although improvements still must be made in sensitivity and specificity of these methods. Currently, there is no commercially available product that has demonstrated sufficient accuracy to be used to detect ciguatoxin in individual fish (10). Better efforts must be made to submit samples of fish suspected of containing ciguatoxin to public health laboratories for analysis.

CFP Treatment

There is no antidote for ciguatoxin, and treatment of patients is usually supportive. There are many traditional herbal remedies for CFP, especially in the Pacific regions. The mechanism and effectiveness of these remedies is unclear, although some of the most popular such as the preparation of the leaves of *Heliotropium foertherianum* have been investigated in pharmacological experiments

(28). Most evidence of effectiveness of these treatments is for their antidiarrheal, antispasmodic, antipruritic, or cardiac-tonic effects rather than acting as an antidote for the toxin itself (15).

There are few randomized controlled trials evaluating conventional medical treatments of CFP. Most research is limited by the infrequency of CFP, lack of scientific resources in endemic areas, lack of a confirmatory diagnostic test, small numbers of patients, and regional variability in the clinical effects of CFP (10). The early administration of activated charcoal is thought to be beneficial (28). Gastrointestinal symptoms usually only require oral or intravenous fluid to avoid dehydration. Rarely, endotracheal intubation and mechanical ventilation may be necessary in cases of respiratory compromise, and intravenous vasopressors may be required along with fluids to treat shock. Other symptomatic treatments include analgesics for headaches and musculoskeletal pain and antihistamines for pruritus. Antiemetic and antidiarrheal medication have had mixed success, as does amitriptyline for neurologic symptoms. Atropine is often used in symptomatic bradycardia. Selective serotonin reuptake inhibitors may be helpful in chronic psychiatric or behavioral effects of CFP (10).

Intravenous hypertonic D mannitol is the best-studied treatment for CFP and is the current treatment of choice as it is the only therapy that has been evaluated by randomized blinded trials (28). IV mannitol 0.5 to 1.0 g/kg administered over a 30-45 minute period within 2-3 days of the ingestion of the toxic fish is reported to alleviate neurological but not gastrointestinal symptoms. Patients with severe symptoms treated during the acute phase of the illness are most likely to benefit

from mannitol treatment (15). However, its efficacy is still controversial, and many clinicians are reluctant to use it, especially as its osmotic effects can worsen dehydration and cardiac failure (10, 28). The mechanism of effect is unclear, but the osmotic properties are likely to play a role in reduction of neuronal edema that is caused by derangement of sodium channel function by the ciguatoxin. Action as a free-radical scavenger may also play a role (11, 22). Initial reports of the effectiveness of mannitol were anecdotal, although there has been a randomized trial showing greater reduction in symptoms in the mannitol group compared to IV glucose, Vitamin B and calcium gluconate. Another double-blind, randomized study found no difference in clinical improvement between groups receiving mannitol and saline (10).

An antagonist to brevetoxins, which is similar to ciguatoxin, called Brevenal has been patented for possible use in neurotoxic shellfish poisoning in animals and humans. It is possible that this may lay the foundation for the development of a specific treatment for CFP (10).

Ciguatera and Climate Change

Climate change is likely to raise sea surface temperatures in higher latitudes. SSTs in the northern Caribbean are expected to increase 2.5°C – 3.5°C during the twenty-first century, promoting growth of *Gambierdiscus* and potentially increasing its range northward along the US Atlantic coastline (14, 20, 24, 29). There is evidence that annual incidence of CFP in the Pacific is positively correlated with seawater warming during El Niño Southern Oscillation (ENSO) events (30). Using a

2-year time period, several Pacific climactic indices such as the Southern Oscillation Index, Pacific Warm Pool Index, and several ENSO indices are correlated with CFP. Warming sea temperatures appear to increase CFP in general, but if sea temperatures exceed a threshold temperature (around 30°C) for long enough, CFP may decrease (29). Some studies do report a seasonal pattern to ciguatera poisoning in the Caribbean, although as environmental conditions change and sea temperatures rise this seasonal pattern may become less strong. CFP prevalence is associated with higher sea surface temperatures in epidemiological studies in the Caribbean, which found more ciguatera in regions that have the warmest and least variable water temperatures. These conclusions are supported by laboratory studies of dinoflagellate, which show that 29°C is optimal for growth (17).

As mentioned above, tropical storms may increase the suitable habitat and growth of ciguatoxic dinoflagellates(11). Changes in storm frequency and intensity due to climate change may also have an impact on CFP incidence.

CHAPTER II: MANUSCRIPT

Title: Ciguatera fish poisoning and climate change: analysis of national poison center data in the United States 2001-2011

Authors: Dan Gingold, Matthew Strickland, Jeremy Hess

Abstract

Ciguatera fish poisoning (CFP) is the world's most common seafood-toxin disease. CFP occurs when humans consume fish that have fed on ciguatera toxin-producing organisms, and is characterized by acute gastrointestinal upset followed by neurological symptoms such as numbness, weakness, and disruption of temperature sensation. Recent studies have demonstrated a relationship between CFP incidence and warmer sea surface temperatures (SST). Also, increased severe storm frequency may create more suitable habitat for ciguatoxic organisms. Climate change is expected to affect SST and storm frequency in the Caribbean, and may cause an increase in CFP prevalence and expansion beyond its current tropical range.

The purpose of this hypothesis-generating ecological time-series study was to determine if CFP incidence is associated with periods of warmer SST and increased storm frequency in the Caribbean over the last decade to inform predictions regarding climate change and CFP.

1,272 CFP-related calls made to US poison control centers between 2001-2011 were identified from the National Poison Data System and analyzed using

descriptive analysis and Poisson regression. Results showed an independent association between monthly CFP calls and warmer SST and tropical storm frequency, using fishing yields as an offset. The optimal lag period for SST was between 5 and 16 months; the variable selected links current monthly CFP calls to the peak August SST of the previous year. The optimal lag period for storms was 18 months. The rate ratio for an increase in storms by one per month was 1.113 (95% CI [1.03, 1.234]), and the rate ratio of a one-degree increase in SST temperature was 1.612 (95% CI [1.167, 2.243]).

These estimates imply that if the maximum Caribbean SST increases by 2.5°C as projected, and storm frequency increases by 10% from 2001-2011 levels, approximately 239 additional calls per year can be expected (95% CI [49.5, 665.9]), a two- to four-fold increase.

Using CFP calls as a marker of CFP incidence, these results support the hypothesis that CFP incidence is positively associated with warming SST and increased tropical storm frequency, and should inform adaptation measures to limit the potential public health impacts of unmitigated climate change.

Introduction

Ciguatera fish poisoning (CFP) is the most common non-bacterial illness associated with fish consumption, affecting 50,000 - 200,000 people annually (21). Ciguatera toxin is produced by benthic dinoflagellate plankton in the genus *Gambierdiscus*, which live on dead coral surfaces and bottom-dwelling algae. Toxin accumulates in tissues of fish that eat the algae and bioaccumulates up the food chain (17). Humans eating contaminated fish are susceptible to the toxidrome caused by the ciguatera toxin, which includes gastrointestinal upset followed by neurologic symptoms that can include paresthesias and hot-cold reversal (10).

CFP is a significant public health problem in endemic areas, including the Caribbean and Pacific Islands. CFP prevalence in these areas is affected by El Niño and warmer sea surface temperatures (SST). CFP is most prevalent in tropical regions of warm and stable SST that remain above 24°C, and laboratory studies have shown that water temperatures of 29°C are optimal for *Gambierdiscus* growth (17, 30). Climate change is projected to expand the range of suitable habitat for the organisms that cause ciguatera by expanding the range of warm SSTs and bleaching coral reefs (20). Increase in storm frequency also damages reefs and increases nitrate-rich soil runoff, which may increase the growth of marine algae and ciguatera toxin-producing organisms (11).

We hypothesize that CFP incidence in the US is associated with warm Caribbean SST and high severe storm frequency. If true, projections of increased SST and storm frequency from climate change suggest CFP prevalence in the US may increase. In addition, this study provides an opportunity to investigate the

epidemiology of CFP in the United States and evaluate the suitability of the National Poison Data System (NPDS) for use in surveillance of CFP and other toxicological exposures. Therefore, our primary objective is to evaluate the association between calls to the NPDS and Caribbean basin SST and frequency of severe storms. Our secondary objective is to perform a descriptive analysis of the epidemiology of CFP reported to the NPDS in the contiguous United States from 2001 to 2011.

Materials and methods

Ciguatera Cases Data

All calls to US poison control centers with substance code “Ciguatera Fish Poisoning” affecting humans during years 2001-2011 were collected from the National Poison Data System (NPDS) run by the American Association of Poison Control Centers (AAPCC). No direct subject recruitment or screening for eligibility was performed. Since these are retrospective data and there is no personal health information in the dataset, no informed consent process is necessary. Emory Internal Review Board (IRB) found this project exempt from IRB approval (Emory IRB #00059983). Calls to poison centers that are coded with a ciguatera coding are not necessarily confirmed cases of ciguatera poisoning; calls that request information about ciguatera due to its inclusion in the differential diagnosis of the case are included in calls to poison centers. Calls can be associated with multiple

substance codes. A dichotomous variable was created to identify those calls exclusively coded with a ciguatera coding and those with multiple substance codes.

Calls coded with “confirmed non-exposure” were excluded from analysis. Variables that were the same for all cases or had high numbers of missing values were excluded. Age was coded as a continuous variable and as a categorical variable.

Day, month, and year of calls was available for all recorded calls. The location of cases was coded by the state or country from which the call originated. Information regarding where the exposure occurred or where the fish was from that caused the exposure was unavailable. A dichotomous variable was created to identify calls from the lower 48 United States (US) states, the District of Columbia (DC), Puerto Rico (PR), and the US Virgin Islands (USVI). Calls were also assigned regions and division locations according to the US census regions. Calls originating from Puerto Rico, US Virgin Islands, US territories, foreign countries, or overseas military or diplomatic locations were coded as from “Other” region.

For descriptive analysis of ciguatera calls, key variables associated with cases include date, state, and ZIP code of call; caller site (home, work, etc.); type of health care facility; exposure site (home, work, etc.); age in years (134 missing values, but some of these missing are coded as “unknown adult” “child”, “teen” etc. which were used in coding the age categorical variables); gender of patient; outcome; reason/route; clinical effect (a string); and therapy (also a string). Cases resulting in moderate or major clinical effects or death were identified by a dichotomous variable. Dichotomous variables were created for the presence of individual clinical effects and implementation of individual therapies for ease of analysis.

Sea Surface Temperature (SST) Data

Monthly SST data contained in the Reynolds/NOAA (OI.v2) SST Data Set is available online from the IRI/LDEO Climate Data Library at Columbia University. Weekly SST values are created on a 1° by 1° spatial grid from in situ (ship and buoy measurements of the top few meters of the ocean surface) and satellite SST plus SST simulated by sea-ice cover, with some adjustment for bias (18, 31). Monthly values are created by linear interpolation of weekly data to daily fields, and then averaging the daily values over the month in the same 1° global spatial grid. Monthly values from years 1999-2011 were used. Land-masking was used to remove values for SST that was over land. Monthly maximum and minimum sea surface temperatures in the Caribbean were found in bounds of 7°N-35°N latitude and 97°W-40°W longitude (this includes a small portion of the Pacific off the coast of Central America but it was unusual that these areas would contain the maximum or minimum temperature). Maximum and minimum monthly SST values along the 34.5°N and 24.5°N latitudes were found by restricting data to a one degree latitude band around these parallels. Monthly maximum and minimum latitudes for the 25°C and 29°C contours were found by limiting the monthly data to all measurements within 0.25°C of the desired contour and finding the maximum or minimum latitude value for each month. Yearly maximums (minimums) were found by taking the largest (smallest) monthly value for that year. The peak August temperature variable assigned the value for August of that year for all months of the year; the same was done for the nadir March temperature variable.

Caribbean SST Anomaly Index Data

Monthly Caribbean SST index values from years 1999-2011 were obtained online from the Earth System Research Laboratory at the National Oceanic and Atmospheric Administration (NOAA) at <http://www.esrl.noaa.gov/psd/forecasts/sstlim/timeseries/>. SST forecasts are based on NOAA Extended Reconstructed Sea Surface Temperatures, version 3b. Linear inverse modeling (LIM) is used to calculate the anomalies relative to 1981-2010 climatology (32). These anomalies are averaged over the Caribbean (bounded by 26°N, 80°W, and the eastern coast of Central America) to create a monthly index value named the “CAR index”).

