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Clinical expression of dengue in beneficiaries of the Instituto Mexicano del Seguro Social in Veracruz, Mexico.

Expresión clínica del dengue en usuarios del Instituto Mexicano del Seguro Social, Veracruz, México.

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ABSTRACT

Objective: To describe and compare the clinical behavior of Dengue Fever (DF) and Hemorrhagic Dengue Fever (HDF) in beneficiaries of the Instituto Mexicano del Seguro Social (IMSS). **Methods:** Transversal study in beneficiaries from Veracruz, selected among those who sought attention at two medical attention units, with probable dengue diagnosis. Surveys were performed to know personal and epidemiological data, as well as a clinical follow up. Blood samples were taken for RT-PCR viral identification and antibodies against Dengue. In the same way, platelet, hemoglobin, and hematocrit tests were performed for their determination. The SPSS 12.0 software was used for the process and analysis of the information, and simple frequencies, proportions, and means were estimated. **Results:** 109 patients were studied, classified as 72 DF and 37 as HDF. 40 isolations were performed, and the circulation of the four types of dengue virus was identified, although most of the isolations corresponded to serotype 2 (Asian-American genotype). In one patient, a simultaneous infection of dengue viruses 1 and 2 was identified. A group of patients did not present hemorrhages, capillary fragility, or liquid permeation, but with important thrombocytopenia and hemoconcentration, all infected with den-1 and den-2. **Conclusions:** The presence of cases with atipical behavior of the diseases were identified. The characteristics and immunologic experience of the populations, as well as the simultaneous circulation of various dengue viruses and their changing structure could be related with the current clinical behavior of Dengue in Mexico. It is important to continue the research to confirm these asseverations.

KEY WORDS: Dengue, Clinical expresion, Mexico

INTRODUCTION

Dengue is one of the arboviruses with more history and currently important worldwide.[1-3] Original from Asia and the Pacific, where today it has endemic characteristics with high incidence rates in hemorrhagic cases and deaths, the disease arrived to the American continent and disseminated to almost all countries that form part of it. Mexico is not the exception, and since its reintroduction in 1978, constant breakouts have happened, which together with the slow introduction and circulation of the four types of dengue virus, producing the infection in almost all the country, an epidemiologic pattern of the disease has been determined, similar to the one observed in Asian countries and from the Pacific cost countries;[4] this means a higher presentation of hemorrhagic cases and the translation of risk groups into children population. However, differently to what occurs in the regions where a large number of hemorrhagic and shock cases are reported, as well as deaths, in our country it has been observed for the last years a shift in the clinical behavior of the infection.

Among other factors of the population and the vector, the antecedent of the circulation of the four dengue virus types in a region, as well as the simultaneous circulation of two or more of them, have been considered as the cause of the breakouts in severe and fatal cases of the infection[5-7] in many countries. However, despite these conditions are present in our national territory, the clinical expression observed is less serious than that reported in Asian countries and even in other countries from the American continent.

In this sense, some years ago, it was foreseen an increase in the amount of severe cases in the country as a consequence of the introduction of serotypes 2 and 3,[8,9] which turned out true, for from 1995 to 1999 when the den-3 was identified as the one with highest circulation, the notifications of infection increased, as well as the number of case with hemorrhage precedents or liquid permeation, with shock, and even lethal.[4] However, from 2000 on, it was when the reintroduction of serotype 2 was identified, and although it was supposed of a similar behavior, its presence was identified in the cases with atypical behavior mentioned above[10] (Chart 1).

Regarding this, it is supposed that there exist structural differences which determine a higher or lesser pathogenecity of the different viruses,[11-14] although up to now the mechanisms of infection and replication of flaviviruses have not been completely understood. Many studies have analyzed the relation between the nucleotides in

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the dengue virus and the sequence of amino acids in the E protein with the virulence of the agent,[15] finding difference among patients with different levels of severity of the disease. According to this, there have also been found differences among the different dengue viruses from different regions, which make us suppose the viral evolution and mutation that may determine a more or less aggressive agent.[16,17]

In Mexico, the increasing notification of cases with the described behavior has represented a serious problem not only for the diagnosis and classification of the cases, but also to establish managing criteria and guidelines that will guarantee a quality attention and, thus, the decrease of complications and deaths. The present work had the purpose to analyze the clinical behavior in the cases confirmed with dengue at the Delegación Veracruz Norte from the Instituto Mexicano del Seguro Social (IMSS) to offer information that helps for treatment and follow up of the cases.

