Dengue: 30 years of cases in an endemic area

Daniela Cristina Sensato Monteiro [iD],[I] **Natália Vasconcelos de Souza** [iD],[I] **Jane Cavalcante Amaral** [iD],[II] **Kaynan Bezerra de Lima** [iD],[II] **Fernanda Montenegro Carvalho de Araújo** [iD],[III] **Izabel Letícia Cavalcante Ramalho** [iD],[III] **Victor Emanuel Pessoa Martins** [iD],[IV] **Jeová Keny Baima Colares** [iD],[II] **Luciano Pamplona de Góes Cavalcanti** [iD],[V] **Danielle Malta Lima** [iD],[I,II,*]

[I] Programa de Pos Graduacao em Biotecnologia, Universidade Estadual do Ceara, Universidade de Fortaleza, Fortaleza, CE, BR. [II] Universidade de Fortaleza, Fortaleza, CE, BR. [III] Laboratorio Central de Saude Publica do Ceara, Fortaleza, CE, BR. [IV] Universidade de Integracao Internacional da Lusofonia Afro Brazileira (UNILAB), Redencao, CE, BR. [V] Departamento de Saude Comunitaria, Universidade Federal do Ceara, Fortaleza, CE, BR.

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*Corresponding author. E-mail: danimalta.pq@gmail.com

The present study aimed to review literature on studies of dengue cases conducted over 30 years in the state of Ceará.

Between November 2015 and January 2016, articles published in Portuguese and English in 7 databases were searched using keywords and a Boolean operator. A total of 191 articles were identified in the databases; 133 were excluded according to the exclusion criteria, and 58 were included in the study.

Of the 58 articles analyzed, 6 reported data from Brazil; including the Northeast region and the state of Ceará; 41 reported data for only the city of Fortaleza; 7 reported data for the state of Ceará; 4 reported data for cities in the interior of the state; and 3 included only children. The studies adopted different approaches and focused on different aspects of the disease. Study outcomes included the identification of serological, epidemiological, clinical, and laboratory characteristics; potential larvicides and biological predators of mosquitoes; potential antiviral agents; vector density characteristics; and educational dengue prevention and control strategies. Additionally, one vaccine trial was included.

Although studies on dengue in the state of Ceará are scarce, they are encompassing, including several lines of research, and the number of studies and reports on dengue in the state of Ceará continues to increase.

KEYWORDS: Dengue; *Aedes Aegypti*; *Aedes Albopictus*; Virus.

■ INTRODUCTION

The first dengue epidemic in Brazil is believed to have occurred between 1846 and 1853 in the cities of São Paulo and Rio de Janeiro (RJ) (1,2). At that time, the disease was known by other names, such as polka (a fashionable dance at the time), polka fever, and break-bone fever (3). However, dengue cases were first reported in medical literature in 1916 in the city of São Paulo and in 1923 in Niterói (1,2). The first epidemic documented from a clinical and laboratory viewpoint occurred in late 1981 and early 1982 in Boa Vista, Roraima; this epidemic was caused by the dengue-1 (DENV-1) and dengue-4 (DENV-4) serotypes (4). In 1955, Brazil succeeded in eradicating *Aedes aegypti* (*A. aegypti*), eliminating the last mosquito source on the 2nd of April in a rural area in the municipality of Santa Terezinha, Bahia (5).

The first cases of *A. aegypti* reinfestation following eradication occurred in 1967 in Belém (Pará) and in 1968 in São Luiz (Maranhão); the source populations were finally eliminated in 1973. *A. aegypti* was again detected in 1976 in Salvador (Bahia) and in 1977 in RJ and then spread to other states (6,7). In 1986, a dengue epidemic (DENV-1 serotype) circulated in the state of RJ and quickly reached Northeast Brazil (7,8). From 1986 to 1990, dengue epidemics were limited to some Brazilian states in the Southeast (RJ, São Paulo and Minas Gerais) and Northeast regions (Alagoas, Bahia, Ceará and Pernambuco) (9).

A. aegypti was reintroduced in the Ceará cities of Aquiraz, Beberibe and Fortaleza in the mid-1980s (10). The first dengue cases occurred in August 1986, originating from tourists from RJ, where a dengue epidemic (DENV-1) was occurring, who were visiting the cities of Fortaleza and Canoa Quebrada (11).

For the dengue cases reported in the state of Ceará over 30 years, seven epidemics were recorded (1987, 1994, 2001, 2008, 2011, 2012 and 2015) (12,13). Ceará has 184 municipalities, 167 of which reported DENV transmission in 2015. From 1986 until 2016, 302,015 dengue cases were reported in the state (14). Dengue has therefore been endemic to Ceará for 30 years, resulting in high incidence rates caused by four circulating serotypes. The present study aimed to review literature on studies involving dengue cases in the state of Ceará conducted during these 30 years.

