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BRIEF COMMUNICATION

A NEW POSSIBILITY FOR SURVEILLANCE: DO WE IDENTIFY ALL CASES OF LEPTOSPIROSIS?

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SUMMARY

Leptospirosis is a febrile disease with a typically underestimated global incidence, especially in regions where dengue is endemic. Therefore, it is difficult to accurately determine the number of leptospirosis cases in these areas, which contributes to significant under-reporting this disease. In this study, we estimated the number of possible leptospirosis cases among dengue-like cases that were reported during 2008, 2010, and 2012 in the city of Fortaleza, northeast Brazil. Patients were evaluated for dengue and leptospirosis using immunoenzymatic tests for IgM antibodies that were specific to each pathogen. Among the suspected cases of dengue that resulted as negative in laboratory tests, 10.8% (2008), 19.2% (2010), and 30.8% (2012) were confirmed to be leptospirosis. Considering the cases reported by the surveillance authority as dengue that were subsequently discarded based on the laboratory test results, we estimate that the number of actual leptospirosis cases may be 26 to 49 times higher than those diagnosed and reported by the Health Services. Furthermore, we believe that approximately 20% of dengue-like cases may be leptospirosis cases in areas where the two diseases are endemic.

KEYWORDS: Leptospirosis; Dengue; Estimation techniques; Epidemiological surveillance; Sentinel surveillance.

Leptospirosis is a sudden-onset, systemic febrile infectious disease that is caused by pathogenic spirochetes that belong to the *Leptospira* genus. This condition is one of the most widely distributed zoonoses worldwide, and is typically endemic in tropical regions[3,26]. The clinical manifestations of leptospirosis vary from an undifferentiated fever syndrome to multiple organ failure and death[2,3]. Symptomatic patients exhibit various non-specific symptoms, such as fever, headache, myalgia, anorexia, nausea, vomiting, diarrhea, arthralgia, eye pain, and cough[12].

Given this range of non-specific clinical symptoms, it is difficult to distinguish leptospirosis from other severe febrile diseases using only their unique clinical and epidemiological criteria[8]. Therefore, several studies have reported challenges in the differential diagnosis of leptospirosis and dengue, as both have similar clinical profiles and seasonal onset, with predominance in the rainy season. This has led to an overestimation of the number of dengue cases in various locations, with a possible concurrent underestimation of the number of leptospirosis cases[6,14,16,22,24,25]. Furthermore, the lack of symptom specificity, low sensitivity of the diagnostic methods, and passive characteristics of the surveillance systems in the majority of affected countries hinder the accurate reporting of the incidence and prevalence of human leptospirosis[1,4]. Therefore, the aim of this study was to estimate the number of possible leptospirosis cases among dengue-like cases, in areas where both diseases are endemic and a structured dengue surveillance system is available.

In this study, we estimated the number of leptospirosis cases among patients with dengue-like symptoms in the city of Fortaleza, northeast Brazil. This study was conducted by recruiting patients who were suspected of having dengue during 2008, 2010, and 2012. Blood samples were collected for serological analysis from patients with suspected dengue who were being treated at the Sao Jose Hospital of Infectious Diseases, and other health facilities. In each study year, active surveillance was performed every month (three times per week in the afternoon) in the wards and outpatient clinics. All patients who exhibited more than five days of symptoms and met the definition of a suspected dengue case, as defined by the Ministry of Health (acute febrile illness accompanied by at least two of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, prostration, and/or rash) were included.

Using the patients' blood samples, the presence of dengue and leptospirosis was evaluated using immunoenzymatic assays to detect IgM antibodies that are specific for each pathogen (Panbio Dengue IgM Capture ELISA® (Australia); Dengue IgM ELISA Test® Bioeasy (Brazil),

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Serion ELISA *classic* Leptospira IgM® VIRION\SERION (Germany) and Panbio Leptospira IgM ELISA® (Australia)). Only cases that were negative for dengue antibodies were subsequently tested for the presence of leptospirosis.

In the first study year (2008), 62 patients with clinically suspected dengue were identified (Table 1). Among these patients, 25 (40.3%) were confirmed to have dengue and 37 (59.7%) were negative for dengue; the dengue-negative cases were considered to be "dengue-like" cases. Among the dengue-like cases, four (10.8%) cases were positive for leptospirosis. In 2010, 57 patients with suspected dengue were identified, and 26 (45.6%) patients were found to be negative for dengue, including five (19.2%) patients who were confirmed to have leptospirosis. In 2012, 50 patients with suspected dengue were identified, and 13 (26.0%) patients were found to be negative for dengue, including four (30.8%) patients who were positive for leptospirosis. Therefore, among the dengue-like cases, 10.8% (2008), 19.2% (2010), and 30.8% (2012) of cases were confirmed to be leptospirosis.