Severe Tropical Storms Data

Data for severe tropical storms (tropical depressions, tropical storms, and hurricanes) for years 1999-2011 are available online from Unisys Weather at <http://weather.unisys.com/hurricane/index.php>. Storms were assigned to months in which they began. Total storm-days for a month are the sum of the durations of all storms that began in that month. Severe storms are indicated by a category 3 or greater hurricane, according to the Saffir-Simpson scale. Data for Accumulated Cyclone Energy (ACE) is available from NOAA at <http://www.aoml.noaa.gov/hrd/tcfaq/E11.html> and at <http://policlimate.com/tropical/ace.dat> (5).

Fishing Yields Data

Caribbean fishing yields during years 2001-2010 are available online from the Food and Agriculture Organization of the United Nations at <http://faostat.fao.org/site/629/default.aspx>. The online query tool for global capture production provided yearly totals for fishing capture of marine and diadromous fishes in marine areas for the Western Central Atlantic ocean area (bounded by 35°N, 40°W, and the eastern coast of North, Central, and South America). These data are in units of metric tons (1,000 kg) and are reported yearly. Fishing yields for 2011 were estimated using data from the previous decade based on a linear regression model (see Figure 5).

Lagged Variables

Lagged variables for weather explanatory variables were created for 3, 6, 12, 18, and 24 month lags. A 3 month lag assigns the value of the original variable in January to the following April. Lagged variables for peak and nadir variables therefore do not have a constant lag period. For example, the previous August maximum SST variable has a 5 – 16 month lag: January values refer to the most recent August 5 months ago, but December values refer to the August 16 months prior.

Analysis Methods

Descriptive analyses of the location, timing, and severity of cases were computed. This analysis was performed for all non-excluded calls and for calls in the

lower 48 states, DC, PR, and USVI (“lower 51”) that were coded exclusively as ciguatera calls.

Poisson regression was used to estimate associations between monthly CFP incidence and SST and storm frequency, using regional annual captured fish production yields as the offset (to control for the effect of a change in fishing yields). Monthly totals for ciguatera calls in the lower 48 US states, DC, PR, and USVI that were exclusively coded for ciguatera exposure were the outcome. Candidate explanatory variables include severe storm totals (by category), total storm days, monthly SST anomaly, each month’s maximum and minimum SST in the Caribbean region and along the 34.5°N and 24.5°N parallels, and the maximum and minimum latitudes achieved each month by the 25°C and 29°C SST contours, as well as variables created to reflect the August maximum and March minimum temperatures for each year. Bivariate correlations between candidate variables were evaluated using Pearson coefficients.

Multiple time lag windows for storms and SST were examined. “Individual variable” regression was performed for all candidate explanatory variables with 0, 3, 6, 12, 18, and 24 month lag times, controlling for month with dummy variables and using the yearly regional fishing yields as an offset. Direction and magnitude of the regression coefficients were examined graphically to select the optimal lag period for each variable. Standard errors were scaled by the Pearson’s chi-square statistic. Variables included in the multivariate model were selected by the individual variable results and manual stepwise elimination in the multivariate

model. The multivariate model used the same monthly control variables and offset as the single variable model.

Rate ratios from the multivariate model were used to calculate the predicted response of the outcome (ciguatera calls) to changes in storms and SST predicted by climate models. Several scenarios were used to produce a range of possible increases in ciguatera calls (along with 95% confidence intervals), and examine the relative estimated effects on ciguatera calls of changes in storm frequency and SST.

All analysis was performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Descriptive Analysis of Ciguatera Calls

There were 1,273 calls associated with the substance code for ciguatera fish poisoning in humans in the US in years 2001-2011. One case was coded as “confirmed non-exposure” and was excluded from descriptive analysis, leaving 1,272 for analysis. 1,232 (96.9%) cases were exclusively coded as ciguatera fish poisoning; the remainder had multiple substances coded, many for paralytic shellfish poisoning and other seafood-associated toxins. 1,102 (86.6%) calls were both exclusively coded as ciguatera and were made from the lower 48 US states, PR, DC, or USVI; these cases were used as the outcome for Poisson regression.

Descriptive statistics for all ciguatera cases, cases exclusively coded as ciguatera (“true cases”), and calls from the lower 48 US states, DC, PR, and USVI are

shown in Table 1, including variables for gender, age, region, site call originated from, site at which patient was managed, exposure route, and outcome. 933 calls had data missing for the data field “Health Care Facility site”; this variable was not analyzed. Descriptive statistics do not differ substantially across cohorts defined by location of call (all vs. lower 48 US states vs. lower 48 US states, DC, PR, USVI), since most calls are included in all cohorts. Distribution of calls by region, age decade, and month are shown graphically in Figures 2, 3, and 4, respectively. The South census region, which includes Florida and other Gulf states, has the largest proportion of calls (55% in full cohort). 460 (36.2%) calls resulted in moderate or major clinical effect (including death). There is a clear seasonal pattern of calls, with more calls being made during the summer months. Table 2a shows frequencies of clinical effects for all cases while Table 2b shows common and classical CFP clinical effects frequencies for all 4 cohorts. The most common symptom was diarrhea (38.7%), followed by vomiting (32.1%) and numbness (22.3%). Table 3a reports frequencies of therapies administered while 3b shows common and selected therapies for all four cohorts.

Descriptive Analysis of Regression Variables

Descriptive statistics for candidate monthly variables for regression are shown in Table 4. Mean, standard deviation, and range (min-max) are given for each variable for each month across years 2001-2011. As expected, there is a seasonal pattern to both storms and SST data: during summer months, water temperatures are warmer, extend farther northward, and storms are more frequent.

Correlations between the dependent variables were assessed using Pearson correlation coefficients (data not shown). Positive correlations existed between monthly SST variables and storm variables as expected, since water temperature and storms exhibit seasonal behavior. These variables were also positively correlated with ciguatera calls, as CFP call rates also increase in the summer. Positive correlations were also present between storm variables and other storm variables, SST variables and other SST variables. The exception to these is the minimum latitude of the 29-degree contour, which was negatively correlated with other SST variables and storm variables.

Time series for some key variables are shown in Figures 6 and 7. The mean CAR index is the average of monthly CAR index values across each year. The August maximum SST is the value in August for the maximum temperature in the Caribbean; the yearly maximum is the maximum SST in the Caribbean for that year. These graphs demonstrate that correlation for these key variables is not only due to seasonal variation, but that broadly they follow each other fairly well year to year. The August maximum regional SST is positively correlated with the August CAR ($R=0.88$, $p<0.001$) and mean yearly CAR ($R=0.66$, $P=0.014$) but not with yearly storms ($R=0.41$, $P=0.16$). Yearly ACE is indeed correlated with yearly total storms ($R=0.75$, $P = 0.003$). The time series for maximum regional temperatures in August and poison center calls exclusively coded as ciguatera from the lower 48 states, DC, PR, and USVI aggregated by year is shown in Figure 8. Ciguatera calls are plotted on the secondary (right) axis. These series do not follow as closely with one another as do the weather variables.

Due to the seasonality of the both dependent and independent variables, “individual variable” analysis was performed using Poisson regression but including dummy variables for month in the model. Results from this analysis are shown in Table 5. Wald statistics and beta-parameter estimates are shown for each variable for each lag possibility, with associations significant at the 0.05 level indicated in bold. Parameter estimates from this table are presented graphically in Figures 9-12, with variables grouped similarly in the table. SST variables are presented with similarly scaled axes. It is clear that for the storm variables, there is a peak of positive correlation at 18 months of lag time, and at this point the total-storms variable (which has the most observations) is associated with the outcome at the 0.05 level (Beta = 0.112, p-value = 0.04). A similar pattern is less obvious among the SST variables. While 12 months is a relatively consistent inflection point, it is not statistically significant across very many of these variables.

Among peak variables, the peak August SST for the previous calendar year described above was significantly positively associated with the outcome in the individual variable model (beta estimate = 0.489, p = 0.004). Nadir variables created from the minimum March regional SST were negatively associated with the outcome. There were other peak and nadir variables that were associated with the outcome, although most lost significance when included in a multivariate model.

Poisson Regression Analysis of the Multivariate Model

Candidate variables for the multivariate model were identified by the strength of their association with the outcome. Many variables no longer had significantly non-zero parameter estimates when included in the Poisson model simultaneously. Significant associations persisted with the total storm variable lagged at 18 months and the peak Caribbean SST from August of the preceding calendar year (variable 5-16 month lag). The beta parameter estimate for the storms variable was 0.107 (95% confidence interval (CI) [0.003, 0.210], $p = 0.043$) and the beta parameter for the peak August Caribbean SST in the previous calendar year (5-16 month lag) was 0.481 (95% CI [0.154, 0.807], $p = 0.004$). Values of the beta parameters did not change substantially with inclusion of borderline variables in the multivariate model (Table 7).

Beta parameters represent the log of the rate ratio for a single unit increase in the associated variable. Therefore, the rate ratio for an increase in storms at one per month is 1.113 (95% CI [1.03, 1.234]). In other words, an increase in one storm per month was estimated to result in an increase in the monthly CFP calls by 11.3% 18 months later. Similarly, the rate ratio of an increase in SST temperature is 1.612 (95% CI [1.167, 2.243]). An increase in the peak August SST by one degree would result in a 61.2% increase in exclusively coded CFP calls in the lower 48 US states, DC, PR, and USVI the following calendar year.

As climate change progresses according to modeled scenarios, the effect of increases in SST on storm frequency is uncertain. Several possible scenarios are displayed in Table 6, including changes in both storms and SST simultaneously (using the final multivariate model). Percent change in storms is relative to the

baseline of our data, years 2001-2011, during which there was an average of 17.5 storms per year (1.46 per month) and 100.2 CFP calls (8.35 per month) (from Table 4). The final columns display total yearly extra CFP calls (with 95% CI ranges) expected over the 2001-2011 baseline in the hypothetical scenario described. If the maximum SST in the Caribbean increases by 2.5°C as climate models predict, and storm frequency increase by 10%, 238.5 additional calls per year can be expected due to this change (95% CI [49.5, 665.9]). This also assumes that fish consumption, clinical recognition, and other factors that would affect CFP calls in the US (fishing consumption, etc.) remain similar to 2001-2011 levels.

The value of the rate ratio for the increase in storms was relatively stable when other variables were included in the model, including additional storm variables and SST variables that were also significant (values between 1.11-1.15, data not shown). There was slightly more variability in the rate ratio for the selected SST variable with the addition of more variables, but it was still relatively stable (values between 1.24 -1.49, data not shown). Using the final model, restricting ciguatera cases to only those with moderate or severe clinical effects resulted in rate ratios of similar values as the original model, but they were not significantly different from 1 (data not shown). This is likely because the 95% CI expanded as a result of the large reductions in monthly calls, as it only included approximately 35% of the total calls.

Discussion

Summary

Using monthly data and Poisson regression, as hypothesized we found that the frequency of ciguatera-related calls to poison control centers in the continental US is associated with both tropical storm frequency and peak SST in the Caribbean basin. An increase of one storm per month was associated with an increase in CFP calls of 11% (95 CI [0.4, 23]), while an increase in one degree SST was associated with a 62% (95% CI [17, 1242]) increase in calls. These associations were identified by taking into account lag structures, as comparing the current month's CFP calls to the current weather did not show a consistent and significant association. For storms, a lag time of 18 months showed the greatest effect on current CFP call frequencies. For maximum Caribbean SST, this lag time was a slightly more complicated, relating current CFP calls to August SST temperatures of the previous calendar year (5 month lag for January calls and a 16 month lag for December calls).

It is very likely that Caribbean SST will increase 2.5°C or greater during the twenty-first century due to climate change (14, 20, 24, 29). Whether storm frequency will increase or decrease is less certain, although regional storms frequency has been linked to SST. Our model demonstrates that for possible moderate increases in both SST and storms, the effect of SST is likely to dominate, with the effect of storm increases in hypothetical models accounting for a small proportion of the expected increase in CFP calls (Table 6). In these scenarios, our model estimates that two to four hundred calls a year could be attributable to

climate change assuming constant population and fish consumption. This represents a large (two-to four-fold) increase in yearly CFP incidence (using poison center calls as a marker for true incidence). While these estimates are uncertain (based on 95% CI could be as low as 45 and as high as 1500), it implies that the fears of an increase in CFP in the US may be justified and that this increase may be significant from both a clinical and public policy perspective.

