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DENGUE AND CHIKUNGUNYA: A REVIEW

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ABSTRACT

Background: Arboviruses are characterized by a clustering of viral diseases, infected by vectors (viruses transmitted by arthropods). The designation of arboviruses is not only being used for its dissemination through arthropods, but is subject to its reproductive cycle that occurs in insects. In Brazil, among the most frequently expressed arboviruses are Dengue, Chikungunya and Zika. The emergence of arboviruses has raised concerns about the main causes of their emergence and the need to develop prevention and control programs. **Objective:** To demonstrate the importance of the Dengue fever and Chikungunya clinical and epidemiological situation in Brazil and how this factor increase the interest in seeking means of prevention and control. **Methods:** Criteria for eligibility and synthesis were based on systematic reviews of intervention research, and did not include narrative reviews, overviews, trials and meta-analyzes. Systematic search strategies were used in two electronic databases Scielo and Google Scholar. **Results:** Dengue fever cases reported in Brazil reach approximately 700,000 cases, decreasing considerably in 2003 and 2004, increasing again in 2005. Chikungunya cases reported by the Ministry of Health are about 9,084 autochthonous suspect cases and 3,554 unconfirmed cases. **Conclusion:** The scientific community and the health services should act directly with the identification of transmission patterns and the impacts of these arboviruses in Brazil, contributing with proposals to control this significant emerging challenge.

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INTRODUCTION

The arboviruses are characterized by a clustering of viral diseases, infected by vectors (Arthropod-borne virus). The arboviruses designation are not only associated with their diffusion through arthropods, but mainly because of their reproductive cycle that occurs in insects (BURT *et al.,* 2012).

In Brasil, among the arboviruses that express more frequency, there are Dengue fever (DEN), Chikungunya (CHIK) and Zika (ZIKA), DEN and ZIKA that belong to the Flaviviridae family and CHIK inserted in the group Togaviridae. The signs and symptoms associated with these arboviruses are expressively similar, affecting the identification and precision of their clinical diagnosis (SINGHI, KISSOON and BANSAL, 2007), mainly because there is not greater knowledge yet of

development of associations of these in the same individual, being totally possible due to that they coexist most of the time in the same geographic regions and by their transmission being carried by the same vectors, Aedesaegypti and Aedesalbopictus. With regard to dengue fever, it has become a major public health challenge in recent years, due to the massive amount of incidence of the disease, making it more constant among the arboviruses that infect humans (ROTH *et al.,* 2012). The intense myalgias and their consequent prostration provoke morbidity, leading the patient to need to move away from his / her daily activities. It is also associated with their mortality, with the possibility of being at maximum levels depending on their form and early treatment and effective treatment. Its transmission occurs mainly through the bite of the Aedesaegypti mosquito, although there is another species, Aedesalbopictus, which has morphology and proliferation efficiency similar to the first one (FONSECA and FONSECA, 2012).There were no significant changes during pregnancy in women who had the virus, from who were not affected by the virus, although this result is striking because there are other studies demonstrating higher levels of prevalence in complications such as fetal death, inadequate birth weight and prematurity, therefore further studies on maternal and fetal repercussions as a consequence of dengue fever infection in the gestational period are required. It is a seasonal disease, more frequent in hot and high humidity seasons, since these conditions are the most favorable for the transmitter mosquito proliferations (TAN *et al.,* 2008). Currently there are no licensed vaccines or specific treatments for CHIKV, and patients are only given non-steroidal anti-inflammatory medications to relieve joint pain and swelling. The evolution of vaccine research began in 1960, with the Chikungunya epidemic in the Americas, and the interest in creating the vaccine, which is now being tested in animals, has re-emerged (PLANT *et al.,* 2015).