■ METHODOLOGY

Between November 2015 and January 2016, articles in the Portal of CAPES Journals, Biblioteca virtual em saúde (BVS), Ebsco Host, Scientific Electronic Library Online (SciELO), PubMed, Science Direct *and Google Scholar* databases were searched. Scientific reports about dengue in Ceará from 1986 until 2016 were identified. The search was performed in both Portuguese and English using the Boolean operator "and" and the following keywords: "Dengue and Ceará", "Dengue and Fortaleza", "Dengue virus and Ceará", "Dengue virus and Fortaleza", "Dengue virus Ceará" and "Dengue virus Fortaleza". To organize the information contained in the scientific articles identified with the descriptors, the articles were fully read, and the objectives, study type, location, period, methods, importance and results were identified. Published scientific reports such as letters, original articles and brief communications to national and international journals were included in the search according to the descriptors and peer reviewed. After preanalysis, scientific literature identified in more than one database that was accounted for as a single work, congress abstracts, theses, dissertations and articles that included no data for the state of Ceará were excluded. A total of 191 articles were identified in the databases; 133 articles were excluded according to the exclusion criteria, and 58 articles were included in the study (Figure 1).
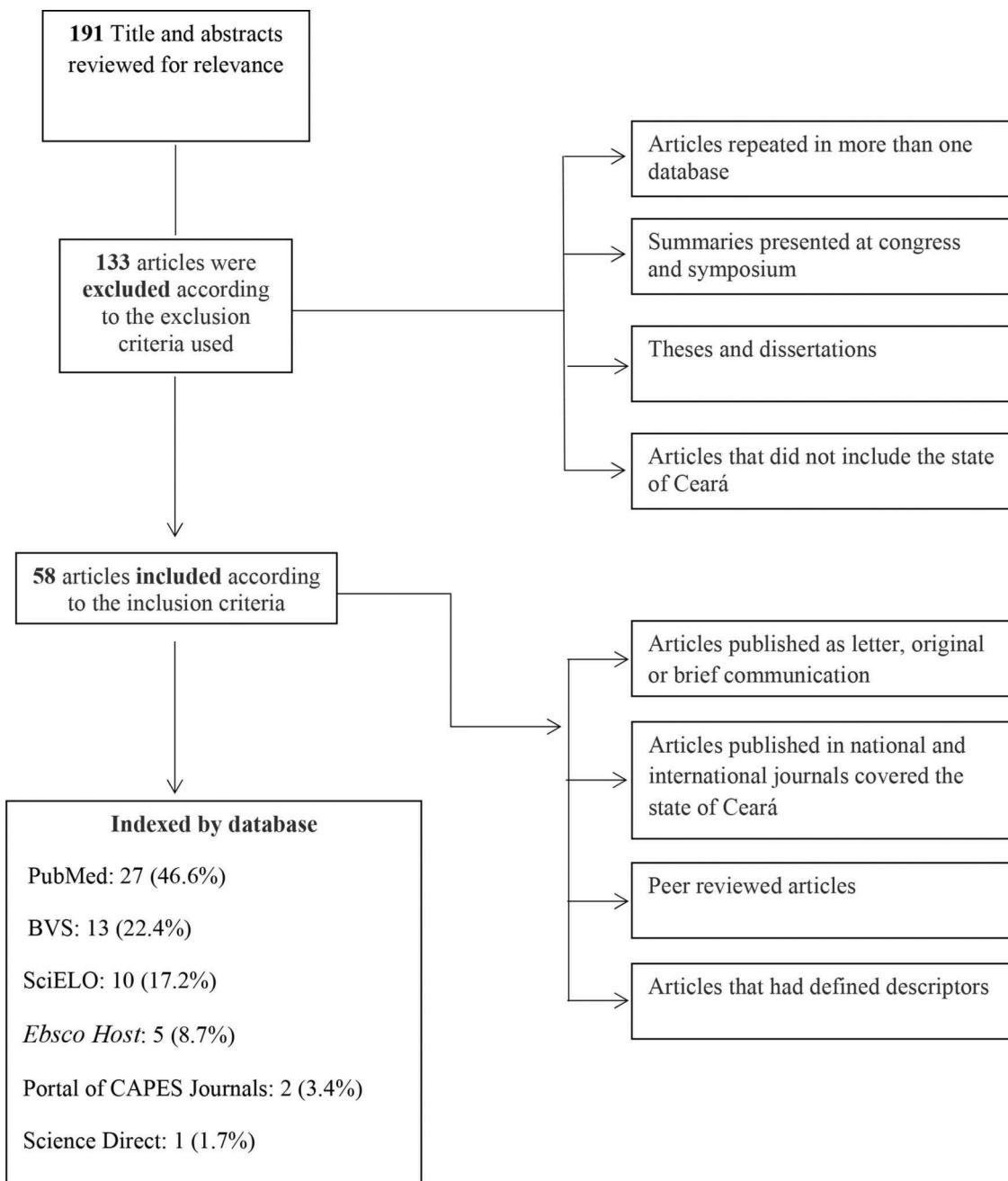

191 Title and abstracts reviewed for relevance

133 articles were **excluded** according to the exclusion criteria used

- Articles repeated in more than one database
- Summaries presented at congress and symposium
- Theses and dissertations
- Articles that did not include the state of Ceará

58 articles **included** according to the inclusion criteria

- Articles published as letter, original or brief communication
- Articles published in national and international journals covered the state of Ceará
- Peer reviewed articles
- Articles that had defined descriptors

Indexed by database

PubMed: 27 (46.6%)

BVS: 13 (22.4%)

SciELO: 10 (17.2%)

Ebsco Host: 5 (8.7%)

Portal of CAPES Journals: 2 (3.4%)

Science Direct: 1 (1.7%)

Figure 1 - Flow chart - Selection of articles. Notes: Biblioteca virtual em saúde (BVS).

Table 1 - Main characteristics of the stratified studies with clinical and laboratory characteristics.

