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## SYNDROMIC SURVEILLANCE: ETIOLOGIC STUDY OF ACUTE FEBRILE ILLNESS IN DENGUE SUSPICIOUS CASES WITH NEGATIVE SEROLOGY. BRAZIL, FEDERAL DISTRICT, 2008

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### SUMMARY

With the aim of identifying the etiology of acute febrile illness in patients suspected of having dengue, yet with non reagent serum, a descriptive study was conducted with 144 people using secondary serum samples collected during convalescence. The study was conducted between January and May of 2008. All the exams were re-tested for dengue, which was confirmed in 11.8% (n = 17); the samples that remained negative for dengue (n = 127) were tested for rubella, with 3.9% (n = 5) positive results. Among those non reactive for rubella (n = 122), tests were made for leptospirosis and hantavirus. Positive tests for leptospirosis were 13.9% (n = 17) and none for hantavirus. Non reactive results (70.8%) were considered as Indefinite Febrile Illness (IFI). Low schooling was statistically associated with dengue, rubella and leptospirosis (p = 0.009), dyspnea was statistically associated with dengue and leptospirosis (p = 0.012), and exanthem/petechia with dengue and rubella (p = 0.001). Among those with leptospirosis, activities in empty or vacant lots showed statistical association with the disease (p = 0.013). Syndromic surveillance was shown to be an important tool in the etiologic identification of IFI in the Federal District of Brazil.

**KEYWORDS:** Epidemiological surveillance; Syndromic surveillance; Dengue; Rubella; Leptospirosis.

### INTRODUCTION

The use of syndromic surveillance in acute febrile diseases has been an important tool for detecting indefinite febrile illnesses<sup>31</sup>. Experiments putting this working model into operation were tested based on the surveillance of dengue fever with the intention of diagnosing leptospirose<sup>6,22</sup> during the surveillance of acute exanthematous febrile illness for identifying cases of dengue and rubella<sup>12</sup> and during the outbreak of acute illness, when cases of dengue, leptospirosis, meningococcal disease and hantavirus were suspected<sup>23</sup>.

The nonspecific clinical manifestations of fever, headache and myalgia are common in cases of hantavirose<sup>3,11,16,20</sup>, rubella<sup>12</sup>, dengue fever, and leptospirosis; the prodromes of which are similar to each other and to other viral diseases. Information based on epidemiological history and specific laboratory findings<sup>16</sup> are important for conclusive diagnosis. Thus, the use of differential diagnosis from the surveillance of acute febrile diseases is important since it contributes significantly to the elucidation of the etiology of these indefinite diseases<sup>3,10,20</sup>.

In the Federal District, nearly 70.0% of suspected dengue fever cases are ruled out by serology, indicating that this disease is the first diagnosis hypothesis<sup>13</sup> for health professionals.

This study used syndromic surveillance in order to identify the etiology of acute febrile diseases in serologically nonreactive individuals

who were suspected cases of dengue, aiming at expanding the etiologic knowledge of these syndromes in the Federal District.

### METHODS

This is a descriptive case sample developed in a specific demand population seen at the Federal District Central Public Health Laboratory (Lacen/DF) from January to May 2008, which corresponds to the rainy season. To select the sample, results of serological tests contained in the epidemiological reports generated by Lacen/DF were used.

Among the 877 eligible patients with acute febrile illness seen during the period studied, each week from eight to ten randomly sampled participants were selected, totaling 144 participants. The order of testing was determined by epidemiological characteristics of these diseases in the population of the Federal District. The sample was calculated by the formula<sup>17</sup>  $n = pq/E^2$ , where "p" means the prevalence of the diseases in question, which was drawn from the data on rubella, leptospirosis and hantavirus infection, confirmed through the Information System for Notifiable Diseases (SINAN) from 2001 to 2006, and "q" represents the percentage of people who did not present with the diseases investigated. (E<sup>2</sup>) of  $\pm 2.5\%$  and a CI of 95% were considered. Subsequently, an interview was set up by telephone with the patient's consent, after which serological material was collected. Those patients who refused to be interviewed were excluded from the study.

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The samples were collected a maximum of 28 days after the onset of symptoms. All sera samples were re-tested for dengue. Samples that were not reactive for dengue were used for the detection of rubella. Tests for leptospirosis were conducted on the samples that were negative for rubella, and those that were negative for leptospirosis were processed for hantavirus. It is important to emphasize that the observed denominators were different depending on the exclusion of positive tests conducted after the confirmation of dengue and other diseases. The protocol did not include testing for co-infections.