Comparison of results to literature

To get a sense of validity of our results it is useful to compare our results to results from the literature. Using the yearly average calls of 100 and US population of 300 million (roughly average for the decade) this implies a yearly incidence of 0.003 per 10,000 residents. This is significantly lower than other reports in the US literature (0.3 in Hawai'i, 5 in Dade County, FL) (10). However, using an expected reporting rate of 1% this may represent a true prevalence of 0.3 per 10,000, which might be a reasonable order of magnitude given that the study area included both high and low CFP incidence areas (25). While estimation of CFP incidence is not very reliable, especially in the United States, the numbers of CFP calls identified in our data are consistent with previous data.

Friedman (2008) reports data from several studies of Caribbean CFP regarding frequency of clinical symptoms(10). Types of symptoms were similar between the Friedman paper and our study, although the percentages of observations with each type of symptom were generally lower in our data. For example, Friedman reports 67-83% having diarrhea (our data: 39%), 30-75%

having abdominal pain (our data: 17%), 45-77% having pruritus (our data: 11%), and 65-100% having weakness (our data: 15%). In general our data had lower percentages for neurologic than gastrointestinal symptoms, which were more balanced in the Friedman data. This may be because our data has more low-severity or unconfirmed cases, and the reports in the literature are more likely to be confirmed and therefore more likely to have more substantial clinical effects.

We observed a strong seasonal trend of CFP, with up to 3 times as many calls in the summer (June, July) than winter months (December, January) (Figure 4). Tosteson (1988) performed an examination of calls to the Puerto Rico poison center and found most cases reported in the spring and summer months also, although 50% of cases were in April during which time fish ingestion is highest in Puerto Rico for religious regions (27). This paper also showed gastrointestinal symptoms as more common than neurologic, although again the percentage of patients with individual symptoms was higher. However, this was a very limited study that lasted only one year in Puerto Rico, while our data are for the entire US which may have less local variability in regard to seasonality.

Available literature provided little guidance on what choice of lag structure for our regression variables was most appropriate. Previous data had selected 13 months or more is an appropriate lag for SST's effect on CFP (13). Our selected 5-16 month lag is not inconsistent with this theory, although more work must be done on this question. Little was available in the literature to suggest lag structures for storms, although since the theoretical process of habitat destruction and re-

colonization is time consuming it makes sense that the most successful lag time for the storm variable (18 months) was longer than that of the SST variable.

Notably, 2005 was a peak year for SST and storms in our data, possibly due to an ENSO/El Nino warming event during the last part of 2004 and early 2005(33). 2005 globally was the hottest year on record (since 1880) to date, and has only been matched by 2010 since (34, 35). While there has been some evidence that Pacific CFP is affected by ENSO events, in our data 2005 did not have a peak in ciguatera calls, although the years after 2005 did experience a rise in ciguatera-related calls (Figures 6, 7, 8) (30).

Limitations

The data used in this study were not collected with this project in mind, and there are limitations with using poison center calls instead of confirmed cases. Poison center calls are coded with the ciguatera substance code if information about ciguatera toxin is discussed, so many times there are several codes for similarly presenting illnesses and the call is to discuss this differential diagnosis. Follow ups to confirm the diagnosis are rare, although ciguatera is always a clinical diagnosis since there are no reliable diagnostic tests or biomarkers for detection in humans.

More importantly, the information about location of the call is limited to what call center took that call, instead of where the person was exposed or where the fish came from. It is common for travelers to present with symptoms upon return from a trip. For this reason, we thought it best to correlate national or regional calls with regional weather instead of making the resolution of these data

finer than is warranted by the method of data collection. We assume broadly that fish causing a ciguatera-associated illness in the continental US are very likely to have come from the Caribbean region and have been exposed to ecological and meteorological conditions in the Caribbean. We also assume that while ciguatoxin can survive freezing and other food preservation methods, fish are consumed around the same time (same year) they are harvested. Lag times are meant to incorporate the ecological lag time between meteorological conditions that increase ciguatoxic dinoflagellate production and the prevalence of ciguatoxic fish higher up the food chain that are harvested.

Ciguatera has been shown to be widely underreported, due to non-specific symptoms that often mimic other gastrointestinal illnesses, common low acuity, and low awareness among providers in the US (25). We therefore view the ciguatera calls to poison centers as a proxy for the true prevalence, and while we expect trends in both calls and true prevalence to be similar it is likely that the number of calls per year grossly underestimates the true prevalence. It is possible changes in clinical awareness of the disease through the decade may have resulted in detection bias, although it is not clear why this would be associated with weather trends (which did not necessarily increase uniformly across the decade). Future projections in CFP do not take into account changes in technology, detection, and clinical and public education and awareness that may affect both the detection of the disease and its true incidence. If CFP does indeed increase in the US as projected, implementation of clinical and public health measures to reduce transmission of the toxin may blunt the expected rise in cases.

We did not control for changes in tourism to endemic areas, and although this is not as likely to be correlated with annual variations in spring as summer SST, it could conceivably be related to storm frequency. However, it is difficult to hypothesize a relationship that would link tourism with the lag structures we observed. Similarly, we did not control for changes in fishing or eating practices that could confound the relationship, although it is likely that significant change in these behaviors would be very local and not necessarily related to regional weather. Changes in SST, storms, or decreased fishing yields might lead to changes in types and ages of fish captured, or cause fishermen to seek out fish in alternate areas previously avoided due to concerns for CFP. This may or may not alter the likelihood of harvesting ciguatera fish. Hopefully controlling for captured fish production captures any systemic effect in these behaviors. An increase in awareness of providers to the effects and presence of ciguatera poisoning during the study period is another potential uncontrolled-for confounder.

With only 10 years of ciguatera call data, we could not estimate the effect of climate change (i.e. a warming, stormier climate) on ciguatera prevalence. Instead, we can only examine the effect of climate variability; i.e., whether there is a correlation between warmer or stormier years and ciguatera prevalence in the US. If there is, this would provide evidence to support the theory that as the regional climate warms and storm frequency increases as is projected by climate models, all other things being equal, ciguatera is likely to increase in range and prevalence in the US.

Selecting variables for the final multivariate model was a difficult process. It was unclear from the beginning how best to capture warming SST data, and while creating many different options for SST measurement and lag structure cast a wide net, it made us more susceptible to type I error in variable selection. Ultimately the variable selected was a relatively intuitive and broad (regional) measure of SST and had a lag structure similar to that presented in the literature. However, due to its lag structure, which relates to the calendar year, we were unable to observe the relationship between lagged months and association we saw for the storm variable (Figure 12). We have higher confidence in the validity of the storm variable we selected since the pattern between lag months and beta parameter significance was as we expected before examining the data: the magnitude and significance of the beta parameter peaked at a particular lag period (in our case, 18 months, not dissimilar to what might be expected from the literature). Even though the magnitude of effect for our SST variable is larger than that for the storms, and therefore is the main driver of projected CFP increase, we must acknowledge greater uncertainty in the validity of the structure and measurement of the SST variable compared to the storm variable.

Finally, the interpretation of our model assumes the chosen independent variables are independent from one another, although we know that SST and storm frequency are likely related to one another, as sea temperatures can drive tropical storm development. It is not likely that SST will actually change without storms or fishing yields changing. The scenario projection results are not necessarily meant to be completely accurate predictions on what will happen as climate change

progresses, since they are based on this relatively simple model. Instead, they are meant to communicate the relative magnitudes of the effects these variables have on CFP calls observed in this study, and estimate the magnitude of the effect of climate change on CFP incidence in the future if this effect acts through SST and severe storm frequency.

Public Health Implications

Increased incidence of CFP in the US would have numerous public health impacts. Burden of disease will increase, resulting in increased utilization of healthcare resources, particularly in emergency departments. In addition, areas that have not experienced high levels of CFP and therefore have low awareness of the condition may begin to see the disease with more frequency. Adaptation measures such as education of health professionals and the public, as well as enhanced surveillance may mitigate these risks. Preventive strategies, such as regulation of fishing industry catches and imports, may prove necessary, although the development of a method for identifying ciguatoxic fish will be essential in developing more effective surveillance, monitoring, and prevention strategies. Further characterization of the temporal and spatial relationships between storms, SST, and CFP may enable the development of a weather-based early warning system for CFP outbreaks that could better target prevention strategies.

Conclusions

While this study somewhat substantiates fears that CFP may increase in the United States due to climate change, more research needs to be done on this subject. It is likely that Caribbean temperatures will increase due to climate change, thereby increasing CFP if other factors in the causal pathway remain stable. However, it remains to be seen how changes in the distribution of suitable habitat for ciguatoxic dinoflagellates (due to SST warming, coral bleaching events, man-made structures, and storm damage) will overlap with US fishing areas to bring CFP to the mainland. More work must be done to identify the proper lag time between weather and SST disturbance and CFP incidence. Additionally, as more data are gathered on CFP, associations between longer climate variability, not just monthly variation, and CFP can be investigated.

While we believe with moderate confidence that our data show a relationship between US CFP and Caribbean SST and tropical storms, we recognize that the structural limitations of these data make this a hypothesis-generating study. The NDPS was sufficient for this study but likely does not accurately represent the epidemiology of the disease in the US. Data on cases with confirmed disease (or ED reports from federal sources from the Research Data Center), perhaps collected first in high-incidence areas, may be better suited to identifying weather-related patterns. Identifying toxic fish and their origin would be very useful in identifying ciguatoxic areas allowing more specific analysis for what weather and climate parameters play a role in CFP.

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TABLES

Table 1: Descriptive statistics of Ciguatera call variables

Variable	All Cases (N = 1,272)	True Cases (N = 1,232)	Lower 48, DC, PR, USVI (N = 1,136)	Lower 48, DC, PR, USVI true cases (N = 1,102)
Male (%)*	600 (48.4)	582 (48.5)	529 (47.9)	515 (48.1)
Median Age (IQR)*	40 (28 - 51)	40 (28 - 51)	40 (28 - 51)	40 (28 - 51)
No. Under 18 (%)	108 (10.3)	103 (10.1)	95 (10.1)	91 (10.0)
No. 0 to 9 (%)	58 (5.1)	54 (4.9)	52 (5.1)	49 (5.0)
No. 10 to 19 (%)	70 (6.2)	67 (6.1)	63 (6.2)	60 (6.1)
No. 20 to 29 (%)	170 (15.0)	165 (15.1)	155 (15.3)	150 (15.3)
No. 30 to 39 (%)	242 (21.4)	233 (21.3)	220 (21.7)	211 (21.5)
No. 40 to 49 (%)	271 (23.9)	263 (24)	241 (23.8)	234 (23.8)
No. 50 to 59 (%)	192 (17.0)	187 (17.1)	167 (16.5)	163 (16.6)
No. 60 to 69 (%)	95 (8.4)	94 (8.6)	87 (8.6)	87 (8.9)
No. 70 to 79 (%)	27 (2.4)	25 (2.3)	22 (2.2)	22 (2.2)
No. 80+ (%)	8 (0.7)	8 (0.7)	7 (0.7)	7 (0.7)
Region*				
Midwest (%)	82 (6.5)	79 (6.4)	82 (7.2)	79 (7.2)
East North Central (%)	59 (4.7)	57 (4.7)	59 (5.2)	57 (5.2)
West North Central (%)	23 (1.8)	22 (1.8)	23 (2.0)	22 (2.0)
Northeast (%)	183 (14.4)	174 (14.2)	183 (16.1)	174 (15.8)
Mid-Atlantic (%)	141 (11.1)	135 (11.0)	141 (12.4)	135 (12.3)
New England (%)	42 (3.3)	39 (3.2)	42 (3.7)	39 (3.5)
Other (%)	49 (3.9)	49 (4.0)	12 (1.1)	12 (1.1)
South (%)	700 (55.3)	685 (55.8)	700 (61.6)	685 (62.2)
East South Central (%)	27 (2.13)	24 (2.0)	27 (2.4)	24 (2.2)
South Atlantic (%)	610 (48.2)	600 (49.0)	610 (53.7)	600 (54.5)
West South Central (%)	63 (5.0)	61 (5.0)	63 (5.6)	61 (5.5)
West (%)	253 (20.0)	240 (19.6)	159 (14.0)	152 (13.8)
Mountain (%)	48 (3.8)	45 (3.7)	48 (4.2)	45 (4.1)
Pacific (%)	205 (16.2)	195 (15.9)	111 (9.8)	107 (9.7)
Call Site				
Health Care Facility (%)	323 (25.4)	312 (25.3)	298 (26.2)	288 (26.1)
Own residence (%)	871 (68.5)	845 (68.6)	776 (68.3)	755 (68.51)
Management site				
Managed on site (non-HCF) (%)	472 (37.1)	462 (37.5)	431 (37.9)	422 (38.3)
Patient in/enroute to HCF (%)	473 (37.2)	460 (37.3)	432 (38.0)	420 (38.1)
Referred by PCC to HCF (%)	259 (20.4)	246 (20.0)	211 (18.6)	202 (18.3)
Route: Ingestion (%)	1,215 (95.5)	1,178 (95.6)	1,076 (94.7)	1,047 (95.0)
Outcome				
Death (%)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Major Effect (%)	28 (2.2)	26 (2.1)	28 (2.5)	26 (2.4)
Minor Effect (%)	288 (22.6)	278 (22.6)	244 (21.5)	237 (21.5)
Moderate Effect (%)	431 (33.9)	419 (34.0)	396 (34.9)	385 (34.9)
No Effect (%)	34 (2.7)	31 (2.5)	31 (2.7)	29 (2.6)
Not followed, nontoxic exposure (%)	11 (0.9)	11 (0.9)	11 (1.0)	11 (1.0)
Not followed, minor effect (%)	262 (20.6)	257 (20.9)	237 (20.9)	232 (21.1)
Unable to follow, potentially toxic (%)	162 (12.7)	159 (12.9)	142 (12.5)	139 (12.6)
Unrelated effect, exposure probably not responsible (%)	55 (4.3)	50 (4.1)	46 (4.1)	42 (3.8)