MATERIALS and METHODS

Previous review and authorization from the Scientific Research Committee from the IMSS, and to analyze the clinical behavior of the infection, a transversal study was performed in patients with initial diagnosis of dengue and who went for medical attention to the first-level medical unit and a hospital of Veracruz, in the Delegación Veracruz Norte of the IMSS. The selection of patients was done by convenience, and one out every five suspected patient seeking attention during august through December 2006 was chosen, using established case-operational definitions.[5] Previous informed signed consent in regards to the study was required from each patient. The used procedures and the follow ups of the cases strictly followed the normative guidelines already established and no invasive procedures alien to the normal follow up of the cases in the medical service sere performed;[19] only a better follow up and recollection control for clinical data were established.

Each patient who accepted participating in the study answered two questionnaires, one for personal background and risk factors, and the other for epidemiological background. In the same way, each had a follow up since his/her inclusion up to their discharge. During their stay at the hospital, two blood samples were taken for viral isolation and genotypification, as well as to determine IgM antibodies against dengue virus. The identification of the virus by RT-PCR and its typifying[20-25] was performed at the Genetic and Molecular Biology Laboratory at the Centro de Investigación y Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV, IPN). The determination of IgM antibodies by ELISA was performed as a routine activity from the Sistema de Vigilancia Epidemiológica (Epidemiological Survey System), and the samples were processed at the Laboratorio Estatal de Salud Pública (State Public Health Laboratory) of Veracruz, using conventional methods.[26] The clinical follow up was performed by the daily interviewing and exploration of the patients, as well as the parameter determination for the

classification for cases: hemoglobin, hematocrit, and platelets. Only cases confirmed with the disease were included in the analysis. The data was registered in specific formats and after it was transferred to a data base; the process and analysis were performed using the SPSS 12.0 statistic package. The simple frequencies, proportions, and central tendency measures were obtained in those variables that allowed it.

RESULTS

During the studied period, 625 patients under suspicion of having dengue sought medical attention in the participating Medical Units; from these, 137 cases were interviewed and finally 109 patients, positive to any of the used Dengue tests, were included, who, after follow up and considering operational criteria of the cases, were classified in two groups: 72 patients with DF and 10 with HDF. However, 16 patients who only presented thrombocytopenia were observed and 11 with only hemoconcentration data (20% increase or decrease in 3 subsequent hematocrits). All of these without hemorrhage or external liquid permeation and who finally were included in the hemorrhagic cases, for it was not possible to confirm by other clinical studies that these events really did not exist. Nevertheless, according to the current clinical classification for Dengue by the WHO,[5] the clinical data of 72 patients were for non-severe Dengue, 27 for non-severe Dengue but with alarm signs, and 10 for severe Dengue.

From all the studied subjects, 49% were males, and mean age was of 26.3±16.6 years. The distribution of patients within the age groups was similar.

The diagnostic tests were performed according to the day of evolution of the patients. Isolations were performed in 40 patients, in which the circulation of the four dengue virus serotypes was identified in this breakout affecting the Puerto de Veracruz, and surrounding municipalities: In total, five were serotype 1, 29 were serotype 2, four were serotype 3, and one was serotype 4; one case was later with an infection by serotypes 1 and 2 simultaneously confirmed by means of two consecutive tests.

In the DF group, 19 isolations were achieved and 21 in the HDF patients' group (Chart 2). The activation of nine samples for genotypification demonstrated the presence of the serotype 2 (Asiatic-American genotype) in all of them; similarly, by means of their phylogenic tree analyses, variations were found (aminoacid substitution: valine for isoleucine) which demonstrates the evolution of the dengue viruses in national territory.[27] However, due to the current technical limitations, the samples of the other serotypes were not genotypified. On the other hand, IgM antibody results were positive in 79 patients; ten of them were also positive to isolation, 13 were negative, and the reset of the samples were not

CHART 1. Data of the presence of liquid permeation and spontaneous hemorrhages in dengue cases with thrombocytopenia. Instituo Mexicano del Seguro Social