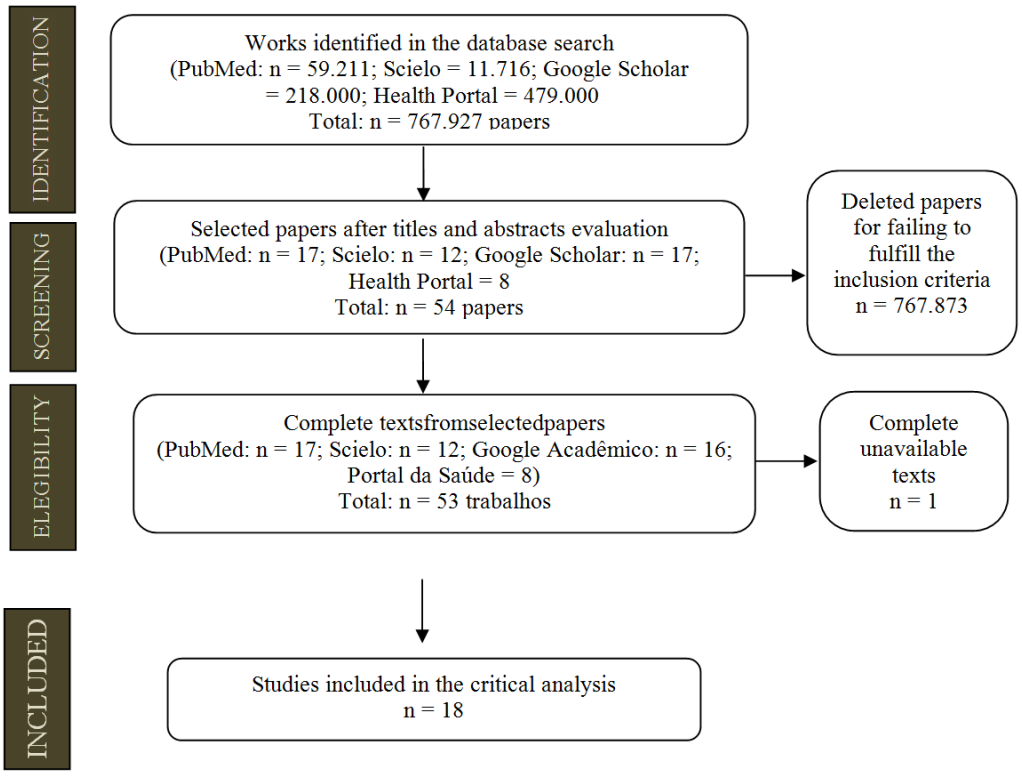
MATERIALS AND METHODS

The researches base was characterized in the systematic study from materials already published in the scientific literature and articles of public domain disseminated by governmental bodies of Brazil. The terms for indexing were used for the bibliographic research: dengue; Chikungunya; Arboviruses; Arboviruses; In national and international languages, available in the main scientific databases: Scielo; PubMed; Lilacs; Google Scholar and the criteria for eligibility and synthesis were based on systematic reviews of intervention research and did not include narrative reviews, overviews (review of the review), essays and meta-analyzes. Systematic search strategies were used in two electronic databases Scielo and Google Scholar. The initial research had 288,927 documents identified, being found in the database PubMed (59,211), Scielo (11,716) and Google Scholar (218,000). In the Pubmed and Scielo the description used was dengue, chicungunya, clinical aspects, epidemiology, prevention. This systematic review study was based on the exclusion of 8,325 articles with experience reports and the inclusion of 54 articles through the evaluation of titles, abstracts and the following keywords: dengue, chincuncunya being: PubMed (17), Scielo (12), Google Scholar (16), Portal of the Ministry of Health (8) and a complete text unavailable, as shown in the flowchart 1.

RESULTS

Dengue fever has an extensive clinical spectrum, the most expressive diseases with differential diagnosis are: viral hepatitis, sepsis, exantemtic diseases (erythema infectiosum, cytomegalovirus, measles, parvovirus, rubeola, infectious mononucleosis, sudden exanthema, and other), pneumonia, influenza, urinary infection, leptospirosis, hantavirus, malaria, enteroviruses, yellow fever, meningococcemia (COSTA, SANTOS and BARBOSA, 2009).