*Number of missing values: Gender (32), Age (223), Decade (139), State/Region (5)

Table 2a: Frequency of clinical effects for all calls

Clinical Effect	All Cases (N = 1,272)
	No. (%)
Abdominal Pain	215 (16.9)
Ataxia	18 (1.4)
Bradycardia	60 (4.7)
Chest pain (incl. noncardiac)	13 (1)
Coma	1 (0.1)
Confusion	10 (0.8)
Constipation	3 (0.2)
Creatinine increased	1 (0.1)
Dehydration	5 (0.4)
Dermal - Irritation/pain	64 (5)
Diaphoresis	18 (1.4)
Diarrhea	492 (38.7)
Dizziness/vertigo	62 (4.9)
Drowsiness/lethargy	49 (3.9)
Dyspnea	10 (0.8)
Edema	20 (1.6)
Erythema/flushed	19 (1.5)
Headache	109 (8.6)
Hypertension	9 (0.7)
Muscle weakness	195 (15.3)
Nausea	369 (29)
Numbness	284 (22.3)
Pain (not dermal, GI, ocular)	114 (9)
Paralysis	5 (0.4)
Peripheral neuropathy	220 (17.3)
Pruritus	132 (10.4)
Vomiting	408 (32.1)
Hypotension	50 (3.9)
Clinical Effect Missing	118 (9.3)

Table 2b: Frequency of select clinical effects

Clinical Effect	All Cases (N = 1,272)	True Cases (N = 1,232)	Lower 51 Cases (N = 1,124)	Lower 51 true cases (N = 1,090)
	No. (%)	No. (%)	No. (%)	No. (%)
Abdominal Pain	215 (16.9)	212 (17.2)	204 (18.1)	201 (18.4)
Bradycardia	60 (4.7)	59 (4.8)	51 (4.5)	50 (4.6)
Diarrhea	492 (38.7)	483 (39.2)	436 (38.8)	428 (39.3)
Headache	109 (8.6)	101 (8.2)	93 (8.3)	87 (8)
Muscle weakness	195 (15.3)	193 (15.7)	178 (15.8)	176 (16.1)
Nausea	369 (29)	358 (29.1)	334 (29.7)	324 (29.7)
Numbness	284 (22.3)	277 (22.5)	264 (23.5)	257 (23.6)
Pain (not dermal, GI, ocular)	114 (9)	112 (9.1)	103 (9.2)	101 (9.3)
Paralysis	5 (0.4)	5 (0.4)	5 (0.4)	5 (0.5)
Peripheral neuropathy	220 (17.3)	213 (17.3)	210 (18.7)	203 (18.6)
Pruritus	132 (10.4)	130 (10.6)	123 (10.9)	121 (11.1)
Vomiting	408 (32.1)	399 (32.4)	374 (33.3)	366 (33.6)
Hypotension	50 (3.9)	49 (4)	44 (3.9)	43 (3.9)
Clinical Effect Missing	118 (9.3)	115 (9.3)	113 (10.1)	111 (10.2)

Table 3a: Frequency of therapies for all calls

Therapy	All Cases (N = 1,272)	
	No.	(%)
Antibiotics(P)	23	(1.8)
Antiemetics(P)	14	(1.1)
Antihistamines(P)	105	(8.3)
Atropine(R)	13	(1)
Benzodiazepines(P)	7	(0.6)
Bronchodilators(P)	1	(0.1)
Charcoal, single dose	5	(0.4)
Dilute/irrigate/wash(P)	144	(11.3)
Fluids IV	161	(12.7)
Food/snack(P)	29	(2.3)
Hyperbaric oxygen(P)	1	(0.1)
Intubation(P)	2	(0.2)
Other emetic(P)	1	(0.1)
Other(P)	653	(51.3)
Oxygen(P)	4	(0.3)
Sedation (other)(P)	1	(0.1)
Steroids(P)	19	(1.5)
Vasopressors(P)	6	(0.5)
Ventilator(P)	2	(0.2)
Therapy missing	413	(32.5)

Table 3b: Frequency of selected therapies

Therapy	All Cases	True Cases	Lower 51 Cases	Lower 51 true cases
	(N = 1,272)	(N = 1,232)	(N = 1,124)	(N = 1,090)
	No. (%)	No. (%)	No. (%)	No. (%)
Antibiotics(P)	23 (1.8)	21 (1.7)	23 (2)	21 (1.9)
Antihistamines(P)	105 (8.3)	100 (8.1)	100 (8.9)	95 (8.7)
Dilute/irrigate/wash(P)	144 (11.3)	136 (11)	123 (10.9)	117 (10.7)
Fluids IV	161 (12.7)	156 (12.7)	145 (12.9)	140 (12.8)
Intubation(P)	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)
Steroids(P)	19 (1.5)	18 (1.5)	17 (1.5)	16 (1.5)
Therapy Missing	413 (32.5)	394 (32)	343 (30.5)	328 (30.1)

Table 4: Descriptive statistics for regression analysis variables

Variable	Years 2001-2011 Mean (SD), Min - Max												
	January	February	March	April	May	June	July	August	September	October	November	December	All Year
Ciguatera Cases													
Ciguatera cases in Lower 48 states, DC, PR, USVI coded exclusively as ciguatera substance	4.5 (3.1)	6.6 (3.4)	6.5 (3.2)	7.3 (4.4)	9.5 (9.7)	11.0 (3.8)	14.2 (4.6)	15.3 (9.3)	7.0 (2.9)	6.4 (3.1)	7.0 (4.9)	4.9 (3.3)	100.2 (26.3)
0 - 9	4 - 16	3 - 15	3 - 17	1 - 37	6 - 18	8 - 22	3 - 28	3 - 12	2 - 12	1 - 16	1 - 12	61 - 137	
Sea Surface Temperature													
Car Index (1981-2010 climatology)	0.09 (0.16)	0.1 (0.17)	0.14 (0.16)	0.16 (0.15)	0.17 (0.12)	0.15 (0.13)	0.15 (0.14)	0.16 (0.11)	0.18 (0.1)	0.16 (0.12)	0.14 (0.14)	0.1 (0.14)	0.1 (0.1)
-0.2 - 0.3	-0.13 - 0.36	-0.09 - 0.41	-0.03 - 0.41	-0.01 - 0.39	-0.06 - 0.4	-0.08 - 0.38	-0.06 - 0.35	-0.01 - 0.38	-0.05 - 0.41	-0.12 - 0.42	-0.14 - 0.29	-0.2 - 0.4	
Max SST in Caribbean	29.1 (0.4)	29.6 (0.5)	30.1 (0.3)	30.3 (0.3)	30.5 (0.1)	30.1 (0.3)	30.2 (0.2)	30.6 (0.3)	30.3 (0.2)	30 (0.2)	29.6 (0.3)	29.3 (0.3)	30 (0.5)
28.7 - 29.9	29 - 30.3	29.6 - 30.6	29.7 - 30.7	30.4 - 30.6	29.6 - 30.6	29.9 - 30.5	30 - 31.2	30 - 30.6	29.7 - 30.3	29.3 - 30.2	29 - 29.9	28.7 - 31.2	
Min SST in Caribbean	16 (1)	29.6 (0.5)	30.1 (0.3)	30.3 (0.3)	30.5 (0.1)	30.1 (0.3)	30.2 (0.2)	30.6 (0.3)	30.3 (0.2)	30 (0.2)	29.6 (0.3)	29.3 (0.3)	20.7 (3.8)
14.5 - 17.9	13.6 - 17.4	14.9 - 17.7	17.7 - 18.7	18.9 - 20.6	21.1 - 22.8	24.4 - 25.6	25.8 - 26.6	24.8 - 26.7	23.1 - 24.2	20.8 - 22.1	17.5 - 19.7	13.6 - 26.7	
Max Latitude of 25° C SST	26 (1.4)	25.8 (0.8)	25.8 (1)	27.6 (1.9)	31.1 (1.5)	37 (1.3)	39.8 (0.6)	41 (0.5)	40.3 (0.6)	38.4 (0.9)	32.2 (1)	28.9 (2.1)	32.8 (6)
24.5 - 29.5	24.5 - 26.5	24.5 - 27.5	25.5 - 32.5	29.5 - 33.5	34.5 - 38.5	38.5 - 40.5	40.5 - 41.5	39.5 - 41.5	36.5 - 39.5	30.5 - 34.5	26.5 - 32.5	24.5 - 41.5	
Min Latitude of 25° C SST	17.8 (2.8)	14.5 (2.4)	14.4 (3)	14.9 (2.7)	16.7 (4.4)	23 (5.8)	32.5 (5)	38.4 (0.9)	35.8 (1)	30.8 (1.3)	26.6 (0.8)	19.7 (1.6)	23.7 (8.9)
12.5 - 20.5	12.5 - 19.5	12.5 - 21.5	12.5 - 20.5	12.5 - 24.5	13.5 - 28.5	18.5 - 36.5	36.5 - 39.5	33.5 - 36.5	29.5 - 32.5	25.5 - 27.5	18.5 - 23.5	12.5 - 39.5	
Max Latitude of 29° C SST	13.5 (0)	13.5 (0)	13.5 (0.4)	15 (0.7)	16.8 (2.2)	27.4 (2.5)	30 (1.4)	31.6 (2.2)	29.5 (1.4)	24.3 (1.5)	18.9 (2.8)	13.3 (0.4)	21.4 (7.3)
13.5 - 13.5	13.5 - 13.5	12.5 - 14.5	13.5 - 15.5	12.5 - 19.5	23.5 - 29.5	28.5 - 33.5	28.5 - 34.5	25.5 - 30.5	21.5 - 26.5	12.5 - 21.5	12.5 - 13.5	12.5 - 34.5	
Min Latitude of 29° C SST	13.5 (0)	13.5 (0)	12.2 (1.3)	10.5 (0)	10.6 (0.3)	10.5 (0)	10.5 (0)	10.5 (0)	10.5 (0)	10.5 (0)	10.5 (0)	10.5 (0)	11.1 (1.1)
13.5 - 13.5	13.5 - 13.5	10.5 - 13.5	10.5 - 10.5	10.5 - 11.5	10.5 - 10.5	10.5 - 10.5	10.5 - 10.5	10.5 - 10.5	10.5 - 10.5	10.5 - 10.5	10.5 - 10.5	10.5 - 13.5	10.5 - 13.5
Max SST at 24.5° N Latitude	25.7 (0.5)	25.4 (0.4)	25.7 (0.5)	26.3 (0.4)	27.4 (0.4)	29 (0.4)	29.8 (0.3)	30.3 (0.2)	29.9 (0.3)	28.8 (0.3)	27.5 (0.4)	26.4 (0.5)	27.7 (1.8)
24.8 - 26.5	24.9 - 26.4	25 - 26.8	25.8 - 26.9	26.7 - 27.9	28.7 - 30	29.3 - 30.5	29.9 - 30.6	29.4 - 30.3	28.3 - 29.4	26.9 - 28.3	25.6 - 27.1	24.8 - 30.6	
Max SST at 34.5° N Latitude	21.3 (0.5)	20.6 (0.7)	20.5 (0.6)	21.7 (0.8)	23.4 (0.8)	26.3 (0.6)	28 (0.5)	28.3 (0.5)	27.4 (0.3)	25.9 (0.3)	23.9 (0.5)	22.5 (0.5)	24.1 (2.9)
20.4 - 22.1	19.5 - 22	19.1 - 21.1	20.5 - 23.4	22 - 24.4	25.5 - 27.5	27.2 - 28.6	27.4 - 29.1	26.9 - 27.9	25.4 - 26.3	23.2 - 24.8	21.5 - 23.2	19.1 - 29.1	
Min SST at 24.5° N Latitude	21.9 (0.6)	21.2 (0.6)	21.7 (0.8)	23.1 (0.4)	24 (0.5)	25.4 (0.5)	26 (0.5)	26.6 (0.5)	27.1 (0.4)	26.7 (0.3)	25.4 (0.4)	23.4 (0.5)	24.4 (2.1)
21.2 - 23	20.2 - 22.1	20.1 - 22.5	22.3 - 23.7	22.9 - 25	24.1 - 25.8	25 - 26.7	25.9 - 27.4	26.4 - 28.1	26.4 - 27.4	24.8 - 26.1	22.7 - 24	20.1 - 28.1	
Min SST at 34.5° N Latitude	18.5 (0.6)	17.8 (0.7)	17.9 (0.4)	18.4 (0.4)	19.9 (0.6)	22.1 (0.5)	25.1 (0.4)	26.5 (0.3)	25.9 (0.6)	23.7 (0.3)	21.6 (0.5)	19.9 (0.8)	21.4 (3.1)
17.5 - 19.5	16.8 - 18.7	17 - 18.5	17.8 - 18.9	18.9 - 20.7	21.1 - 22.8	24.4 - 25.7	26.2 - 27.2	24.8 - 26.8	23.1 - 24.2	20.8 - 22.2	18.2 - 20.7	16.8 - 27.2	
Severe Storms													
Total storms	0 (0)	0 (0)	0 (0)	0.09 (0.3)	0.36 (0.67)	0.73 (0.79)	2 (1.55)	4.64 (1.91)	5.91 (1.92)	2.64 (2.25)	0.91 (1.22)	0.27 (0.47)	17.5 (5.8)
0 - 0	0 - 0	0 - 0	0 - 1	0 - 2	0 - 2	0 - 5	3 - 8	4 - 9	0 - 7	0 - 4	0 - 1	9 - 31	
Hurricanes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.09 (0.3)	0.73 (1.1)	1.64 (1.12)	3.45 (1.13)	1.36 (1.8)	0.45 (0.69)	0.09 (0.3)	7.8 (3.7)
0 - 0	0 - 0	0 - 0	0 - 0	0 - 0	0 - 1	0 - 3	0 - 4	1 - 5	0 - 5	0 - 2	0 - 1	3 - 16	
Tropical Depressions	0 (0)	0 (0)	0 (0)	0 (0)	0.09 (0.3)	0.09 (0.3)	0.36 (0.67)	0.45 (0.52)	0.73 (0.65)	0.27 (0.47)	0.09 (0.3)	0 (0)	2.1 (1.4)
0 - 0	0 - 0	0 - 0	0 - 0	0 - 0	0 - 1	0 - 2	0 - 1	0 - 2	0 - 1	0 - 1	0 - 1	0 - 0	0 - 5
Tropical Storms	0 (0)	0 (0)	0 (0)	0.09 (0.3)	0.18 (0.4)	0.55 (0.69)	0.91 (0.94)	2.55 (1.13)	1.73 (1.68)	0.82 (0.87)	0.18 (0.4)	0.18 (0.4)	7.6 (2.2)
0 - 0	0 - 0	0 - 0	0 - 1	0 - 1	0 - 2	0 - 3	1 - 5	0 - 4	0 - 4	0 - 1	0 - 1	4 - 11	
Category 3 or greater storms	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.27 (0.65)	1.09 (0.83)	1.73 (0.9)	0.55 (0.82)	0.09 (0.3)	0 (0)	3.7 (1.7)
0 - 0	0 - 0	0 - 0	0 - 0	0 - 0	0 - 0	0 - 2	0 - 2	0 - 3	0 - 3	0 - 2	0 - 1	0 - 0	2 - 7
Total storm-days	0 (0)	0 (0)	0 (0)	0.91 (3.02)	1.82 (4.49)	5.09 (5.49)	14.18 (15.61)	35.45 (15.56)	54.36 (15.47)	16.91 (13.88)	7.64 (10.26)	2 (3.49)	138.4 (46.7)
0 - 0	0 - 0	0 - 0	0 - 10	0 - 15	0 - 15	0 - 49	17 - 66	27 - 81	0 - 43	0 - 34	0 - 9	70 - 245	
Accumulate Cyclone Energy	0.4 (1.4)	0 (0)	0 (0)	0.2 (0.8)	0 (0.2)	1.5 (1.8)	11.5 (19.7)	26.9 (17.8)	66.7 (39.7)	17.7 (15.4)	6.1 (7.8)	1.8 (4)	132.7 (66)
0 - 4.8	0 - 0	0 - 0	0 - 2.6	0 - 0.5	0 - 5.8	0 - 60.4	3.4 - 64.7	11.2 - 155	2.6 - 50.9	0 - 26.7	0 - 13.2	51 - 250	