Year Criteria	1995 (%)	1997 (%)	1999 (%)	2001 (%)	2003 (%)	2005 (%)	2006 (%)
Liq. Permeation	9	16	20	34	20	19	16
Hemorrhages	43	20	32	22	23	17	13
Both	48	64	48	40	20	11	9
None	0	0	0	4	37	52	62

Source: Sistema de Vigilancia Epidemiológica, IMSS. (Epidemiology Surveilllance System, IMSS)

CHART 2. Isolation results and serology according to classification, IMSS 2006

Serotype Aisolate	F.D.	DcPp	DcHc	F.H.D.	Total
1	1	2	1	1	5
2	14	5	5	5	29
3	4	0	0	0	4
4	0	0	0	1	1
1-2	0	0	0	1	1
IgM antibodies					
Positive	53	9	5	2	69
Total	72	16	11	10	109

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CHART 3. Clinical aspects according to classification, IMSS 2006

VARIABLE	F.D. n=72 (%)	DcPp n=16 (%)	DcHc n=11 (%)	F.H.D. n=10 (%)
Gender (male./fem.)	31/41	9/7	7/4	6/4
Age (mean) years	21	21	27	25
Fever	72 (100)	16 (100)	11 (100)	10 (100)
Head ache	71 (99)	16 (100)	11 (100)	10 (100)
Myalgias	72 (100)	14 (88)	11 (100)	10 (100)
Arthralgias	72 (100)	15 (94)	11 (100)	10 (100)
Ocular pain	71 (99)	15 (94)	11 (100)	10 (100)
Exanthema	21 (29)	5 (31)	6 (55)	0
Diarrhea	19 (26)	5 (31)	4 (36)	3 (30)
Vomit	29 (40)	10 (63)	7 (64)	9 (90)
Abdominal pain	70 (97)	14 (88)	11 (100)	10 (100)
Hemorrhages	0	0	0	2 (20)
Plasma leakage	0	0	0	3 (30)
Hemoconcentration	0	0	11 (100)	8 (80)
Thrombocytopenia	0	16 (100)	0	10 (100)

processed. The largest proportion of positive cases was for those with HDF. Taking in consideration both groups, DF and HDF, 43% of cases included in the first group were males, and 59% were also hemorrhagic. Regarding the first infection signs and symptoms, we found that all the cases referred the presence of fever, headache, mialgias, artralgias, and ocular pain. The exanthema, diarrhea, vomit, and persistent vomit were less frequent in DF cases, but not abdominal pain, which in proportion was higher in the latter.

Liquid permeation and capillary fragility were observed in two patients, who presented petechiae and one, besides all, ecchymosis and hematomas; the hemorrhages were present as gingival in one of the cases and in different levels in the other. Two of the cases presented permeation and hemorrhages simultaneously and a clinical frame with a higher severity. Thrombocytopenia was present in 74% of the hemorrhagic cases, and hemoconcentration in 66% of these; only 19% of the total hemorrhagic cases present thrombocytopenia and hemoconcentration simultaneously.