Portal of the Ministry of Health (8) and a complete text unavailable, as shown in the flowchart 1



Source: Schematic representation of methods identification, screening, eligibility and inclusion of articles in the review, adapted according to the PRISMA Flow Diagram.

There is no specific treatment for Dengue (DEN), and only symptomatic care and hydration are initially indicated, according to the protocol specified by the Ministry of Health which was created with the purpose to prevent the delay for the diagnosis of the most severe forms of the disease or interference in the treatment. Thus, the proposal is that people who are suspected of being infected by the diseases be separated into four specific groups, according to the anamneses records and physical examinations to be orientated to the respective actions appropriated for each occurrence. In the case of Chikungunya (CHIK), its incidence reaches any age group or sex, but the signs and symptoms are more severe in children and elderly, with three stages: acute, subacute and chronic. It is an infection that almost never leads to death and may be presented in an asymptomatic way. When symptoms occur, they usually come in the form of: chills, myalgias, headache, back pain, arthralgia, nausea and vomiting, high fevers that last days to weeks (PÉREZ SÁNCHEZ *et al.,* 2014). Dengue (DEN) presents itself with a differential diagnostic due to clinical and epidemiological factors; however, its differentiation from Chikungunya (CHIK) is basically the severity of arthralgias, which in this case is presented with greater intensity, whereas hemorrhage indicates a diagnosis oriented to Dengue (DEN) (Chokephaibulkitand PERNG, 2014).In both cases, it is essential to know which destinations the patient recently visited to provide a more specific diagnosis. The tests to identify them are ELISA (Enzyme-linked immunosorbent assay) and PCR (Polymerase Chain Reaction), however there is no effective antiviral treatment by then, and its prophylaxis is performed by controlling the vector (CHOKEPHAIBULKIT and PERNG, 2014).

Virus characteristics: The dengue virus integrates the Flavivirus gender of the Flaviviridae family; it is a RNA virus, with single filament, enveloped and with four serotypes: DEN-1, DEN-2, DEN-3 and DEN-442; The cross-protection among all is only made in a transitional form, since the same individual can manifest the disease in up to four times during his/her life. It is also possible, to coexist different serotypes in the same region, increasing the chances of occurrence complications such as hemorrhagic dengue fever (TAN *et al.,* 2008).As previously mentioned, the symptomns of the classic Dengue (DEN), normally characterized by high fever with sudden onset, with a temperature ranging from 39º to 40ºC, associated with muscular myalgias, eye pains, asthenia, severe headache, inappetence, red patches on the skin associated or not with pruritus. In addition to all this, the patient may still experience vomiting and diarrhea between the second and sixth day of infection. Generally, in a variable period between 3 to 7 days the temperature begins to decrease and the symptoms presented regress, but the asthenia remains for subsequent weeks (CHOKEPHAIBULKIT and PERNG, 2014).The issue that deserves greater attention is when the disease develops for hemorrhagic dengue fever, which can occur soon after reinfection by the virus, generating symptoms that are much more aggravated than the classic DEN. Usually it begins with the same signs and symptoms of classic DEN, but followed by hemorrhage (SINGHI, KISSOON and BANSAL, 2007). It is observed in relation to the vector that the Aedesaegypti mosquito has diurnal habits, especially in the early morning and late afternoon, preferring urban and household contacts sites and essentially feeding on human blood. The mosquito propagation occurs when the female puts the eggs in places with standing water, hatching and giving origin to the larvae. The elapses time between this hatching of the egg and the adult mosquito lasts approximately 10 days, and suffers strong elements influence such as temperature, which intensifies this process; The egg can survive up to a year out of water, waiting for appropriated environmental conditions for its development (FONSECA and FONSECA, 2002).The virus is acquired by the mosquito when it feeds on the blood of a patient in the course of viremia, which begins one day before the onset of fever and continues until the sixth day of the disease. The virus lodges in the salivary glands of the mosquito, proliferating and remaining there, transforming the arthropod in an infecting while living; after the female is infected, the virus is inoculated with its saliva when it stings a healthy individual, and the female can also transmit the virus by transovarial form to the offspring, promoting the disease dissemination (CHOKEPHAIBULKIT and PERNG, 2014). After inoculation into the human host, the virus invades the cells, reproduces, breeds viral progenitors and thus begins the viraemia period, distributing the virus to the whole body. Viral replication swell monocytes and, indirectly, lymphocytes produce cytokines. In some cases they will have pro-inflammatory effects and will cause the onset of symptoms, such as fever for example; others end up stimulating the production of antibodies, binding to the viral antigens constituting immunocomplexes (FONSECA and FONSECA, 2002).