Table 5: Individual Variable Regression Results

Variable	Wald Chi-Squared Statistic, Months Lag						Beta, months lag					
	0	3	6	12	18	24	0	3	6	12	18	24
Regional SST Variables												
CAR Index	0.05	2.11	1.57	1.5	0.21	0.62	0.101	-0.655	-0.556	0.533	0.191	0.356
Max SST in Caribbean	0.23	0.01	2.86	2.4	1.94	3.06	0.107	0.024	-0.325	0.318	0.245	0.347
Min SST in Caribbean	0	1.51	1.99	1.1	0.87	5.94	-0.002	-0.115	-0.118	0.107	-0.078	-0.253
Warm SST Extent Variables												
Max latitude of 25 degrees	0.17	0.52	1.03	0	0.09	6.13	0.022	-0.034	-0.051	0.009	-0.015	-0.136
Max latitude of 29 degrees	3.24	0.85	0.29	4.1	2.21	0.01	0.067	-0.032	0.023	0.069	0.058	0.004
Min Latitude of 29 degrees	0.06	0.06	0.47	2.1	0.04	0.69	-0.040	-0.028	0.109	-0.224	-0.029	-0.125
Min Latitude of 25 degrees	13.22	11.3	1.46	5.5	3.44	5.9	0.067	0.062	0.025	0.039	0.039	0.042
SST at Parallel Variables												
Max SST at 24.5N	1.84	0.02	1.64	0.9	0.27	0.46	0.222	-0.022	-0.201	0.162	0.087	0.124
Max SST at 34.5N	0.17	0.56	0.95	1.3	0.09	8.03	0.046	-0.076	-0.108	0.130	0.036	-0.336
Min SST at 24.5N	4.21	0.18	0.62	0.2	0.12	2.44	0.251	-0.048	0.093	-0.047	0.040	0.192
Min SST at 34.5N	0.6	2.42	6.97	2.9	7.15	6.86	-0.099	-0.186	-0.291	0.219	-0.310	-0.345
Storm Variables												
Total storms	0.4	0.01	0.58	0.2	4.22	0.67	-0.031	0.006	-0.046	0.019	0.112	-0.042
Hurricanes	1.21	0	0.01	0.6	0.8	0.1	-0.084	-0.001	-0.007	0.057	0.081	-0.024
Total storm-days	0.81	0.59	0.3	0.1	1.01	0.84	-0.005	-0.006	-0.004	0.002	0.007	-0.006
Tropical Depressions	2.08	1.27	2.27	0.3	0.62	3.04	-0.227	0.205	-0.321	-0.075	0.132	-0.252
Tropical Storms	1.52	0.12	0.07	0	2.34	0.05	0.094	-0.035	-0.027	0.003	0.159	0.020
Category 3 or greater storms	0.13	0.65	0.06	0.5	1.72	0.1	-0.044	-0.132	-0.040	0.084	0.195	0.040
ACE	0.29	1.54	0.17	0.2	0.01	0.33	-0.002	-0.007	0.002	0.002	0.000	-0.002

Table 6: Rate Ratios and excess CFP calls expected for hypothetical scenarios compared to 2001-2011 baselin

Hypothetical Scenario	Rate Ratio Estimate	Standard Error	Confidence Limits	Rate Ratio	Pr > ChiSq	Extra CFP calls	Extra CFP Confidence Limits	
Increase in 1 storm per month	1.11	0.06	1.00	1.23	0.043	11.3	0.4	23.4
Increase in 1 degree for one month	1.62	0.27	1.17	2.24	0.004	61.9	16.7	124.5
Increase in 1 degree for one month and 1 storm per month	1.80	0.31	1.28	2.53	0.001	80.1	28.3	153.0
Increase in storm frequency 10%	1.02	0.01	1.00	1.03	0.043	1.6	0.1	3.1
Increase in storm frequency 25%	1.04	0.02	1.00	1.08	0.043	4.0	0.1	8.0
Increase in max August SST 2.5°C	3.33	1.39	1.47	7.53	0.004	233.3	47.2	654.4
Increase in max August SST 3.5°C	5.38	3.14	1.72	16.89	0.004	439.3	71.8	1592.0
Increase in max August SST 2.5°C and increase storm frequency 10%	3.38	1.41	1.49	7.65	0.003	238.5	49.5	665.9
Increase in max August SST 3.5°C and increase storm frequency 10%	5.60	3.26	1.79	17.55	0.003	460.7	78.7	1658.0
Increase in storm frequency 10%	0.98	0.01	0.97	1.00	0.043	-1.5	-3.0	-0.1
Increase in storm frequency 25%	0.96	0.02	0.93	1.00	0.043	-3.8	-7.4	-0.1
Increase in max August SST 2.5°C and decrease storm frequency 10%	3.28	1.37	1.45	7.42	0.004	228.2	44.8	643.3
Increase in max August SST 3.5°C and decrease storm frequency 25%	5.18	3.03	1.65	16.27	0.005	418.7	64.9	1530.5

Table 7: Sensitivity of beta estimates to multivariate model selection

Dependent Variables Included in Model	Total Storms, 12 months lag			August Max SST, last year (5-16 month lag)		
	Beta estimate	Wald 95 % CI Lower	Upper	Beta estimate	Wald 95 % CI Lower	Upper
Final Model: Total storms (12 month lag) last year August Max SST, month dummies	0.107	0.003	0.210	0.481	0.154	0.808
Final Model plus Min SST at 34.5N (12 month lag)	0.108	0.009	0.208	0.677	0.343	1.011
Final Model plus Min latitude of 25 degrees (12 month lag)	0.102	-0.002	0.205	0.383	0.013	0.753
Final Model plus March Min latitude of 25 degrees last year (10-21 month lag)	0.110	0.005	0.214	0.396	-0.065	0.856
Final Model plus Last March Min latitude of 25 degrees (1-12 month lag)	0.116	0.014	0.217	0.392	0.056	0.727
Final Model plus Max latitude of 29 degrees (12 month lag)	0.138	0.024	0.251	0.433	0.090	0.777
Final Model plus Min SST at 34.5N (12 month lag), Min latitude of 25 degrees (12 month lag)	0.103	0.004	0.203	0.579	0.205	0.953

FIGURES

Figure 1: Ciguatera fish poisoning distribution

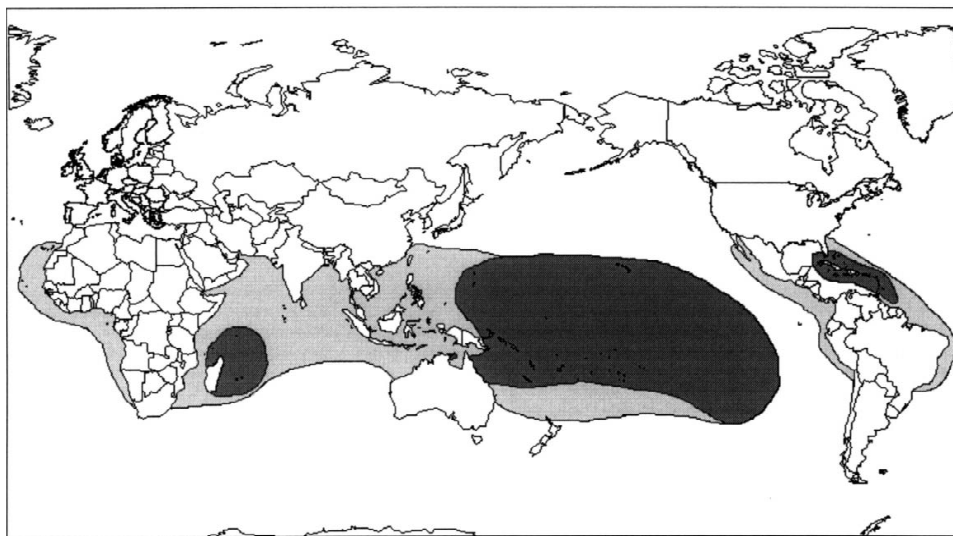


Figure 1: Global distribution of ciguatera, with areas of high-to-moderate risk (heavy shading) and low or uncertain risk (lighter shading) identified (15).