In Chart 3 the information of signs and symptoms is presented in a detailed way for the DF groups (n=72) as well as for the HFD (n=37), and which in turn were categorized according to the presence of thrombocytopenia (N=16), hemoconcentration (n=11), and those who besides hemorrhagic data also presented thrombocytopenia, hemoconcentration, or both (n=10),
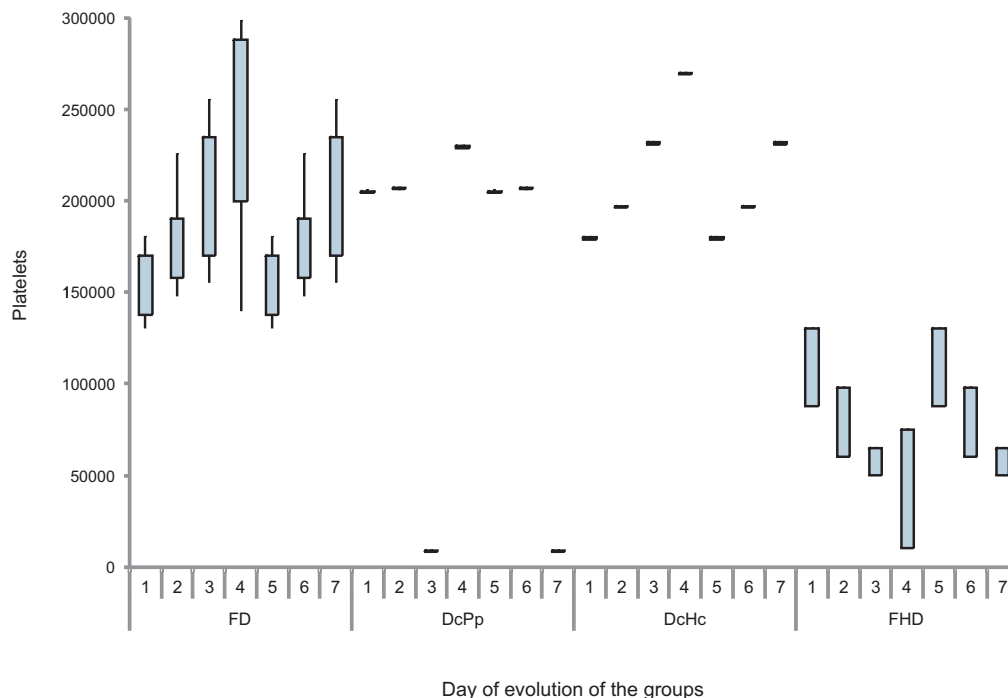
It is important to point out that the presence of atypical presentation with thrombocytopenia or hemoconcentration without hemorrhages were only identified in subjects infected with serotypes 1 and 2 (Chart 2).

Due to the presence of the outbreak of dengue in the city and the medical attention demand generated, performing tests to determine platelets and hematocrit, as well as the rest of the clinical parameters considered for the follow up was limited, if we consider that only in 70% of the cases it was possible to obtain at least three useful samples to determine platelets and hemoconcentration. This fact only allowed the classification of the cases and limited the possibility of adequate comparison between the groups, as well as the description of each of the laboratory parameters in the time (Graphs 1 and 2)
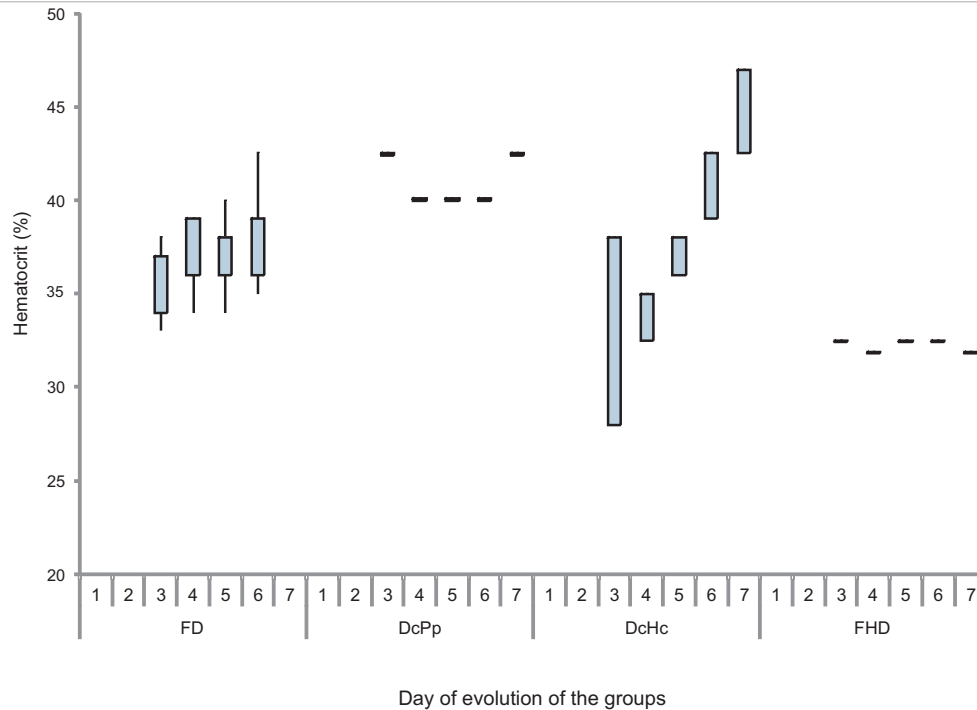
DISCUSSION

Worldwide literature refers some aspects considered as risk factors for HDF;[28-30] however, the background of having suffered a previous infection by any of the serotypes has been considered the most important risk factor for hemorrhagic manifestation under a re-infection.[31] According to epidemiologic evidence,[32-34] the validity of this theory has been questioned. Following this context, it is mentioned that the virulence of the infecting serotype[35,36] is a factor that could determine the organic damage and the clinical expression of the disease.