Epidemiology: The first Brazilian epidemics were clinically and laboratorially recorded between 1981 and 1982 in the city of Boa Vista, Roraima. Between 1986 and 1987 a potential outbreak proportions plagued the state of Rio de Janeiro, and since then there have been new outbreaks of outbreaks in several brazilian states. In 2002, the highest incidence rates were recorded in Brazil, notifying an average of 700.000 cases. After this period, the number of occurrences of the disease considerably reduced in 2003 and 2004, returning to increase in 2005. Until the beginning of July 2010, 789,055 cases of dengue fever in the country were identified, representing an increase of over 150% over the same period in 2009. Among the totals, 2,271 cases were of Hemorrhagic Dengue Fever (HDF), registering 367 deaths. The highest incidence of cases was recorded in the Southeast region with 51.2% of the notifications, followed by the Central-West region with a percentage of 23.7%, Northeast 11.3%, North Region 8.5% and South 5.3%.

Clinical Aspects: Dengue virus infection can occur asymptomatic until it causes its severity endangering the person's life. There are factors associated with both the virus and the host, thus determining its worsening. The clinical symptoms of the infection begin after the incubation phase (3 to 7 days), the first characterized by fever, following the critical effervescence phase and finally the recovery phase (SINGHI, KISSOON and BANSAL, 2007). Generally, the fever observed at the beginning of the cycle is higher than 38ºC, and patients complain of retro-orbital cephalea, diarrhea, vomiting, joint pain, nausea, prostration and myalgias. Palpable liver, bruises, bleeding in venous puncture sites, macular rash, mild manifestations of hemorrhagic events and petechiae in the hands and feet, face and armpits can still be observed; In children the symptoms are milder and fever is higher (SIMMONS, 2012).

Virus Characteristics: Chikungunya fever is defined to be a diseases caused by Chikungunya virus (CHIKV), transmitted

by arthropods of the genus Aedes infected, and it is retransmitted to wild and domestic animals. This is a single-stranded RNA virus belonging to the genus Alphavirus, family Togaviridae (PÉREZ SÁNCHEZ *et al.,* 2014). The potential symptom of this disease is polyarthralgia, with the possibility to progress to chronic arthritis, but the symptoms related to the term "Chikungunya" it is originated in the Makonde language (Mozambique), and define its meaning by "the one who is contorted", because of the position resulting from patients with arthralgias (SIMMONS *et al.,* 2012). In 25% of the cases, the infection appears asymptomatic and in symptomatic cases, polyarthralgia is the factor that characterizes the infection and in approximately 7 to 15 days the acute signs disappear, but in 10 to 12% of the cases pains in the joints may last for months or years, with or without fever, being designated as a chronic phase (NUNES *et al.,* 2015). The CHIK virus is infected by Ae. Aegypti with urban habitat in tropical areas and by Ae.Albopictus, with habitat in rural areas, but, however, it has been more and more identified in urban and periurban locations (KUCHARZ and CEBULA-BYRSKA, 2012). The two main vectors observed are Ae. Aegypti and in 2006 Ae.Albopictus was manifested as another vector of this virus. In recent infections Ae.Albopictus has an expressive relevance due to the adaptive mutations of the viral genome, increasing its viral replication, making it easier to circulate in the different regions in which they were found (NUNES *et al.,* 2015). CHIKV is a virus transmitted through the bite of mosquitoes of the genus Aedesssp, the constitution of the eggs happens through blood shedding by females, identifying them as the only one that has the infection (PLANTE *et al.,* 2015). Recently, the virus was also discovered in males, with the possibility of indirectly performing transovarial transmission, although males cannot directly transmit to humans, they can be the transmitters for females during mating (ROUGERON, 2015).Specifically, there are two types of transmission cycles: The first is called the wild cycle involving wild apes which inhabit in the forests that have Aedessp, as Ae. Furcifer, Ae. Taylori, Ae. Luteocephalus, Ae. Africanus and Ae.Neoafricanus being responsible for an outbreak with lower rates; and the second, urban cycle that occurs directly between the mosquitosAe.Aegypti and the human and are agents with a reginal and global focal points. Gradually, Ae.Albopictus has spread to other continents, and it is thought to be the second vector with the highest transmission efficiency of CHIKV (PARDIGON, 2009).