Date	Study Design	Objective	Main Results	Reference
			Clinical and laboratory characteristics of the studies	
1995	Descriptive	To evaluate the cases of hemorrhagic dengue fever in the city of Fortaleza in 1994.	Of the 27,033 confirmed cases in the state and 19,306 in Fortaleza, 178 were suspected to be hemorrhagic dengue, which was confirmed in 26 patients, 11 of which had shock.	20
1998	Descriptive	To conduct a seroepidemiological survey to evaluate the prevalence of dengue after the dengue epidemic (1994) in Fortaleza, Ceará.	A total of 1,341 serum samples were evaluated, and of these, 44% were dengue positive and 56% were dengue negative.	21
1998	Retrospective	To detect the presence of the dengue virus before the 1994 epidemic.	Serological diagnosis was confirmed in 24.4% of the participants by detecting anti-IgM antibodies and confirming dengue infections in Fortaleza in November 1993, six months before the epidemic.	22
2006	Descriptive	To report a case of DENV-2 and DENV-3 coinfection.	The first case of simultaneous infection by DENV-2 and DENV-3 in Brazil was documented.	23
2009	Descriptive	To report a case of aplastic anemia induced by dengue virus infection.	Dengue can induce aplastic anemia by directly invading the bone marrow. This rare complication must be identified early. Immunosuppressive therapy may induce complete remission.	24
2010	Descriptive	To report cases of optic neuritis after dengue virus infection.	Two cases of bilateral neuritis after dengue virus infection were described.	25
2011	Retrospective	To analyze the main pain-related complaints in patients with dengue.	Of the 94.8% patients who presented with at least one pain complaint, patients diagnosed with DHF (40.1%) had more painful symptoms than those diagnosed with CD, and the main complaints were headache (79.9%) followed by myalgia (78.6%).	26
2011	Descriptive	To detect cases of hantavirus in patients with clinical suspicion of dengue.	One patient was IgM-positive for hantavirus and two were IgG-positive for hantavirus. Therefore, it is important to improve epidemiological surveillance for hantavirus in the state of Ceará.	27
2012	Retrospective	To correlate laboratory tests during the progression of dengue fever with symptoms to predict the severity of the disease.	In patients with CD, thrombocytopenia and elevated transaminase levels were observed; in those with DHF, the thrombocytopenia and elevated transaminase levels were similar to those in patients with SD, while the hemoconcentration was not. The results can be used as markers for more severe forms of the disease.	28
2012	Descriptive	To determine the frequency of CNS infection by the dengue virus in individuals with fatal outcomes.	Clinical manifestations and positive laboratory results in CSF may indicate the presence of DENV and lead to the consideration of CNS invasion in fatal cases.	29
2012	Retrospective	To evaluate the prevalence of dengue in patients with suspected viral meningitis.	Dengue should be suspected in patients in endemic areas with neurological manifestations, and appropriate treatment should be adopted to avoid fatality.	30
2012	Descriptive	To report a fatal case of coinfection with severe dengue and melioidosis.	Melioidosis should be considered among differential diagnoses in endemic disease areas.	31
2013	Retrospective	To report myocarditis due to dengue, which is rarely diagnosed.	Myocarditis caused by DENV occurred in four confirmed cases. Therefore, there is a need to assess cardiac function in all patients with acute dengue who may benefit from therapy to prevent death from heart disease.	32
2013	Retrospective	To describe the clinical spectrum of dengue in children and adolescents.	The main signs and symptoms of dengue are fever, abdominal pain, and vomiting. A unique clinical profile, including gastrointestinal symptoms and hepatic involvement, was obvious.	15
2014	Descriptive	To report the first case of dengue fever in an indigenous child who died.	With positive immunohistochemical results, the case was confirmed as severe dengue. Doctors should consider dengue as a diagnostic hypothesis among the indigenous populations in Brazil.	17
2014	Retrospective	To evaluate the new WHO 2009 classification of dengue.	The revised classification for detecting severe clinical manifestations has allowed better detection in patients with SD and can thus reduce fatalities.	33
2015	Descriptive	To investigate the hypothesis that some specific comorbidities increase the likelihood of DF progressing to DHF in adults.	The progression to DHF was associated with hypertension and skin allergy. Therefore, these patients should remain in healthcare facilities to monitor progression.	34
2015	Descriptive	To describe clinical manifestations and renal involvement in cases of dengue in renal transplant patients.	Of the renal transplant recipients, 10 were diagnosed with dengue, 5 were hospitalized, 4 developed DHF, and none died.	35

Table 1 - Continued.

| | | | Clinical and laboratory characteristics of the studies | |
Date	Study Design	Objective	Main Results	Reference
2015	Descriptive	To diagnose possible cases of leptospirosis in dengue-negative patients in samples from 2008, 2010, and 2012.	Patients with suspected dengue and those negative for dengue were tested for leptospirosis; 10.8% (2008), 19.2% (2010), and 30.8% (2012) were confirmed to have leptospirosis. The authors estimate that 20% of dengue cases may actually be cases of leptospirosis in endemic disease areas.	36
2015	Descriptive	To identify acute febrile episodes to describe the density of incidence, efficacy, and seroprevalence.	This study captured and monitored patients with dengue who were selected to participate in a phase III dengue vaccine trial. Of 235 children with acute febrile episodes, 50 (21.3%) were considered likely to have dengue, and 18 (7.7%) had virologically confirmed dengue.	16
2015	Descriptive	To analyze cases of severe dengue in the early postoperative period of renal transplantation.	After performing renal transplantation, two severe cases of dengue were reported. The authors report the importance of screening for dengue before transplantation in endemic disease areas.	37
2015	Descriptive	To investigate leptospirosis in patients with clinical suspicion of dengue.	Of the patients analyzed, 48 (55.8%) were positive for dengue in at least one of the tests, and 5 (7.35%) were positive for leptospirosis.	38
2016	Retrospective	To report the detection of undeclared dengue deaths.	Ninety dengue deaths were detected that were not suspected during disease progression. The authors suggest the need to improve primary health care to identify cases of fatal dengue and thus prevent death.	39

Notes: DENV: dengue virus, CD: classic dengue fever, SD: severe dengue, DHF: dengue hemorrhagic fever, CSF: cerebrospinal fluid, CNS: central nervous system, IgM: immunoglobulin M, IgG: immunoglobulin G; WHO: World Health Organization.

RESULTS AND DISCUSSION

Of the 7 databases analyzed, only Google Scholar did not contain articles related to the descriptors of the present work.

Of the 58 reports analyzed, 6 (10.3%) reported data from Brazil, including the Northeast region and the state of Ceará; 41 (70.6%) reported data for only the city of Fortaleza; seven (12%) reported data for the state of Ceará; and four (6.8%) reported data for cities in the interior of the state (one in Icaraí (Caucaia); one in Juazeiro do Norte, Crato and Barbalha; one in Tauá and one in Pacoti) (Tables 1 and 2). Of the reports analyzed, 39 (67.2%) included only adults, 16 (27.5%) included children and adults, and 3 (5.2%) included only children (15-17).

Epidemiological aspects

A literature study about dengue and the control of *A. aegypti* in Ceará, based on epidemiological bulletins, found that five dengue epidemics, with high incidence rates, occurred in Ceará between 1986 and 2011, and children were most affected from 2008 to 2010. Annually, during the studied period, an average of 120 municipalities reported infestation with *A. aegypti,* and 84 reported dengue transmission (18).

In 2014, the city of Fortaleza was a World Cup host city, and a study was performed to investigate the potential for a dengue epidemic in the 12 World Cup host cities (19). Real-time seasonal climate forecasts were performed based on several international sources, and epidemiological predictions for dengue in Brazil were analyzed. The results showed reduced risks of dengue in the cities of Brasília, Cuiabá, Porto Alegre and São Paulo. Some cities were considered to have moderate risk (Belo Horizonte, Salvador and Manaus), and some cities, such as Recife, Natal and Fortaleza, located in Northeast Brazil, were considered to have high risk (19).

Clinical and laboratory aspects

For the period analyzed (1986-2016), we selected manuscripts that described the clinical and laboratory aspects of the disease in Ceará (Table 1).