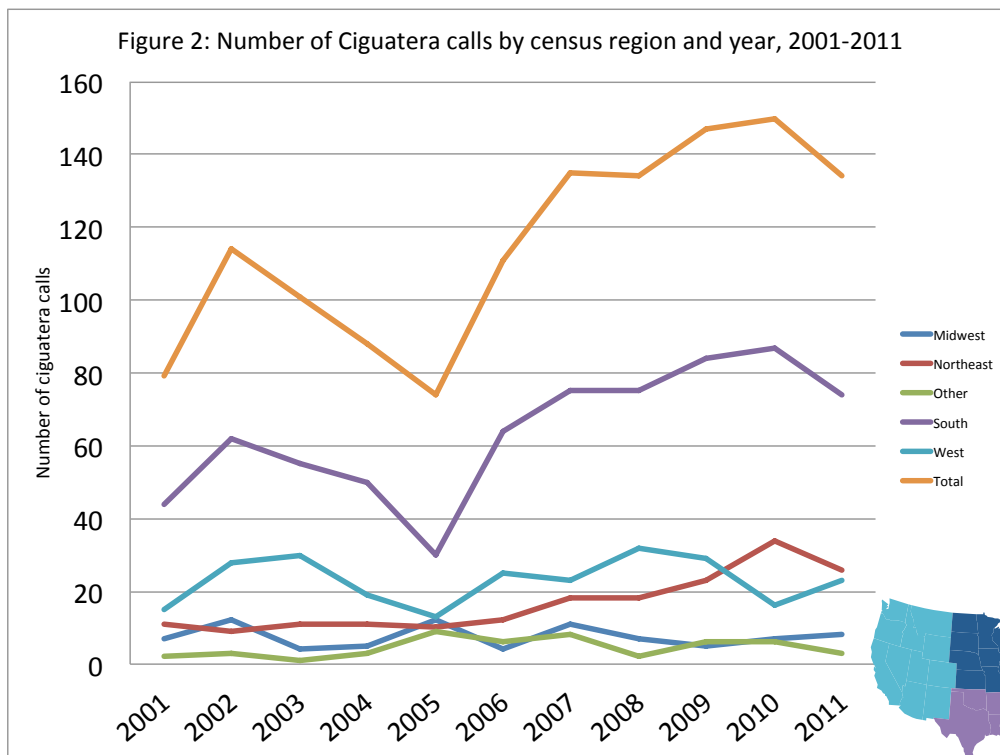


Figure 3: Number and percent of calls by age group, 2001-2011

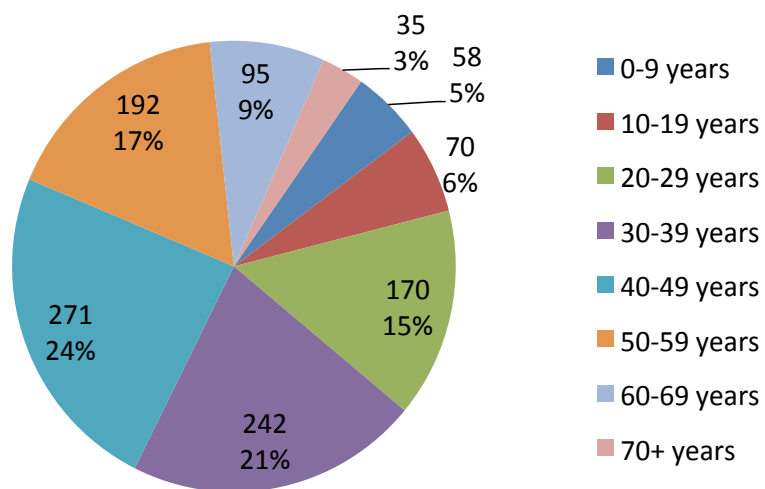
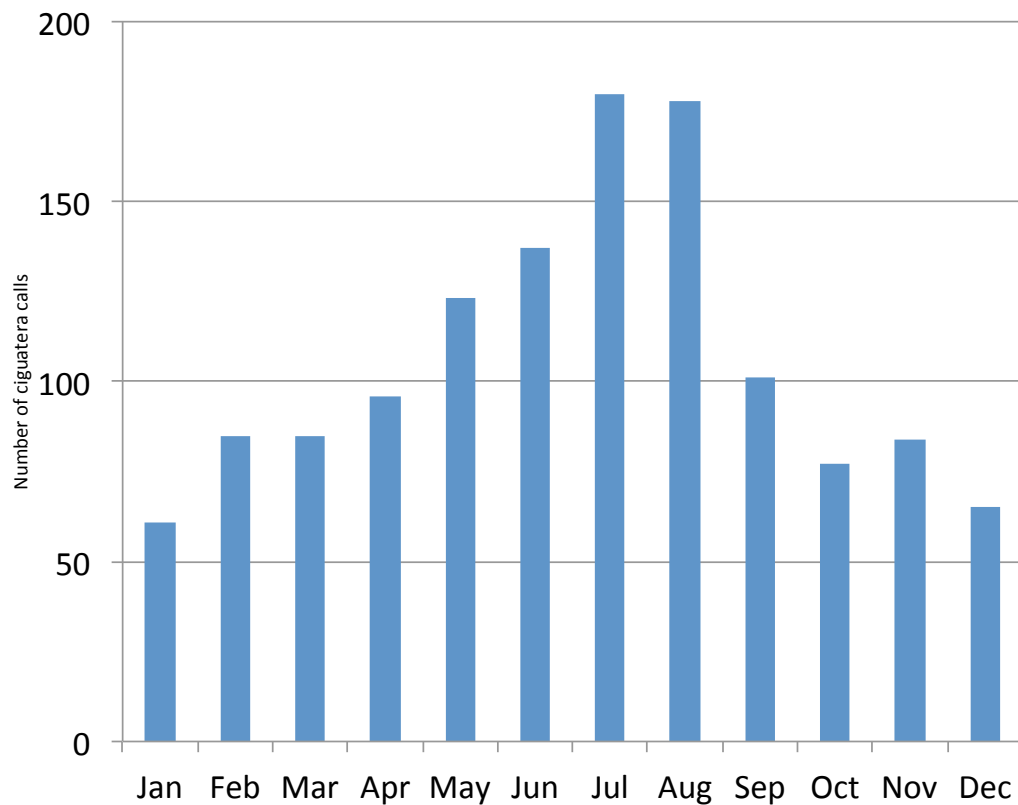
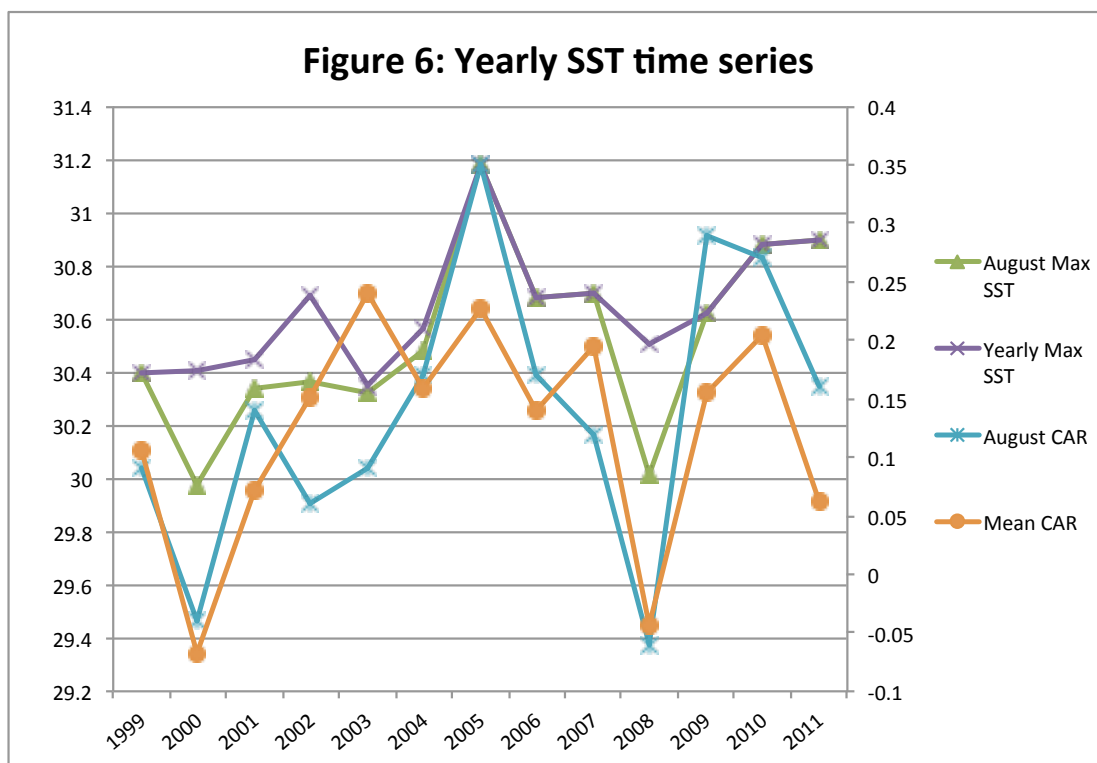