Epidemiology: The native inoculation of CHIK in Brazil was identified in September 2014, in the city of Oiapoque, Amapá (HONÓRIO, 2015). Perhaps this incursion occurred because of the outbreak in the Caribbean in 2013; However, previously there had been other epidemics reaching Africa and Asia (WEAVER and LECUIT, 2015). In the passing of 2014, 2,772 cases of CHIK were reported in six Brazilian states: Amapá with 1,554 registered cases, Bahia with 1214, Federal District with 2, MatoGrosso do Sul, Roraima and Goiás with only 1 case each. They were registered and confirmed by laboratory in the following states: Maranhão, Pernambuco, Pará, Ceará, Goiás, Amazonas, São Paulo, Rio de Janeiro, Paraná, Minas Gerais, Rio Grande do Sul39. The Ministry of Health revealed data in 2015 of autochthonous cases found in 735 cases in Amapá and 778 cases in Bahia associated with the African genotype (HONÓRIO, 2015).The Ministry of Health still reports 9,084 autochthonous cases suspected of CHIK, which 3,554 are unconfirmed, 123 identified by laboratory criteria and 3,431 by clinical-epidemiological criteria; 5,217 still being investigated (HONÓRIO, 2015). Researches were initiated in the 1960s, studies for the CHIK vaccine, but it is not licensed yet (WEAVER and LECUIT, 2015). The US National Institutes of Health is already developing studies of the CHIK vaccine, and it is being tested in humans.

Clinical Aspects: The clinical manifestations of Chikungunya fever (CHIK) are very similar to those in Dengue fever (DEN), and therefore viremia phase begins one day before the symptoms remain for 7 days. The incubation phase varies from 1 to 12 days, affecting the individual with high fever, joint pain, photophobia, headache, myalgia and axanthema(TAUIL, 2014).During disease onset, virus isolation and reverse transcriptase polymerase chain reaction (RT-PCR) is performed, it is the most used method because of its susceptibility and accuracy, and also because at this stage it has larger amounts of viral particles in the bloodstream, and in the posterior phase an antibody screening is carried out, in other words, its diagnosis is carried out by laboratory tests with viral isolation, serology and molecular techniques (KUCHARZ and CEBULA-BYRSKA, 2012).The hemogram of a person affected by Chikungunya presents leukopenia with lymphopenia; Since thrombocytopenia is more uncommon and the hemosedimentation rate is usually high; During the acute phase C-reactive protein manifests itself high and can remain so for several weeks (ROUGERON, 2015). After one week after the incubation period, viral RNA can be detected within 2 to 6 days; Specific IgM antibodies demonstrate positive results, and then specific IgG antibodies can be identified persisting for months or years. Due to the high cross-reaction with other arboviruses, the property of the antibody screening methods is not high (KUCHARZ and CEBULA-BYRSKA, 2012).In the later phase when the response occurs through an antibody, the respective research is done through ELISA and immunofluorescence technique that identifies the responses of the IgG and IgM3 antibodies. Clinical and epidemiological parameters are used to define each case. Clinical criteria such as high fever (> 38.5 ° C) and severe arthralgia or acute arthritis are being explained by other reasons and epidemiological parameters such as the visit or residence of the patient in endemic localities before the onset of symptoms (HONÓRIO, 2015).