Larvicides and biological predators/antiviral drugs/vectors

Larvicides and biological predators are used as methods to fight the spread of mosquitoes. In the present review, following stratification of the 58 selected reports, 13 (22.4%) were found to address the use of larvicides and biological predators against *A. aegypti* (40-52) (Table 2). Other studies examined the vectors *A. aegypti* and *Aedes albopictus* (*A. albopictus)* (53-58) or investigated antiviral drugs against dengue (59,60). The main findings of these studies are listed below (Table 2).

Educational actions

After stratification, two reports about educational actions were found. The first was performed in Icaraí (Caucaia) and concerned dengue prevention and control actions, evaluating the limitations and difficulties found. The seventeen individuals who participated in the study were distributed into three groups: eight were users of a Basic Health Unit, four were endemic disease control agents, and five were health care professionals. Data were collected by participant observation and professional/user interactions that occurred throughout the study. The study concluded that actions that

Table 2 - Main results of published studies on biological predators, larvicides, antiviral drugs and vectors.

Study Design	References	Fish Species	Objective	Main Results
		Biological Predators, Larvicides, Antiviral Drugs, and Vectors		
Experimental	40	Betta splendens (B. splendens), Poecilia reticulata	To evaluate the oviposition behavior of A. aegypti in containers containing B. splendens and P. reticulata.	B. splendens was better at controlling Aedes mosquitoes than P. reticulata and can be used to prevent A. aegypti females from depositing eggs in water containers.
Experimental	41	B. splendens	To estimate the survival of B. splendens in domestic containers and their efficacy in controlling premature stages of A. aegypti compared to the larvicide Bacillus thuringiensis israelensis (Bti).	B. splendens may be suitable for the biological control of A. aegypti in large domestic water containers, but measures should be taken to ensure prolonged survival and the presence of fish in the containers.
Experimental	42	B. splendens, Poecilia sphenops, Trichogaster trichopterus, and Astyanax fasciatus	To evaluate the competence of fish on the predation of A. aegypti larvae under laboratory conditions.	Females and males of T. trichopterus and A. fasciatus and females of B. splendens and P. sphenops were the most competent fish for A. aegypti larvae predation.
Experimental	43	B. splendens	To evaluate the use of larvivorous fish in cement tanks as a form of biological control for A. aegypti larvae.	B. splendens showed potential for biological control in cement tanks, reducing the infestation by 320-fold in this type of container.
Experimental	44	B. splendens, T. trichopterus, and P. reticulata	To evaluate the survival of predator fish larvae in water with larvicides used to control Aedes.	B. splendens presented the lowest mortality rate, and the combined use of predatory and larvicidal fish in large water tanks is feasible.
		Native Plants As Larvicides		
		Plant Species Used		
Experimental	45	Constituents of the natural liquids of the cashew nutshell: anacardic acid, cardol, and cardanol	To evaluate the antioxidant and larvicidal actions of the components anacardic acid, cardanol, and cardol.	The three components were shown to be promising agents to control A. aegypti and function as antioxidants, acetylcholinesterase inhibitors, and A. aegypti larvicides.
Experimental	46	Cashew nut shell: sodium anacardate	To evaluate the insecticidal activity of sodium anacardate isolated from cashew nut shell liquid against the eggs and pupae of A. aegypti.	Sodium anacardate presented toxicity against A. aegypti eggs, larvae, and pupae and may be a viable, low-cost alternative to control Aedes.
		Essential Oils		
		Type of Oil		
Experimental	47	Alpinia zerumbet, Citrus limonia, Citrus sinensis, S. jambolana, Ocimum americanum, Ocimum gratissimum, Hyptis suaveolens	To evaluate the larvicidal activity of nine plants found in Northeast Brazil against A. Aegypti larvae.	O. americanum and O. gratissimum have LC_{50} values of 67 ppm and 60 ppm, respectively, and the authors suggest a beneficial use of these essential oils for controlling A. aegypti.
Experimental	48	Capraria biflora	To evaluate the larvicidal activity of C. biflora against A. aegypti.	C. biflora oil contains 14 essential oil constituents and shows good larvicidal activity against A. aegypti.
Experimental	49	Leaves of Hyptis martiusii Benth	To evaluate the insecticidal activity of the chemical components of the volatile oils of H. martiusii Benth.	Twenty-six compounds, representing 93.2% of the leaf essential oils, were characterized, and the leaf essential oil and 1,8-cineole showed an insecticidal effect against A. aegypti larvae.
Experimental	50	Seed extract of Myracrodruon urundeuva	To isolate m-pentadecadienyl-phenol from M. urundeuva seeds and test its activity in three life stages of A. aegypti to elucidate its mode of insecticidal action.	m-Pentadecadienyl-phenol was shown to be a potent larvicide, with inhibitory activity on pupae and in the egg incubation phase.
		Chemicals		
		Organophosphate		
Experimental	51	Temephos	To evaluate the susceptibility of A. aegypti eggs and larvae to the organophosphate temephos.	Resistance to temephos was observed, demonstrating that populations of A. aegypti are under strong temephos selection pressure, compromising efficacy.

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Table 2 - Continued.