GRAPH 1. Platelets according to the day of evolution of the groups, IMSS 2006

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GRAPH 2. Hematocrit according to the day of evolution of the groups, IMSS 2006.

Day of evolution of the groups

The information available up to date suggests that the genetic changes that the dengue viruses have experimented[11,17] may derive in a weaker of stronger aggressiveness.[12-14] According to this, the structural differences found in the dengue viruses from different regions[16,38,39] could explain their epidemiological behavior, thus the importance of identifying the circulation of different dengue viruses, as well as the typifying of these to identify these changes and their relation with the clinical presentation.

The analysis of the data generated institutionally has allowed the identification of changes in form and frequency in which the hemorrhagic manifestations present, according to the cases reported to the system during the last years (Chart 1). This has strongly called the attention for, even in recent clinical reviews, this profile has not been considered.

The results of the present study confirm these facts and allow demonstrating in a sample of confirmed cases the evolution that the clinical behavior of the disease has presented based in the first HDF outbreaks occurred in our country and their clinical expression[40] (Chart 4).

According to the above, it has been manifested that the circulation of the four dengue virus serotypes that cause the disease, as well as the immunologic experience of the population acquired through repeated outbreaks may be one of the mechanisms responsible of this phenomenon. In the same way, the genetic variations that may exist among the dengue viruses even in the same region may determine changes in its virulence, which may also be an attributable factor. This is apparent when considering the expected potential risk by the identification of serotype 3 in Mexico, and the Asian-American genotype of serotype 2 in the state of Yucatan,[8,9] when an increase in the number of hemorrhagic cases was expected, and which has partially happened, for there does exist a real increase in the DF cases incidence, but the hemorrhagic cases incidence has considerably decreased, limiting its presence to the cases in which data of infection in its simple form are observed, but accompanied by important thrombocytopenia or hemoconcentration.

Other of the important findings of this work is the fact of demonstrating the level of endemicity of infection in Mexico, by identifying the simultaneous circulation of the four dengue viruses in an outbreak, as well as the occurrence of cases that may be infected with more than one serotype. On the other hand, the identification of the Asian-American genotype as causative of most part of the cases and the atypical presentation of the infection suggest that the structural variations of the dengue viruses[27] as well as the immunological experience of the population, among other factors, may condition a less or more severe clinical presentation. In this sense, if it is true that the cases with the clinical behavior described do not appear to be serious, the institutional experience has observed that a considerable proportion of them present late severe manifestations that, if not identified on time, may lead to death, especially when considering other important risk factors as age, diabetes, and hypertension. For this reason, and due to the fear of medics and patients in many medical units, it has become the norm to admit any patient who presents thrombocytopenia, which has translated in a decrease of complication in mortality, but has increased the costs of hospital attention.

CHART 4. Clinical aspects according to year. IMSS.

VARIABLE*	1995-2003 [40]		2006	
	FD n= 329	FHD n= 898	FD n= 72	FHD n= 37
Gender (male./fem.)	158/171	450/448	31/41	22/15
Age (mean) years	28	27	21	24
Fever	97	99	100	100
Headache	91	90	99	100
Myalgias	90	88	100	95
Arthralgias	80	85	100	97
Ocular pain	72	70	99	97
Exanthema	36	41	29	30
Vomit	34	60	40	70
Abdominal pain	36	59	97	95
Hemorrhages	0	49	0	5
Plasma leakage	0	61	0	8
Hemoconcentration	0	8	0	51
Thrombocytopenia	0	82	0	70

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The results obtained in this study are subject to methodological limitations inherent to the number of studied cases, which, in spite the presence of an outbreak, was determined by the availability of resources for the diagnosis y the strict follow up of the patients. Nevertheless, if it is true that some of the information obtained does not allow statistically significant associations, it is also true that even with the reduced number of studied cases; it is possible to notice a change in the presentation of hemorrhagic data in the patients. This is important for the phenomenon is also present in other states of the country.