The ELISA method was used for detection of IgM with the commercial PANBIO reagent for dengue and the MAC-ELISA (Evandro Chagas Institute) method was used for inconclusive cases. For identification of rubella IgM, Behring's commercial reagent was used, and for leptospirosis, the Bio-Manguinhos's commercial reagent was used. Tests for hantavirus used the reagent with Andes Hantavirus antigens produced by the Malbrán Institute (Buenos Aires, Argentina).

Statistical analysis applied the exact chi-square ( $\chi^2$ ) when over 20% of the expected frequencies were less than five with  $p \leq 0.05$  and then the frequencies and percentages were evaluated. The data were processed using Statistical Analysis Software (SAS) version 9.1.3. The study was submitted to and approved by the Brazilian Federal District Healthcare Secretary Council on Ethics in Research (Opinion No. 215/2007).

## RESULTS

The etiology of 27.1% of cases (39/144) of patients with acute febrile syndrome was identified. In 11.8% (17/144) of those investigated ( $CI_{95\%}$ : 6.47-17.14%) were diagnosed with dengue (Table 1). Rubella was confirmed in 3.9% of the patients, i.e., 5/127 of the samples that were negative for dengue ( $CI_{95\%}$ : 0.51-7.42%). The diagnosis of leptospirosis was made in 13.9% of patients, representing 17/122 negative sera for rubella ( $CI_{95\%}$ : 7.84-20.50%). No cases of hantavirus were identified. Among the samples tested, one was inconclusive for rubella and two had indeterminate results for leptospirosis. The remaining 102 serology samples (70.8%) tested negative for the diseases investigated, and were classified as acute indefinite febrile illness (IFI).

**Table 1**

Reagents for the serological diagnosis of dengue, rubella and leptospirosis, Federal District, January to May 2008

Disease	n	Reagent	%	CI <sub>(95%)</sub>
Dengue	144	17	11.8	6.47 - 17.14
Rubella	127	5	3.9	0.51 - 7.42
Leptospirosis	122	17	13.9	7.84 - 20.50

Regarding the results of confirmed cases by disease and sex (Table 2), there was a higher proportion of women in all the diseases studied, although this difference was not statistically significant ( $p = 0.956$ ). The age group of 20 years old and over was the most represented in all the febrile diseases, without statistical significance ( $p = 0.185$ ). With respect to race/color, among the confirmed dengue cases, 47.1% were white, 29.4% black, and 23.5% were mulatto. Considering the patients identified with rubella according to race or color, 40.0% were white,

40% mulatto, and 20.0% Asian. In patients diagnosed with leptospirosis, 64.7% reported being mulatto. In the IFI group, 51.0% of the respondents considered themselves to be mulatto. In the comparison of cases relating race/color of patients with dengue, rubella and leptospirosis, a statistically significant difference ( $p = 0.035$ ) was found.

With regard to educational level (Table 2), 62.5% of those with one to three years of education were affected by dengue and 25.0% with leptospirosis. IFI was more present in the groups with 4-7, 8-11, and 12 years or more of education, representing 75.8%, 74.3% and 77.8% respectively. When comparing the association between years of education and the profile of febrile illness, there was statistical difference ( $p = 0.009$ ).

In evaluating the clinical manifestations presented by patients with dengue, 100% of the cases reported myalgia, 94.1% headache and exhaustion, 82.3% retro-orbital pain, and 82.2%, arthralgia and inappetence. As noted among the clinical cases of rubella, 100.0% of those investigated reported headache and exhaustion, while 80.0% were noted in each of the following categories: myalgia, arthralgia, inappetence, exanthem/petechia, and dyspnea. In the group of patients diagnosed with leptospirosis, 94.1% had headache and myalgia, and 82.2%, exhaustion, retro-orbital pain, and arthralgia. Among the IFI group, the most frequent symptoms included myalgia (98.0%), headache (97.0%), exhaustion (95.1%), and arthralgia (82.3%). In the comparison of dyspnea in dengue and leptospirosis cases ( $p = 0.012$ ) and the findings of exanthem/petechia in cases of dengue and rubella ( $p = 0.000$ ) show statistical differences.

When considering infection with leptospira and occupational exposure of patients in this sample (Table 3), 41.7% of patients performed activities in vacant lots, with statistical significance ( $p = 0.013$ ). The remaining patients diagnosed with leptospirosis had other exposures, such as breeding animals ( $p = 0.289$ ), contact with rats ( $p = 0.534$ ), grease traps ( $p = 0.705$ ), water tanks and septic tanks ( $p = 1.000$ ) each, trash/debris ( $p = 0.417$ ), water/mud ( $p = 0.258$ ), and rivers/streams ( $p = 0.4170$ ), without statistical significance.