		Biological Predators, Larvicides, Antiviral Drugs, and Vectors		
Study Design	**References**	**Fish Species**	**Objective**	**Main Results**
Experimental	52	Temephos and the pyrethroid cypermethrin	To describe resistance to temephos and the pyrethroid cypermethrin in three populations and to use biochemical and molecular assays to characterize resistance mechanisms.	Two populations of A. aegypti were under strong temephos selection pressure, compromising the efficacy of this organophosphate, and resistance to cypermethrin was observed in two of the three populations studied.
		Vector/Mosquito		
		Mosquito		
Experimental	53	A. albopictus	To publish the first record of A. albopictus in an urban area in the city of Fortaleza, state of Ceará.	Thirteen specimens of A. albopictus were identified (all female), and their introduction into Fortaleza was favored by the migration of people from other regions.
Descriptive	54	A. aegypti and A. albopictus	To identify the areas of occurrence, breeding sites, and associations with A. aegypti and other Culicidae.	The absence of one of the species at the breeding sites increased infestation by the other species, and breeding sites not infested by A. albopictus had twice the prevalence of A. aegypti.
Experimental	55	A. aegypti	To evaluate the daily survival probability of A. aegypti.	Survival analyses indicated that the mortality of A. aegypti varied with the age of the mosquitoes and with the local environment.
Experimental	56	A. aegypti	To estimate the variability of the survival rate of A. aegypti and determine how the climate is related to this variation.	The mortality of mosquitoes varies with age as well as with environmental and meteorological conditions. The climate in Fortaleza may impact the mortality of older mosquitoes that are potentially better pathogen vectors.
Experimental	57	A. aegypti and A. albopictus	To analyze the probability of vertical dengue virus transmission in A. aegypti and A. albopictus mosquitoes in the city of Fortaleza.	The vertical transmission of dengue virus in populations of A. aegypti and A. albopictus was found to be significant in the urban area of Fortaleza.
Experimental	58	A. aegypti and A. albopictus	To compare the incidence of dengue fever in relation to the rainfall in the city of Fortaleza since 1986.	The proportion of houses infested with mosquito vectors correlated inversely with the intensity of antimosquito interventions, and the vector population developed independently of rainfall.
		Plant Species Used	**Antiviral Drugs**	
Experimental	59	Spondias tuberosa and Spondias mombin	To evaluate new antiviral agents for controlling dengue virus. Spondias spp. extracts against DENV-2 were evaluated in C6/36 cells in vitro.	The main phenolic components rutin and quercetin showed substantial potential against dengue virus.
Experimental	60	Seeds of Dimorphandra gardneriana, Adenanthera pavonina and Caesalpinia ferrea.	To verify whether D. gardneriana, A. pavonina, and C. ferrea can be used as phytotherapy for dengue.	This was the first study to evaluate the antioxidant and antiviral effects of sulphated galactomannans against DENV-2. The results are promising and suggest that they act early during viral infection.

Notes: LC_{50}: lethal concentration 50; DENV-2: dengue virus 2.

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strengthened the power and responsibility of individuals over their own history and their local citizenship were needed (61). The second report was a case study involving six blocks, with each block corresponding to 40 houses in Fortaleza. The aim of the study was to evaluate the implementation of an intervention strategy to decrease the amount of *A. aegypti*. Fortaleza is divided into six administrative regions (SERs), and in this study, one block in each of the six SERs was selected to understand the ecological, biological, and social complexity and diversity in Fortaleza. The results showed a complex interaction between socio-environmental inequalities and dengue control. The ethnographic data and interviews of those in the studied SERs reflected the environmental and socioeconomic complexity of a large city in a developing country such as Brazil, which has struggled with the serious public health problem of dengue (62).

Two reports concerning risk factors associated with dengue were included. One case-control study analyzed low-income housing development on the coast of Fortaleza with the aim of increasing the efficacy of control measures against dengue during a dengue outbreak. A total of 211 households were investigated using a questionnaire to collect socioeconomic, behavioral, and environmental risk data for cases and controls. Cases were defined according to the national guidelines for the control of dengue based on the detection of dengue IgM antibodies; 34 cases and 34 controls were investigated. An analysis of the epidemic in a low-income housing development showed the presence of several known risk factors because human behavioral components are difficult to manipulate. However, other factors, such as the frequency of visits by vector control agents, could be solved by making simple changes within municipal services (63).

Another study evaluated the implementation of an intervention strategy to decrease the amount of *A. aegypti* in 2012 and 2013. Participants were divided into 10 intervention groups and 10 control groups, and activities such as workshops, cleaning campaigns, and student and older inhabitant mobilization were conducted. Differences in social participation, commitment and leadership were observed between the groups, and a higher efficacy was observed in the intervention group than in the control group. Social participation and environmental management are viable and promising alternatives to vector measures for dengue vector control (64).

■ CONCLUSION

Dengue remains a serious public health problem and constitutes a threat to the Brazilian population. The tropical climate of Brazil favors the proliferation of dengue and the four serotypes (DENV-1 to DENV-4) that circulate in Brazil. Vector control is still the most effective means of protection against the spread of the disease but remains ineffective against the numerous epidemics occurring every year in Brazilian cities. Serological diagnostic tests also need to be improved because cross-reactions with other arboviruses often occur.

From the present review, we conclude that although studies on dengue in the state of Ceará are scarce, they are encompassing, including several lines of research, and the number of studies and reports on dengue in the state of Ceará continues to increase.

■ AUTHOR CONTRIBUTIONS

Monteiro DCS contributed to the study design, data collection, analyzed and interpreted data. Cavalcanti LPG and Colares JKB assisted with the design of the study survey, data interpretation and manuscript reviews. Araújo FMC assisted with data interpretation, and manuscript writing and review. Martins VEP and Ramalho ILC reviewed the manuscript. Souza NV, Amaral JC and Lima KB participated in the conceptualization of the study, data collection and manuscript reviews. Lima DM conceived the study, participated in the study design, coordination, and reviewed the manuscript. All authors read and approved the final version of the manuscript.