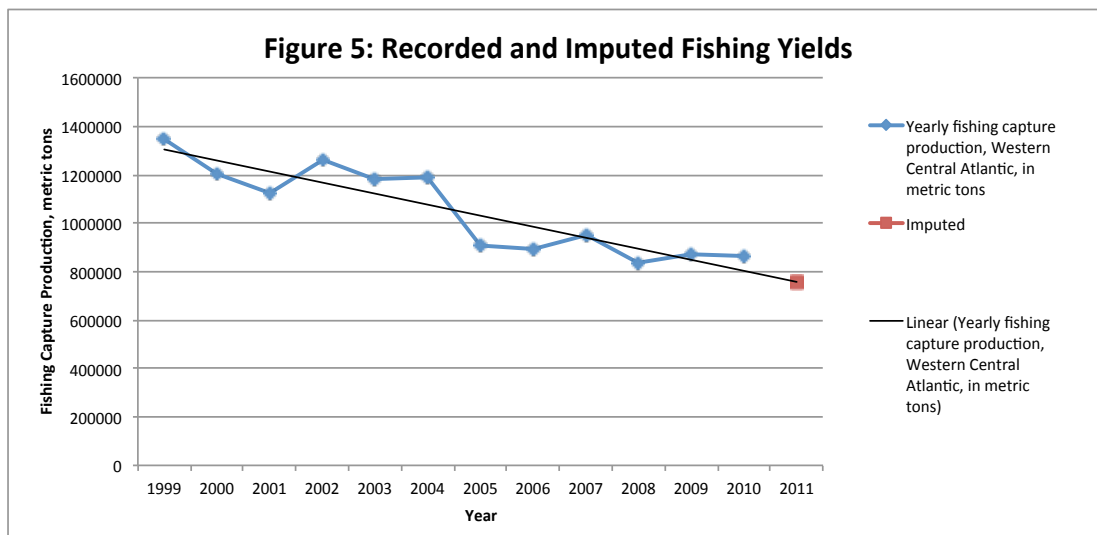
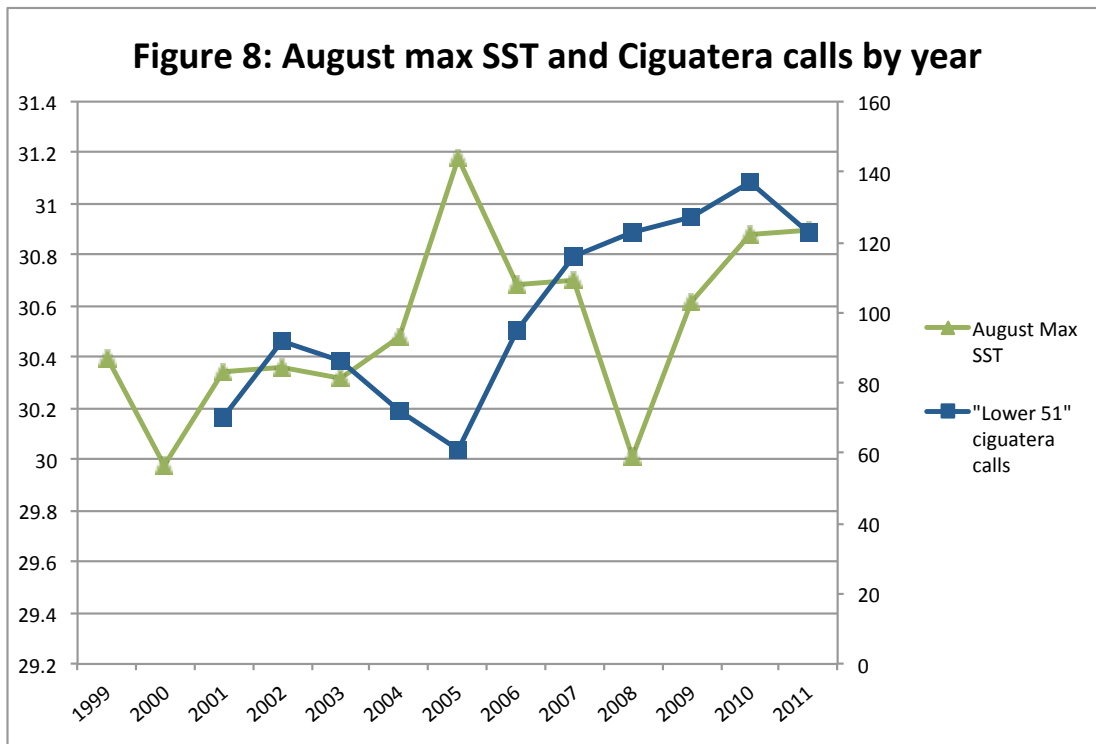
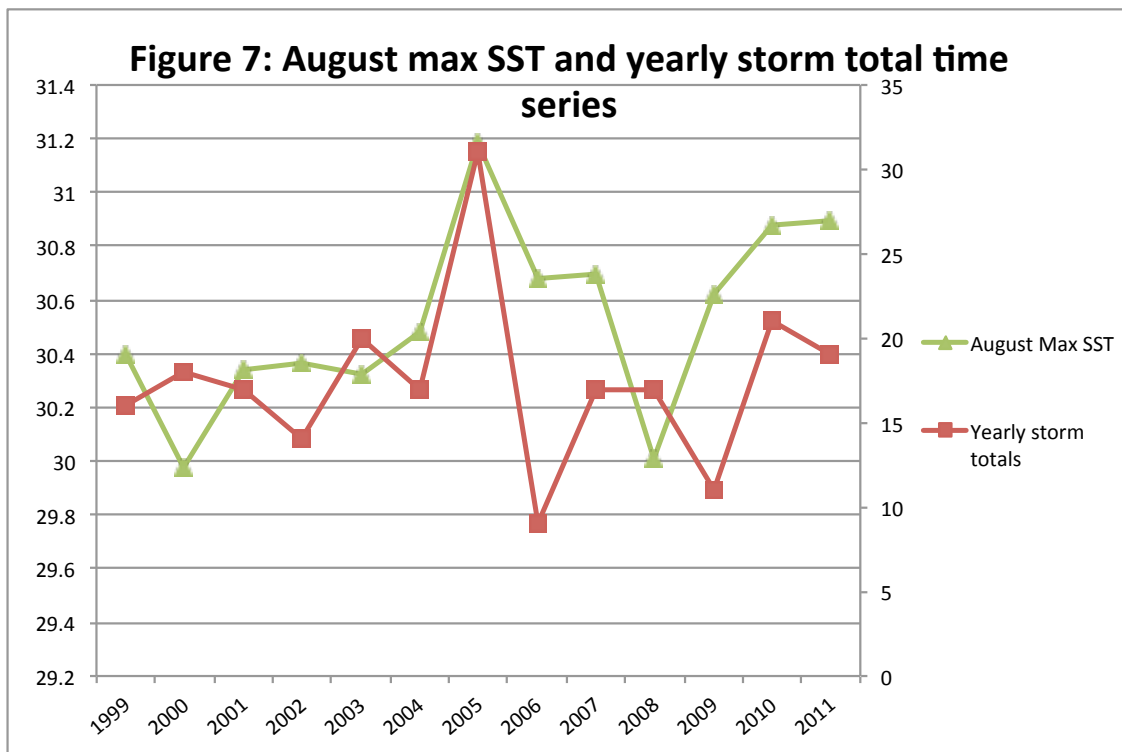
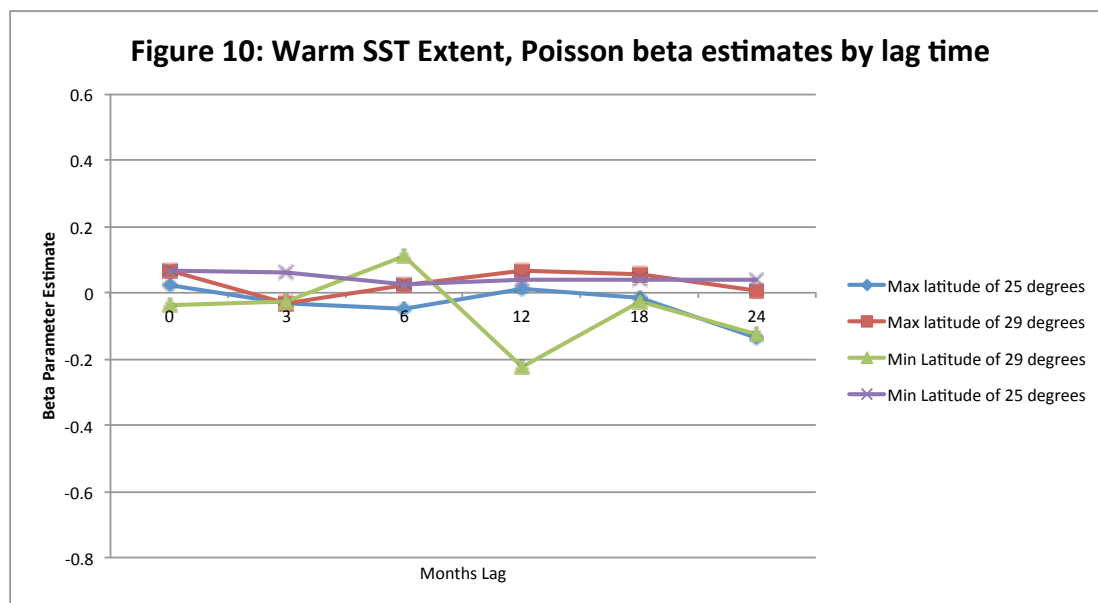
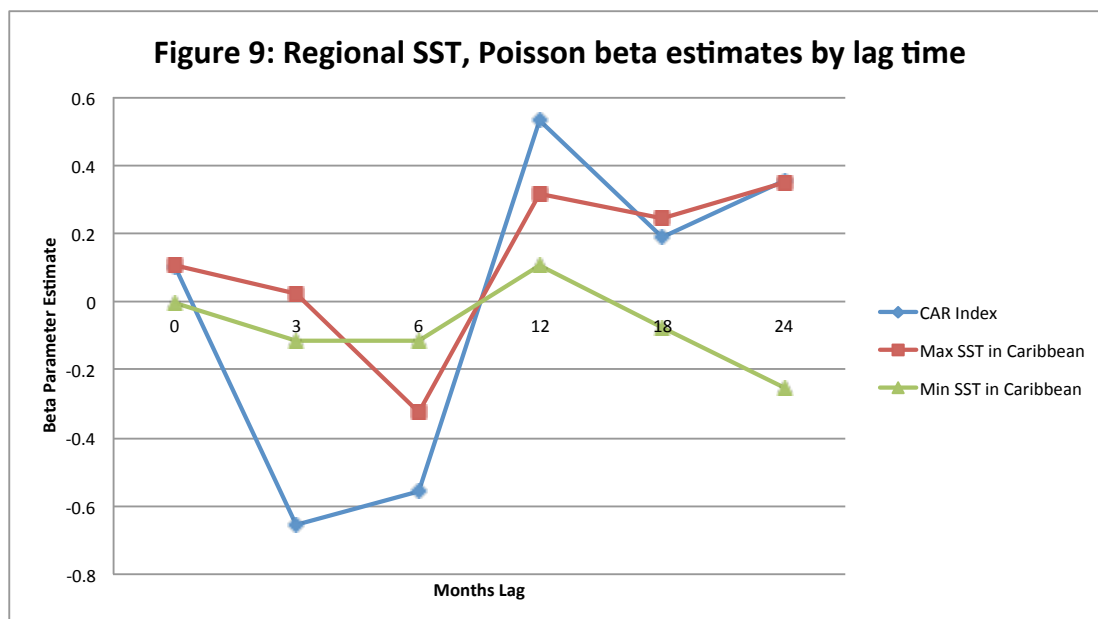