In regards to the temporal distribution of dengue fever by month of onset of symptoms, 41.7% of infections occurred in January, 29.4% in February, 11.8% in both March and in April, and 5.9% in May. In January, 60.0% of patients were affected by rubella and the remaining cases (20.0%) were recorded between February and April. Leptospirosis comprised 23.5% of patients between January and February, 35.3% in March, 11.8% in April, and 5.9% in May. In the IFI group, the onset of symptoms was present in 14.7%, 19.6%, 25.5%, 22.5% and 17.6% in January, February, March, April, and May, respectively (Fig. 1).

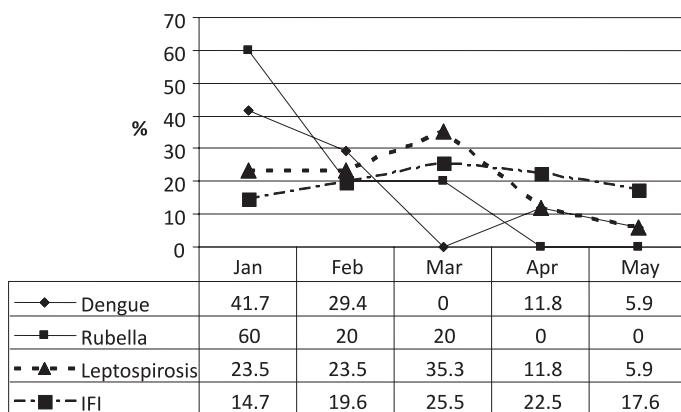
## DISCUSSION

The proportion of positive dengue, leptospirosis and rubella found in this study was 27.1% among cases of acute febrile illness in the Federal District. A similar study conducted in Venezuela in 1998 established the etiology of dengue fever, rubella, Epstein-Barr virus, and cytomegalovirus in 77.9% of cases<sup>12</sup>. In Jaen, Peru, a study carried out between 2004 and 2005 identified 65.4% of diseases, including malaria, leptospirosis, dengue, Rickettsia and Bartonellosis<sup>31</sup>. These differences in the proportions observed in the diagnostic confirmation between the Federal District study and the others are probably due to the period of observation, as this paper only addressed the first five months of the

**Table 2**  
Reagents for the serological diagnosis of dengue, rubella and leptospirosis, Federal District, January to May 2008.

Variables	Dengue n (%)	Rubella n (%)	Leptospirosis n (%)	IFI n (%)
<b>Sex (p = 0.956)</b>				
Female	9 (52.9)	3 (60.0)	10 (58.8)	62 (60.8)
Male	8 (47.1)	2 (40.0)	7 (41.2)	40 (39.2)
<b>Age range (p = 0.185)</b>				
10 - 19	-	-	3 (17.6)	18 (17.6)
20 - 29	2 (11.8)	4 (80.0)	5 (29.5)	27 (26.5)
30 - 39	6 (35.3)	-	4 (23.5)	22 (21.6)
40 - 49	4 (23.5)	1 (20.0)	3 (17.6)	18 (17.6)
50 and over	5 (29.4)	-	2 (11.8)	17 (16.7)
<b>Race/skin color (p = 0.035)</b>				
White	8 (47.1)	2 (40.0)	5 (29.4)	31 (30.4)
Black	5 (29.4)	-	1 (5.9)	18 (17.6)
Asian	-	1 (20.0)	-	1 (1.0)
Mullato	4 (23.5)	2 (40.0)	11 (64.7)	52 (51.0)
<b>Schooling*(p = 0.009)</b>				
None	-	-	-	3 (100.0)
1-3 years	5 (62.5)	-	2 (25.0)	1 (12.5)
4-7 years	4 (12.1)	-	4 (12.1)	25 (75.8)
8-11 years	4 (5.7)	4 (5.7)	10 (14.3)	52 (74.3)
12 years or more	4 (14.8)	1 (3.7)	1 (3.7)	21 (77.8)

p-value for exact  $\chi^2$  test; \* Years of schooling.



**Fig. 1** - Percentage of positive reactions for dengue, rubella, leptospirosis and IFI according to the month of symptom onset, Federal District, 2008.

year, while the other studies gathered data during a longer period of observation.

Confirmation of dengue accounted for 11.8% of all the cases investigated. A survey from patients suspected of having leptospirosis<sup>13</sup>

in Barbados in 1995, 1996, and 1997, identified 44.0%, 33.0%, and 42.0%, respectively. In Vietnam, in 2001, the percentage of dengue diagnosis identification was 33.4% during an investigation of acute indefinite febrile illness<sup>19</sup>. Finally, it is worth noting that the findings mentioned above showed percentages that were higher than those values observed in the Federal District; however, they initiated their studies to investigate diseases other than dengue and extended them for longer periods of observation.