■ REFERENCES

1. Teixeira MG, Barreto ML, Guerra Z. Epidemiologia e medidas de prevenção do dengue. Inf Epidemiol SUS. 1999;8(4):5-33. Apud Meire R. "Urucubaca" Gripe ou Dengue? In: Clínica Médica. Gráfica O Estado de São Paulo. 1916;273-85. https://doi.org/10.5123/S0104-16731999000400002
2. Barreto ML, Teixeira MG. Dengue no Brasil: situação epidemiológica e contribuições para uma agenda de pesquisa. Estudos Avançados. 2008;22(64):53-72. Apud Pedro A. O dengue em Nictheroy. Bras Med. 1923;1:173-7. https://doi.org/10.1136/bmj.1.3239.173
3. Henchal EA, Putnak JR. The dengue viruses. Clin Microbiol Rev. 1990; 3(4):376-96. Apud Sabin AB. Dengue, In T. Rivers and F. Horsfall (ed.). 1959. Viral and rickettsial infections of man. J. B. Lippincott Co. Philadelphia. p361-73. https://doi.org/10.1128/CMR.3.4.376
4. Osanai CH, Travassos da Rosa AP, Tang AT, do Amaral RS, Passos AD, Tauil PL. [Dengue outbreak in Boa Vista, Roraima. Preliminary report]. Rev lnst Med Trop Sao Paulo. 1983;25(1):53-4.
5. Braga IA, Vale D. Aedes aegypti: histórico do controle no Brasil. Epidemiol Serv Saúde. 2007;16(2):113-8. Apud Franco O. Reinfestação do Pará por Aedes aegypti. Rev Bras Malariol Doenças Trop. 1969;21(4):729-31. https://doi.org/10.5123/S1679-49742007000200006
6. Tauil PL. [Critical aspects of yellow fever control in Brazil]. Rev Saude Publica. 2010;44(3):555-8. Apud Franco O. Reinfestação do Pará por Aedes aegypti. Rev Bras Malariol Doenças Trop. 1969;21(4):729-31. https://doi.org/10.1590/S0034-89102010005000014
7. Nogueira RM, Schatzmayr HG, Miagostovich MP, Farias MF, Farias Filho JD. Virological study of a dengue type 1 epidemic at Rio de Janeiro. Mem Inst Oswaldo Cruz. 1988;83(2):219-25. https://doi.org/10.1590/S0074-02761988000200012
8. Pontes RJ, Ruffino-Netto A. [Dengue in a urban locality of southeastern Brazil: epidemiological aspects]. Rev Saude Publica. 1994;28(3):218-27. https://doi.org/10.1590/S0034-89101994000300010
9. Fundação Nacional de Saúde. Evolução temporal das doenças de notificação compulsória no Brasil 1980-1998. Boletim Epidemiológico Edição Especial. Brasília. 1999; Available from: http://bvsms.saude.gov.br/bvs/periodicos/boletim_epi_edicao_especial.pdf.
10. Lima JT. Risco de reurbanização de febre amarela no Brasil. Cad Saude Publica. 1985;1(3):377-84. https://doi.org/10.1590/S0102-311X1985000300010
11. Vilar MC, Rouquayrol MZ, Timbo MJ, Gomes IL. Epidemia de dengue no Ceará 1986-1988. Rev Bras Prom Saude. 1989;5(1):60-5.
12. Secretaria da Saúde do Estado do Ceará. Boletim epidemiológico dengue, chikungunya e zika. Coordenadoria de Promoção e Proteção à Saúde Núcleo de Vigilância Epidemiológica. [cited December 8th, 2017]. Available from: https://www.saude.ce.gov.br/wp-content/uploads/sites/9/2018/06/boletim_arboviroses_se48_08_12_2017.pdf.
13. Cavalcanti LPG, Barreto FKA, Oliveira RMAB, Canuto IFP, Lima AAB, Lima JWO, et al. Trinta anos de dengue no Ceará: história, contribuições para ciência e desafios no cenário atual com tripla circulação de arbovírus. J Health Biol Sci. 2018;6(1):65-82. https://doi.org/10.12662/2317-3076jhbs.v6i1.1415.p65-82.2018
14. Secretaria Municipal de Saúde (SMS). Prefeitura de Fortaleza. Boletim Semanal da Dengue. Célula de Vigilância Epidemiológica. Ano de 2017. 36° Semana Epidemiológica. [Internet] [cited January 25th, 2019]. Available from: https://saude.fortaleza.ce.gov.br/images/Boletins/Dengue/2017/36_Boletim-dengue--Boletim-Epidemiolgico-36_2017.pdf.

15. Pires Neto Rda J, de Sá SL, Pinho SC, Pucci FH, Teofilo CR, Evangelista PD, et al. Dengue infection in children and adolescents: clinical profile in a reference hospital in northeast Brazil. Rev Soc Bras Med Trop. 2013; 46(6):765-8. https://doi.org/10.1590/0037-8682-1716-2013

16. Dayan G, Arredondo JL, Carrasquilla G, Deseda CC, Dietze R, Luz K, et al. Prospective cohort study with active surveillance for fever in four dengue endemic countries in Latin America. Am J Trop Med Hyg. 2015; 93(1):18-23. https://doi.org/10.4269/ajtmh.13-0663

17. Sacramento RH, de Melo Braga DN, Sacramento FF, de Carvalho Araújo FM, Lima AA, de Lima Pompeu MM, et al. Death by dengue fever in a Brazilian child: a case report. BMC Res Notes. 2014;7:855. https://doi.org/10.1186/1756-0500-7-855

18. Lima EP, Goulart MO, Albuquerque MR, Victor FM, Pinto NB. Série histórica da dengue e do Aedes aegypti no Ceará. Rev Bras Prom Saude. 2013;26(3):340-8. https://doi.org/10.5020/18061230.2013.p340

19. Lowe R, Barcellos C, Coelho CA, Bailey TC, Coelho GE, Graham R, et al. Dengue outlook for the World Cup in Brazil: an early warning model framework driven by real-time seasonal climate forecasts. Lancet Infect Dis. 2014;14(7):619-26. https://doi.org/10.1016/S1473-3099(14)70781-9

20. Vasconcelos PF, de Menezes DB, Melo LP, Pesso ET, Rodrigues SG, da Rosa ES, et al. A large epidemic of dengue fever with dengue hemorrhagic cases in Ceará State, Brazil, 1994. Rev Inst Med Trop Sao Paulo. 1995; 37(3):253-5. https://doi.org/10.1590/S0036-46651995000300012

21. Vasconcelos PF, Lima JW, da Rosa AP, Timbó MJ, da Rosa ES, Lima HR, et al. Dengue epidemic in a Northeastern Brazil: random epidemiological serum survey. Rev Saude Publica. 1998;32(5):447-54. https://doi.org/10.1590/S0034-89101998000500007

22. Da Cunha RV, Miagostovich MP, Petrola Z, De Araújo ESM, Cortez D, Pombo V, et al. Retrospective Study on Dengue in Fortaleza, State of Ceará, Brazil. Mem Inst Oswaldo Cruz. 1998;93(2):155-9. https://doi.org/10.1590/S0074-02761998000200003

23. Araújo FM, Nogueira RM, de Araújo JM, Ramalho IL, Roriz ML, de Melo ME, et al. Concurrent infection with dengue virus type-2 and DENV-3 in a patient from Ceará, Brazil. Mem Inst Oswaldo Cruz. 2006;101(8):925-8. https://doi.org/10.1590/S0074-02762006000800017

24. Albuquerque PL, Silva Júnior GB, Diógenes SS, Silva HF. Dengue and aplastic anemia–a rare association. Travel Med Infect Dis. 2009;7(2):118-20. https://doi.org/10.1016/j.tmaid.2009.01.001

25. Aragão RE, Barreira IM, Lima LN, Rabelo LP, Pereira FB. [Bilateral optic neuritis after dengue viral infection: case report]. Arq Bras Oftalmol. 2010;73(2):175-8. https://doi.org/10.1590/S0004-27492010000200015