DISCUSSION

After reviewing the data analysis on dengue fever worldwide, between 1999 and 2004, only 58 studies were verified, each of which, Brazil supported 28 studies (48.3%), not counting systematic reviews about studies on health geo-processing, which, still uncommon (CARVALHO and SOUSA-SANTOS, 2005). Among the studies on the spatialisation of dengue fever cases, two (28.6%) did not perform any geo-processing technique and with dengue vectors, four (80.0%) did not use any geo-processing technique. According to data from the SINAN (Information System for Notification of Diseases Grievance), the number of dengue fever cases in Brazil has been increasing since 2009, from 406 thousand to about 1.5 million in 2013 alone, totaling 4.2 million notifications in the period mentioned (HONÓRIO, 2015).In relation to Chikungunya, 3,657 cases of suspicion were registered in eight cities until December 2014 and, until then, this amount has multiplied and evolved in the whole country; 38,332 cases were identified in 696 municipalities, beginning to cause the infection to compromise the capacity to be treated in the

Brazilian health system44. In 2015, 1,534,932 cases were identified, with 811 deaths confirmed with notification of 17,131 autochthonous cases of suspected Chikungunya virus, with 350 cases being confirmed (THIBERVILLE *et al.,* 2013). The Chikungunya indicates lower incidences of deaths in percentage less than 1% than the rates of Dengue fever to worldwide levels. Compared to Dengue fever, Chikungunya has attributes that increase the spread of disease by increasing the probability of significant epidemics. Such characteristics have more proportion of symptomatic cases (> 90%), a shorter extrinsic incubation period (2 to 7 days), a longer period of viremia (2 before and 10 after fever) and a shorter extrinsic incubation period (in the mosquito). Viral replication in the Aedesalbopictus mosquito in addition to A. aegypti increases the geographical extention of regions with a potential viral circulation (PINTO JUNIOR, 2014). Chikungunya infection is similar to dengue fever, not only in relation to the incubation period, but the symptoms of fever, pain and skin rash appear in both pathology cases. In 25% of the people Chikungunya is asymptomatic and may cause symptoms years later to the initial infection, mainly in the elderly population (TAUIL, 2014).

The monitoring of serotypes by epidemiological surveillance is essential for the implantation of vaccines in groups at risk (residents of areas favorable for vector evolution) and people previously infected, in this case, it is necessary to know the ones already infected, in this case its needed to know the infected serotype (these groups have already been identified in advance by epidemiological profile studies). It should also be observed the spread of the virus in the world as a surveillance strategy in order to prevent future epidemics, thus, how to determine an effective treatment of the disease (PINTO JUNIOR, 2014).The number of infected mosquitoes is increasing in areas of high socioeconomic level, because habits such as aquatic plant cultivation and wrong disposal contribute to the mosquito breeding (COSTA, SANTOS and BARBOSA, 2009). The fact that there are no vaccines or specific drugs available to the vector control teams, ends up determining for them a preventive mission. The Ministry of Health advocates the early identification of cases in indicated areas, broadening the diagnostic back and training of health teams (PLANTE *et al.,* 2015). From the foregoing, it is understood that the scientific community, together with the health services, must assume the role of monitoring the epidemiological picture of these arboviruses, identifying the transmission patterns and the impacts of the disease in Brazil and, mainly, contributing with proposals for facing this significant emerging challenge.

Conflict of interest

The authors declare that they have no competing interests.

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