The confirmed diagnosis of rubella in this sample was 3.9%, lower than the percentage found in Zulia, Venezuela (1998) and in Niteroi, Rio de Janeiro, Brazil (1994 to 1998), from exanthematic diseases, with observed frequencies of 38.2% and 21.0% for rubella, respectively<sup>12,15</sup>. Another survey of suspected dengue cases in Yucatan, Mexico (1988 to 2001) as described by BUSTOS *et al.*<sup>7</sup> showed a detection of 10.0% of subjects with rubella. In Venezuela, VALERO & MALDONADO<sup>32</sup> also found 1.2% of rubella from the presumptive diagnosis of dengue in the period 1998 to 2001. It should be emphasized that in 2007 there was a marked increase of the rubella virus in some Brazilian municipalities<sup>5</sup>, the consequences of which were felt in the Federal District by the increased vaccination of high risk groups. Possibly, this fact accounts for the low proportion of positive results found, reflecting the end of the rubella outbreak in the Federal District.

**Table 3**

Types of exposure among patients with leptospirosis, Federal District, January to May 2008

Exposure	Leptospirosis				P
	No		Yes		
	n	%	n	%	
<b>Breeding animals</b>					0.289
Yes	39	81.2	9	18.7	
No	64	88.9	8	11.1	
<b>Contact with rats</b>					0.534
Yes	19	90.5	2	9.5	
No	82	84.5	15	15.5	
<b>Grease traps</b>					0.705
Yes	10	90.9	1	9.1	
No	93	85.3	16	14.7	
<b>Water tanks</b>					1.000
Yes	2	100	-	0.0	
No	101	85.6	17	14.4	
<b>Septic tanks</b>					1.000
Yes	2	100	-	0.0	
No	101	85.6	17	14.4	
<b>Vacant lots</b>					0.013
Yes	7	58.3	5	41.7	
No	96	88.9	12	11.1	
<b>Trash/debris</b>					0.417
Yes	11	78.6	3	21.4	
No	92	86.8	14	13.2	
<b>Water/mud</b>					0.258
Yes	28	80	7	20.0	
No	75	88.2	10	11.8	
<b>Rivers/streams</b>					0.417
Yes	11	78.6	3	21.4	
No	92	86.8	14	13.2	

p-value for exact  $\chi^2$  test.

Diagnostic confirmation of leptospirosis from suspected dengue cases with nonreactive serology showed a positive rate of 13.9%. Studies using syndromic surveillance from reports of suspected dengue, such as the LIBRATY *et al.*<sup>14</sup> study in the city of Kamphaeng Phet, Thailand from 1994 to 1999, found an incidence of 19.0%. In Puerto Rico (1996), 27.0% of leptospirosis<sup>22</sup> cases were detected after discarding dengue suspect cases. Mato Grosso do Sul, Brazil, (2000 to 2001) showed a rate of 15.9%<sup>26</sup> from suspected dengue and viral hepatitis cases. In comparison with other studies cited, the similarities are evident, except in relation to the survey conducted in Puerto Rico. In the Federal

District, the high incidence of leptospirosis became evident as a result of the anicteric hepatitis outbreak among patients who sought the health care system. It should be noted that the study also allowed clarification of the diagnosis, especially when the discarded cases of dengue were submitted to syndromic surveillance, confirming the studies mentioned previously.<sup>13,14,18,22,26</sup>.

On the other hand, labor performed in vacant lots showed statistical significance. The literature has pointed to epidemiological data on the transmission of leptospira to people who are exposed to water that has been contaminated by rat urine, especially during the rainy season<sup>2,28</sup>, during occupational and recreational activities in rainwater and runoff<sup>24,27</sup>, not to mention a close relationship with the socio-economic conditions of the population<sup>1,26</sup>. Based on the literature, it seems permissible to think that the transmission of leptospirosis in the survey area was related to exposures at home and at work, since the hydrographic formation does not favor basin flooding and basic sanitation reaches almost the entire urban Federal District population.

The relationship between self-reported race/color and illness/disease showed a statistically significant difference for dengue and whites and blacks, rubella and whites, and leptospirosis and mulattos. The risk of developing dengue hemorrhagic fever, in a study by TORRES<sup>30</sup>, demonstrates that a higher incidence occurred with whites as compared to blacks. According to data from 2007 to 2008 in Brazil, nearly 60.0% of patients diagnosed positive for rubella and leptospirosis were white<sup>4</sup>, a result which coincides with our findings for rubella, but differs for leptospirosis.