26. Ponte HJ, Pucci FH, Moreira Filho HF, Teófilo CR, Pires Neto RJ. Evaluation of pain manifestations in patients admitted to a reference hospital with presumptive dengue fever diagnosis. Rev Dor. 2011;12(2):104-7. https://doi.org/10.1590/S1806-00132011000200005

27. Lima DM, Sabino-Santos Junior G, Oliveira AC, Fontes RM, Colares JK, Araújo FM, et al. Hantavirus infection in suspected dengue cases from State of Ceará, Brazil. Rev Soc Bras Med Trop. 2011;44(6):795-6. https://doi.org/10.1590/S0037-86822011000600031

28. Azin FR, Gonçalves RP, Pitombeira MH, Lima DM, Branco IC. Dengue: profile of hematological and biochemical dynamics. Rev Bras Hematol Hemoter. 2012;34(1):36-41. https://doi.org/10.5581/1516-8484.20120012

29. Araújo FM, Araújo MS, Nogueira RM, Brilhante RS, Oliveira DN, Rocha MF, et al. Central nervous system involvement in dengue: a study in fatal cases from a dengue endemic area. Neurology. 2012;78(10):736-42. https://doi.org/10.1212/WNL.0b013e31824b94e9

30. Araújo F, Nogueira R, Araújo Mde S, Perdigão A, Cavalcanti L, Brilhante R, et al. Dengue in patients with central nervous system manifestations, Brazil. Emerg Infect Dis. 2012;18(4):677-9. https://doi.org/10.3201/eid1804.111522

31. Macedo RN, Rocha FA, Rolim DB, Vilar DC, Araújo FM, Vieira NN, et al. Severe coinfection of melioidosis and dengue fever in Northeastern Brazil: first case report. Rev Soc Bras Med Trop. 2012;45(1):132-3. https://doi.org/10.1590/S0037-86822012000100028

32. Torres AF, Braga DN, Muniz F, Mendonça C, Oliveira DN, de Souza ET, et al. Lymphocytic myocarditis at autopsy in patients with dengue fever. Braz J Infect Dis. 2013;17(5):619-21. https://doi.org/10.1016/j.bjid.2013.03.009

33. Cavalcanti LP, Mota LA, Lustosa GP, Fortes MC, Mota DA, Lima AA, et al. Evaluation of the WHO classification of dengue disease severity during an epidemic in 2011 in the state of Ceará, Brazil. Mem Inst Oswaldo Cruz. 2014;109(1):93-8. https://doi.org/10.1590/0074-0276140384

34. Teixeira WM, Paixão ES, Costa Mda C, Cunha RV, Pamplona L, Dias JP, et al. Arterial hypertension and skin allergy are risk factors for progression from dengue to dengue hemorrhagic fever: a case control study. PLoS Negl Trop Dis. 2015;9(5):e0003812. https://doi.org/10.1371/journal.pntd.0003812

35. Costa SD, da Silva GB Jr, Jacinto CN, Martiniano LV, Amaral YS, Paes FJ, et al. Dengue Fever Among Renal Transplant Recipients: A Series of 10 Cases in a Tropical Country. Am J Trop Med Hyg. 2015;93(2):394-6. https://doi.org/10.4269/ajtmh.15-0038

36. Fontes RM, Cavalcanti LP, Oliveira AC, Bezerra LF, Gomes AM, Colares JK, et al. A new possibility for surveillance: do we identify all cases of leptospirosis? Rev Inst Med Trop Sao Paulo. 2015;57(5):443-6. https://doi.org/10.1590/S0036-46652015000500014

37. Maia SH, Brasil IR, Esmeraldo Rde M, Ponte CN, Costa RC, Lira RA. Severe dengue in the early postoperative period after kidney transplantation: two case reports from Hospital Geral de Fortaleza. Rev Soc Bras Med Trop. 2015;48(6):783-5. https://doi.org/10.1590/0037-8682-0205-2015

38. de Melo Bezerra LF, Fontes RM, Gomes AM, da Silva DA, Colares JK, Lima, DM. Serological evidence of leptospirosis in patients with a clinical suspicion of dengue in the State of8 Ceará, Brazil. Biomedica. 2015; 35(4):557-62.

39. Cavalcanti LP, Braga DN, da Silva LM, Aguiar MG, Castiglioni M, Silva-Junior JU, et al. Postmortem Diagnosis of Dengue as an Epidemiological Surveillance Tool. Am J Trop Med Hyg. 2016;94(1):187-92. https://doi.org/10.4269/ajtmh.15-0392

40. Pamplona Lde G, Alencar CH, Lima JW, Heukelbach J. Reduced oviposition of Aedes aegypti gravid females in domestic containers with predatory fish. Trop Med Int Health. 2009;14(11):1347-50. https://doi.org/10.1111/j.1365-3156.2009.02377.x

41. de Oliveira Lima JW, de Góes Cavalcanti LP, Pontes RJ, Heukelbach J. Survival of Betta splendens fish (Regan, 1910) in domestic water containers and its effectiveness in controlling Aedes aegypti larvae (Linnaeus, 1762) in Northeast Brazil. Trop Med Int Health. 2010;15(12):1525-32. https://doi.org/10.1111/j.1365-3156.2010.02658.x

42. Cavalcanti LP, Pontes R, Regazzi AC, de Paula Júnior FJ, Frutuoso RL, Sousa EP, et al. [Efficacy of fish as predators of Aedes aegypti larvae, under laboratory conditions]. Rev Saude Publica. 2007;41(4):638-44. https://doi.org/10.1590/S0034-89102006005000041

43. Pamplona Lde G, Lima JW, Cunha JC, Santana EW. [Evaluation of the impact on Aedes aegypti infestation in cement tanks of the municipal district of Canindé, Ceará, Brazil after using the Betta splendens fish as an alternative biological control]. Rev Soc Bras Med Trop. 2004;37(5):400-4. https://doi.org/10.1590/S0037-86822004000500006

44. Paiva CN, Lima JW, Camelo SS, Lima Cde F, Cavalcanti LP. Survival of larvivorous fish used for biological control of Aedes aegypti (Diptera: Culicidae) combined with different larvicides. Trop Med Int Health. 2014;19(9):1082-6. https://doi.org/10.1111/tmi.12341