The comparison of the clinical behavior in the groups does not allow establishing clear differences in the initial presentation and the evolution of the patient; however, there are some data, as the presence of hepatomegaly and splenomegaly that still represent an important sign that reflects the severity of the infection. In addition, the presence of digestive data such as diarrhea, nausea, vomit, and abdominal pain are also related to this sense. Due to above, it important to take these signs in consideration for a timely handling of the cases. On the contrary, it highlights the lesser proportion with which exanthema was documented in the HDF group, which may be related with the atypical behavior previously mentioned. In the same way, contrary to what happened in Mexico at the beginning of the epidemic in the cases classified as hemorrhagic,[40] data of capillary fragility and liquid permeation are more frequent than hemorrhages and are registered in a lesser proportion of the cases.

The use of the information presented does not limit solely to the description of the phenomenon, but further more, it has been useful to establish the strategy of the follow up for the patients suspected of having dengue, in whom, whether they present hemorrhages or not, the determination of hematocrit and hemoglobin to rule out hemoconcentration is performed, as well as the platelet counting, which defines the measures to be taken. Since the identification of this problem in 2000, the IMSS has performed the training and diffusion of this information in each of the affected Delegations and the result of this anticipatory conduct, as well as the experience obtained by the medical staff, has reflected in a better handling and follow up of patients, in such a way that despite the number of hospitalized patients, institutional lethality was zero. Due to the fact that there are no specific antiviral medicines against dengue viruses, the anticipation in the clinical handling in each case represents the opportunity that the patient has to stop the evolution of the disease to stages in which complications could lead even to his/her death.

The manifestation or detection of late hemorrhages in a small proportion of these cases with atypical behavior, as well as the impossibility of ruling them out in the rest of the patients, in addition to the lack of an adequate reference pattern, has caused the consequence of classifying these cases as HDF, which may be reflected in an inadequate estimation of the individual risk and problem. This fact makes evident the need of a permanent screening not only of the clinical profile of the cases, but also of the different agents that may cause diseases similar to dengue, with the purpose of really knowing the magnitude of the problem and to better the attention by means of defining diagnostic criteria and operational definitions[41] which allow decreasing the risk of complications and death, and optimize, at the same way, the resources.

Currently, the classification proposed by the WHO-PAHO[5] is currently being evaluated in different countries, which allows the evaluation of the condition of the patient and establishes the steps to follow according to non-severe and severe Dengue. However, using this classification, the patients with thrombocytopenia and hemoconcentration described here would be classified as non-severe Dengue with alarm signs; institutional experience has proven that these patients can suddenly worsen and crash and even die. Thus, the concern in using the non-severe term, for it might generate a false sense of safety. The proposal is to eliminate this term and focus in Dengue as one disease that can present different degrees of severity, and that must be carefully monitored to avoid complications. It is important to consider that this proposal in the WHO is only for the clinical approach of the disease, and that the classification should be defined according to the epidemiological point of view to know the real magnitude of the problem and in which, up to now, the classification of DF and HDF established by the ICD-10[42] is still used.

It is important to continue this research to establish the relation that there exists among the immunologic background of the population and the dengue viruses, and the genotypes isolated in the country with the expression of the disease[43] and the presence of thrombocytopenia,[44,45] as well as for the pathofysiological implications that represents[46,47] for the presence of hemorrhages and the evolution of the patient. In this way, we target to better the criteria to asses the severity of the cases. In regards to this, the flow of the obtained information is essential to offer the first-level doctor, elements that serve as basis to ensure an adequate handling and a favorable prognosis for the patients with this disease who demand attention.

Finally, it is a constant the fact of imminent danger for the increase of many diseases, specifically those of viral origin, transmitted by phenomenon vector that is already occurring in our country, where we currently find hyperendemic areas to dengue, with a permanent spread of this and other diseases that share the ecological niche, such as Leptospirosis. For this reason, it is important the orchestration of integral strategies that will allow us identify and control this group of diseases, based in the joint participation of authorities and community.

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