A statistically significant association was observed among those interviewed with 1-3 years of education and dengue and leptospirosis, as well as among those who had more years of education and rubella and IFI. VASCONCELOS *et al.*<sup>33</sup> found no correlation between dengue and schooling in Ceara, Brazil in 1994. In Salvador, Bahia, Brazil, in 1998, it was found that the higher the education level, the lower the incidence of dengue<sup>29</sup>; an association between lower education and leptospirosis was also observed<sup>9</sup>. In summary, research suggests some uncertainty as to the association of schooling with dengue.

The manifestations of the main signs and symptoms present in the definition of suspected dengue "cases" were present in more than 80.0% of the diseases diagnosed in this study, except retro-orbital pain with the occurrence of rubella. Dyspnea was statistically associated with dengue and leptospirosis, while exanthem/petechia was associated with dengue and rubella. Some studies in the investigation of dengue, leptospirosis, and exanthem diseases attested to clinical manifestations of fever, myalgia, headache, and exhaustion similar to the sample in the present study, while in other studies, the percentages were below 80.0%<sup>8,10</sup>. This evidence reinforces the difficulty of purely clinical differentiation in diagnostic elucidation<sup>10,11,14</sup> of acute febrile disease and the relevance of syndromic surveillance to identify these etiologies.

When analyzing the question of the seasonality of acute febrile diseases, the highest occurrence of dengue fever was observed in the first quarter of the year, with 79.5% of the cases, an epidemiological pattern similar to that found by SMITH *et al.*<sup>25</sup> in Brazil. The seasonal observation of cases of leptospirosis in the Federal District resembles the historical dataset (1967 to 1977) collected in San Paulo<sup>21</sup>, which coincides

with findings from the literature that identified a greater transmission of dengue and leptospirosis during the rainy season<sup>1</sup>.

### CONCLUSION

This study highlighted an increase in the diagnosis of dengue, rubella, and leptospirosis in unconfirmed cases of dengue, highlighting the importance of the syndromic approach towards acute febrile diseases resulting from the expansion of surveillance. Moreover, this strategy reduced the underreporting of acute febrile diseases in the Federal District, allowing for a better understanding of the epidemiology of such diseases, in addition to promoting more effective control measures.

### FINAL THOUGHTS

To strengthen the surveillance of acute febrile syndromes through the surveillance of dengue, the study results indicate the following needs:

1. For patients suspected of dengue and who fit the case definition, epidemiological research should consider the possibility of risk exposure to leptospirosis and/or recent contact with exanthematic cases, thus widening the scope of the investigative framework.
2. During the investigation of exanthematic cases, consider the possibility of dengue.
3. When confronted with a negative serology result for dengue, consider all the clinical manifestations presented and evaluate the possibility of a new serology, since the initial serology may not have presented titers of detectable antibodies.
4. Develop a protocol for acute febrile syndromes, focusing on care, and epidemiological and laboratory surveillance.
5. Train human resources in terms of health services, epidemiological, and laboratory surveillance focusing on acute febrile syndromes.

### RESUMO

#### **Vigilância sindrômica: estudo etiológico de doenças febris agudas a partir dos casos suspeitos de dengue com sorologia não reagente. Distrito Federal, Brasil, 2008**

Com o objetivo de identificar a etiologia de doenças febris agudas, em suspeitos de dengue com sorologia não reagente, realizou-se estudo descritivo com 144 pessoas utilizando amostras de soro coletados na convalescença, entre janeiro e março de 2008. Todos os exames foram re-testados para dengue, sendo as amostras negativas, processadas para rubéola (n = 127). Dentre as não reagentes para rubéola, submeteu-se ao teste para leptospirose (n = 122), e em se permanecendo sem diagnóstico, testou-se para hantavirose. Confirmou-se dengue em 11,8% (n = 17), rubéola em 3,9% (n = 5) e leptospirose em 13,9% (n = 17). Os resultados não reagentes foram considerados como doença febril aguda indiferenciada (DFI) em 70,8% dos casos. Verificou-se associação estatística em baixa escolaridade nos casos de dengue, rubéola e leptospirose (p = 0,009), assim como dispnéia para dengue e leptospirose (p = 0,012), e exantema/petéquias para dengue e rubéola (p = 0,001). Dentre os doentes com leptospirose, as atividades em terreno baldio mostraram-se com diferença estatística significativa (p = 0,013). A vigilância sindrômica demonstrou-se como importante ferramenta na identificação de doenças febris agudas no Distrito Federal.

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