45. Oliveira MS, Morais SM, Magalhães DV, Batista WP, Vieira IG, Craveiro AA, et al. Antioxidant, larvicidal and antiacetylcholinesterase activities of cashew nut shell liquid constituents. Acta Trop. 2011;117(3):165-70. https://doi.org/10.1016/j.actatropica.2010.08.003

46. Farias DF, Cavalheiro MG, Viana SM, De Lima GPG, da Rocha-Bezerra LC, Ricardo NM, et al. Insecticidal action of sodium anacardate from Brazilian cashew nut shell liquid against Aedes aegypti. J Am Mosq Control Assoc. 2009;25(3):386-9. https://doi.org/10.2987/08-5851.1

47. Cavalcanti ES, Morais SM, Lima MA, Santana EW. Larvicidal activity of essential oils from Brazilian plants against Aedes aegypti L. Mem Inst Oswaldo Cruz. 2004;99(5):541-4. https://doi.org/10.1590/S0074-02762004000500015

48. Souza LG, Almeida MC, Monte FJ, Santiago GM, Braz-Filho R, Lemos TL. Constituintes químicos de Capraria biflora (Scrophulariaceae) e atividade larvicida de seu óleo essencial. Quim Nova. 2012;35(11):2258-62. https://doi.org/10.1590/S0100-40422012001100032

49. Araújo EC, Silveira ER, Lima MA, Neto MA, de Andrade IL, Lima MA, et al. Insecticidal activity and chemical composition of volatile oils from Hyptis martiusii Benth. J Agric Food Chem. 2003;51(13):3760-2. https://doi.org/10.1021/jf021074s

50. Souza TM, Cunha AP, Farias DF, Machado LK, Morais SM, Ricardo NM, et al. Insecticidal activity against Aedes aegypti of m-pentadecadienyl-phenol isolated from Myracrodruon urundeuva seeds. Pest Manag Sci. 2012;68(10):1380-4. https://doi.org/10.1002/ps.3316

51. Lima EP, de Oliveira Filho AM, de Oliveira Lima JW, Ramos Júnior AN, de Góes Cavalcanti LP, Pontes RJ. [Aedes aegypti resistance to temefos in counties of Ceará State]. Rev Soc Bras Med Trop. 2006;39(3):259-63. https://doi.org/10.1590/S0037-86822006000300006

52. Lima EP, Paiva MH, de Araújo AP, da Silva EV, da Silva UM, de Oliveira LN, et al. Insecticide resistance in Aedes aegypti populations from Ceará, Brazil. Parasit Vectors. 2011;4:5. https://doi.org/10.1186/1756-3305-4-5

53. Martins VE, Martins MG, de Araújo JM, Silva LO, Monteiro HA, Castro FC, et al. [First report of Aedes (Stegomyia) albopictus in the state of Ceará, Brazil]. Rev Saude Publica. 2006;40(4):737-9. https://doi.org/10.1590/S0034-89102006000500027

54. Martins VE, Alencar CH, Facó PE, Dutra RF, Alves CR, Pontes RJ, et al. [Spatial distribution and breeding site characteristics of Aedes albopictus and Aedes aegypti in Fortaleza, State of Ceará]. Rev Soc Bras Med Trop. 2010;43(1):73-7. https://doi.org/10.1590/S0037-86822010000100016

55. Degallier N, Servain J, Lucio PS, Hannart A, Durand B, de Souza RN, et al. The influence of local environment on the aging and mortality of Aedes aegypti (L.): case study in Fortaleza-CE, Brazil. J Vector Ecol. 2012;37(2):428-41. https://doi.org/10.1111/j.1948-7134.2012.00247.x

56. Lucio PS, Degallier N, Servain J, Hannart A, Durand B, de Souza RN, et al. A case study of the influence of local weather on Aedes aegypti (L.) aging and mortality. J Vector Ecol. 2013;38(1):20-37. https://doi.org/10.1111/j.1948-7134.2013.12005.x

57. Martins VE, Alencar CH, Kamimura MT, de Carvalho Araújo FM, De Simone SG, Dutra RF, et al. Occurrence of natural vertical transmission of dengue-2 and dengue-3 viruses in Aedes aegypti and Aedes albopictus in Fortaleza, Ceará, Brazil. PLoS One. 2012;7(7):e41386. https://doi.org/10.1371/journal.pone.0041386

58. Pontes RJ, Freeman J, Oliveira-Lima JW, Hodgson JC, Spielman A. Vector densities that potentiate dengue outbreaks in a Brazilian city. Am J Trop Med Hyg. 2000;62(3):378-83. https://doi.org/10.4269/ajtmh.2000.62.378

59. Silva ARA, Morais SM, Marques MMM, Lima DM, Santos SCC, Almeida RR et al. Antiviral activities of extracts and phenolic components of two *Spondias* species against dengue virus. J Venom Anim Toxins incl Trop Dis. 2011;17(4):406-13. https://doi.org/10.1590/S1678-91992011000400018

60. Marques MM, de Morais SM, da Silva AR, Barroso ND, Pontes Filho TR, Araújo FM, et al. Antiviral and Antioxidant Activities of Sulfated Galactomannans from Plants of Caatinga Biome. Evid Based Complement Alternat Med. 2015;2015:591214.

61. Sales FM. [Health education actions for the prevention and control of dengue fever: a study at Icaraí, Caucaia, Ceará State, Brazil]. Cien Saude Colet. 2008;13(1):175-84. https://doi.org/10.1590/S1413-81232008000100022

62. Caprara A, Lima JW, Marinho AC, Calvasina PG, Landim LP, Sommerfeld J. Irregular water supply, household usage and dengue: a bio-social study in the Brazilian Northeast. Cad Saude Publica. 2009;25 Suppl 1:S125-36. https://doi.org/10.1590/S0102-311X2009001300012

63. Heukelbach J, de Oliveira FA, Kerr-Pontes LR, Feldmeier H. Risk factors associated with an outbreak of dengue fever in a favela in Fortaleza, north-east Brazil. Trop Med Int Health. 2001;6(8):635-42. https://doi.org/10.1046/j.1365-3156.2001.00762.x

64. Caprara A, Lima JW, Peixoto AC, Motta CM, Nobre JM, Sommerfeld J, et al. Entomological impact and social participation in dengue control: a cluster randomized trial in Fortaleza, Brazil. Trans R Soc Trop Med Hyg. 2015;109(2):99-105. https://doi.org/10.1093/trstmh/tru187