Figure 4: Total number of calls by month, 2001-2011









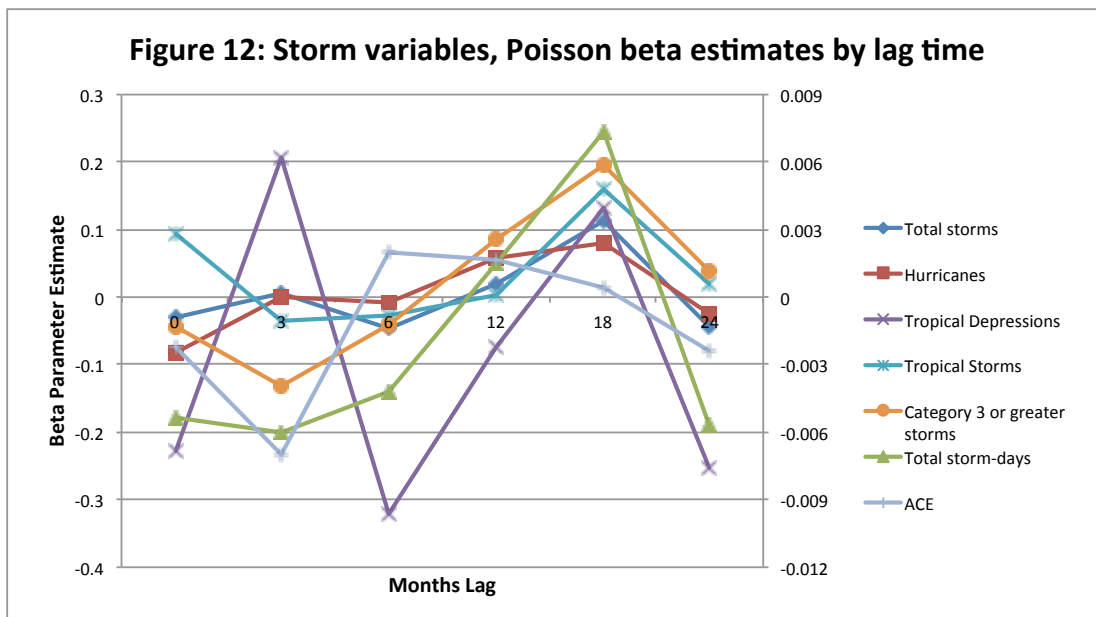
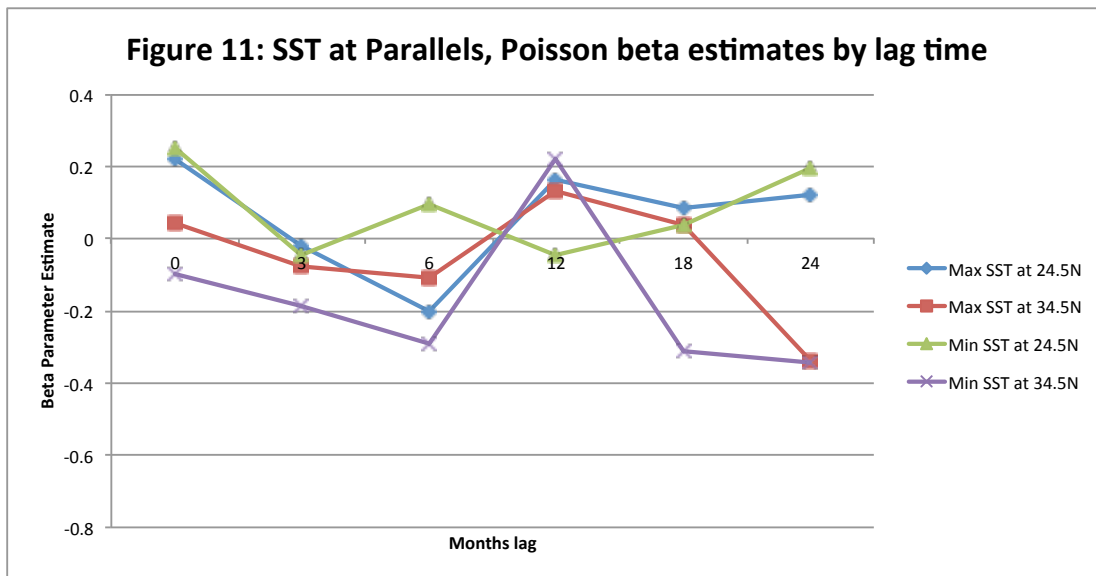
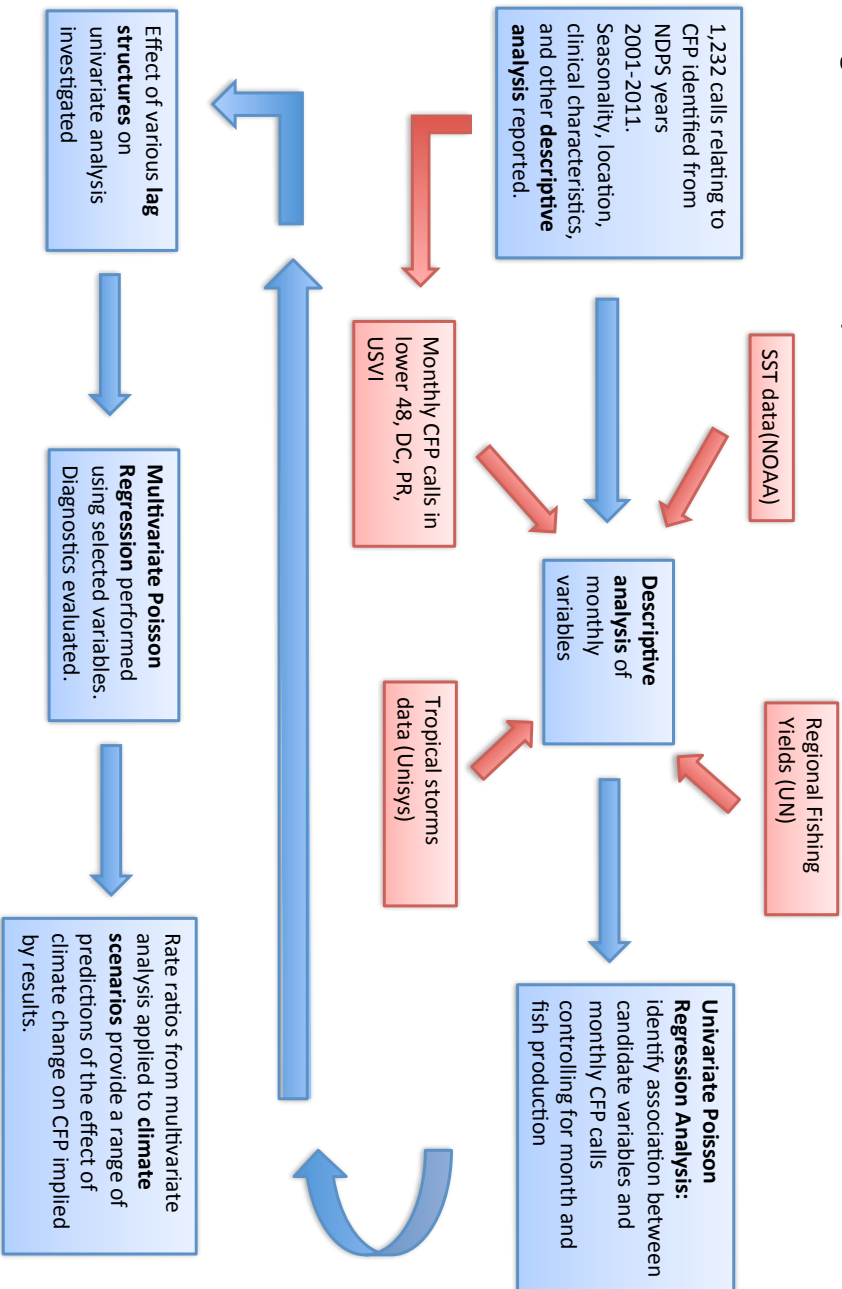


Figure 13: Data analysis Flowchart



Chapter III

Summary

Ciguatera fish poisoning is a potent neurotoxin that causes gastrointestinal upset and neurologic symptoms such as paresthesias and is an important public health problem in the Caribbean basin (10). Warm sea surface temperatures have been shown to play a role in the growth of the plankton that produce the toxin (11, 17). Additionally, damage to coral reefs by tropical storms may also provide additional habitat suitable for the plankton (11, 15, 19). Climate change is expected to increase SST 2.5°C – 3.5°C in the Atlantic basin over the coming century (14, 20, 24, 29). While predictions of storm frequency are more uncertain, storm severity is also likely to increase (3, 4). It has been suspected that as warmer SSTs push northward along the Atlantic coast, the incidence of CFP in the United States will increase (14, 20, 29).

The purpose of this hypothesis-generating study is to determine if CFP incidence is associated with periods of warmer SST in the Caribbean over the last decade to inform predictions of the effect of climate change on CFP. In addition, this study provides an opportunity to investigate the epidemiology of CFP in the United States and evaluate the suitability of the National Poison Data System (NPDS) for use in surveillance of CFP and other toxicological exposures.

Calls to US poison centers regarding CFP were gathered for years 2001-2011. Descriptive analysis of these calls was performed. In addition, Poisson regression analysis was used to evaluate whether the number of calls was associated with

Caribbean SST and tropical storm frequency, using regional fishing yields as an offset. Several lag structure were tried as the lag time between increased SSTs or storms and an increase in CFP incidence is unknown (13, 15).

We found a total of 1,272 calls over the 10-year period, with an average of 100.2 calls per year (range 74-152). There was a strong seasonal pattern as expected, as CFP is more common in the summer months when the water is warmer. Most (55%) calls originated in the South census region. The most common GI symptom reported was diarrhea (38.7%) while the most common neurological symptom was numbness (22.3%).

Regression analysis showed an independent association between CFP calls and warmer SST and tropical storm frequency. The optimal lag period for SST was variable, between 5 and 16 months; the variable selected links current monthly CFP calls to the peak August SST of the previous calendar year. The optimal lag period for storms was 18 months. Rate ratios were calculated from the beta coefficients of the multiple variable Poisson regression. The rate ratio for an increase in storms at one per month is 1.113 (95% CI [1.03, 1.234]), and the rate ratio of an increase in SST temperature is 1.612 (95% CI [1.167, 2.243]).

These estimates imply that if the maximum temperature in the Caribbean increases by 2.5°C as climate models predict, and storm frequency increase by 10% from 2001-2011 levels, approximately 239 additional calls per year can be expected due to this change (95% CI [49.5, 665.9]) all other things remaining equal.

Public Health Implications

Climate change is likely to increase SST in higher latitudes, expanding the range of acceptable habitat for *Gambierdiscus* northward along the Atlantic coast of the US (17, 20). Quantification of the association of CFP with climatic variables combined with climate projections could provide predictions regarding future CFP prevalence and range in the US. Our data are not conclusive but support the hypothesis that CFP in the US is related to SST in the Caribbean basin. As the climate warms, CFP may be among the diseases increases in both incidence and range, and expands outside its traditional endemic areas.

Increased incidence of CFP in the US would have numerous public health impacts. Burden of disease will increase, resulting in increased utilization of healthcare resources, particularly in emergency departments. In addition, areas that have not experienced high levels of CFP and therefore have low awareness of the condition may begin to see the disease with more frequency. Indeed, an MMWR from CDC recently reported several CFP outbreaks in New York City in 2010-2011 (36). This may lead to increased misdiagnosis and missed opportunities for prevention. Adaptation measures such as education of health professionals and the public, as well as enhanced surveillance may mitigate these risks. If certain fish are implicated in the disease, more regulation of the sale of at-risk fish may be necessary (barracuda are no longer able to be sold to eat in the US due to the high risk of CFP). Education of commercial fisherman and fish distributors about CFP and increased effort at avoiding potentially toxic fishing areas may be necessary.

In addition, higher levels of prevention strategies may be necessary, including regulation of fishing industry catches and fishing imports. The lack of an effective bioassay makes surveillance of ciguatoxic fish difficult. More work in developing a method for identifying ciguatoxic fish will be essential in developing more effective surveillance, monitoring, and prevention strategies. Studies focused on high-incidence areas that are able to follow fish from capture to consumption may be able to more specifically identify ciguatoxic areas and characterize the creation and persistence of these areas, assisting fishermen in avoiding ciguatoxic fish. Characterizing the temporal and spatial relationships between storms, SST, and CFP may enable the development of a weather-based early warning system for CFP outbreaks that could better target prevention strategies.

We hope that these results will play a small part to inform the scientific and lay community about the increasing body of evidence regarding the public health impacts of unmitigated climate change. There is strong evidence the anthropomorphic alteration of our planet's climate will have significant impact on public health in the US and across the globe. This study adds to the growing list of conditions likely to be exacerbated by climate change, and augmenting the projections of these health effects should provide policy makers additional incentive to put into place mitigation policies aimed at decreasing carbon and other greenhouse gas emissions to combat climate change.

POSSIBLE FUTURE DIRECTIONS

Additional research in numerous areas would further inform this research question. Simply having more years available for poison center calls would increase the power of the study and may help with avoiding type I errors. More years of CFP call data may also allow correlation with longer-term climactic indicators, which could test the hypotheses generated by this study. A different surveillance system that would be better able to identify confirmed ciguatera cases, or information regarding the origin of CFP-causing fish would address two main limitations of our dataset and provide more reliable results. A prospective, active survey may be able to better characterize the epidemiology of CFP and provide a less biased estimation of true CFP prevalence.

Better CFP identification and surveillance would be facilitated by the development of a cheap and reliable assay for ciguatoxin, either recognizing the presence in fish specimens or in human patients. Such assays have not yet been produced but would assist clinicians in accurately identifying patients suffering from CFP and also regulators or public health workers trying to identify contaminated food products in order to prevent the disease.

Other methods of linking SST or storms to CFP could be attempted. Perhaps more local approaches, such as attempting to link SST warming events, high frequency (or intensity) storm events, or coral bleaching events to CFP outbreaks or clusters, would be helpful in investigating the mechanism (and lag structure) of this association. This approach, however, may be less useful in predicting regional

effects of climate change on CFP incidence. A similar analysis based on a larger database of CFP cases, like ED visits captured in data from the federal Research Data Center, might be able to corroborate our results.

Basic science investigation on the presence of toxic dinoflagellates on man-made ocean structures is needed to characterize the effect of these structures on toxic dinoflagellate prevalence and incidence.

Lastly, more specific and confident projections in climate research would better inform projections of the effect of warming SST or changes in storm frequency. Currently prediction of tropical storms is not very precise and it is unknown how climate change will affect tropical storm creation either on a regional or a global level. Improvements in modeling and mechanism of cyclone formation are key to understanding how storms will play a role in our changing climate.

APPENDIX A: IRB EXEMPTION**EMORY**
UNIVERSITY

Institutional Review Board

DATE: August 8, 2012

RE: Determination: No IRB Review Required
eIRB00059983 Title: *Ciguatera fish poisoning and climate change: analysis of cross-sectional national Poison Control data in the United States 2001-2011*
PI: Daniel Gingold, MD/MPH candidate

Dear Mr. Gingold:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will conduct a secondary data analysis of a dataset from the National Poison Data System maintained by the American Association of Poison Control Centers (AAPCC). The purpose of this study is to identify what climactic variables impact ciguatera poisoning in the United States, where few epidemiologic studies of this disease have been performed. Results from this study may inform policy makers in attempts to implement adaptation measures, such as additional education of health professionals and enhanced surveillance, and provide additional information that will be helpful in projecting the potential public health impacts of unmitigated climate change.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Carol Corkran, MPH, CIP
Senior Research Protocol Analyst
This letter has been digitally signed