In the study period, the Health Secretary of Ceara, Fortaleza, Brazil, reported 39,077 (2008), 7,017 (2010), and 43,596 (2012) suspected cases of dengue (Table 1)[21]. However, among these cases, 4,534 (11.6%), 2,235 (31.9%), and 4,629 (10.6%) cases, respectively, were discarded for dengue for showing dengue-negative laboratory results (the dengue-like cases)[21]. In addition, 4,846, 1,030, and 3,756 patients, respectively, were confirmed to have dengue using only the clinical and epidemiological criteria in this period[21].

In that same period, the Health Secretary's laboratory reported only 19 (2008), 17 (2010), and 29 (2012) confirmed cases of leptospirosis[21]. According to our estimated prevalence of leptospirosis among dengue-like cases in those years, 490, 429, and 1,426 leptospirosis cases may not have been identified by the Health Services. Based on these numbers, approximately 26 to 49 unidentified leptospirosis cases may exist for each confirmed case in Fortaleza. On average, we estimated that approximately 20.3% of dengue-like cases per year may be leptospirosis cases in areas where both diseases are endemic.

Our data corroborate the findings of RAFIZAH *et al*. (2003), who reported that 8.4% of the Malaysian fever syndrome cases that they investigated were actually leptospirosis cases, indicating a high prevalence in a region where leptospirosis is often underestimated[23].

Among the cases we analyzed, 7.7% (13/169) of patients with clinically suspected dengue were positive for leptospirosis. Several studies have demonstrated that the differential diagnosis of dengue and leptospirosis is difficult in tropical regions where both diseases are endemic[5,6,24]. Furthermore, the early and accurate diagnosis of leptospirosis is of utmost importance for effective clinical management, as the appropriate treatments for dengue and leptospirosis are substantially different. For example, antibiotic therapy is more effective for reducing the duration and severity of leptospirosis when applied early in the course of infection[9], and delays in the prescription of antibiotic therapy may result in progression to more severe forms[19].

The difference in the number of leptospirosis cases that we estimated in 2012 (compared to those in 2008 and 2010) is likely due to the lower number of samples that were collected in 2012, and the fact that a significant dengue epidemic occurred during 2012 in Fortaleza. In the event of a dengue epidemic, our observed values might be overestimated, given the increased sensitivity of the epidemiological surveillance system in capturing suspected cases. However, our findings suggest that the real number of leptospirosis cases might be far greater than that detected by the Health Secretary, since during the period of study only 65 leptospirosis cases were confirmed by the Health Service, whereas we estimate an occurrence of 2,345 cases. This discrepancy is likely due to the health system's ability to capture the most severe cases, resulting in an underestimation of the real incidence of the disease[11].

One of the factors that contributes to the overestimation of dengue cases is when this infection is confirmed just by clinical and epidemiological criteria. The use of these criteria as the only basis for dengue diagnosis may be risky and may lead to diagnostic failures, due to its nonspecific symptoms, which are similar to those of other pathologies, like leptospirosis[7,10,20]. However, given the high number of suspected dengue cases during epidemic periods in Brazil, confirmation of a dengue case can be made only with clinical and epidemiological assessments. Thereby, during the study period, 9,632 dengue cases were confirmed by the Health Services using only clinical and epidemiological criteria. Despite the high number of cases, these patients were not included in

Table 1
Estimation of the number of leptospirosis cases in Ceara in 2008, 2010 and 2012

A: Dengue and leptospirosis in the city of Fortaleza[24]	**2008**	**2010**	**2012**
Reported cases of dengue	39,077	7,017	43,596
Confirmed cases of dengue through laboratory criteria	29,697	3,752	35,211
Confirmed cases of dengue through clinical and epidemiological criteria	4,846	1,030	3,756
Excluded cases of dengue (dengue-like cases) in the laboratory	4,534	2,235	4,629
Confirmed cases of leptospirosis	19	17	29
B: Study findings			
Estimated cases of under-reported leptospirosis	490	429	1.426
Estimation of under-reporting for leptospirosis cases	25, 8:1	25, 2:1	49, 2:1

Source: A: Health Secretary of the State of Ceara, 2014 (data not published)**; B:** Study findings.

our estimation of unidentified leptospirosis cases, as we only included patients with dengue-negative test results (dengue-like cases). Therefore, it is possible that dengue confirmed cases, with no specific laboratory testing, were leptospirosis cases, and these would further increase our estimated number of unidentified cases of leptospirosis.

It is important to emphasize that 37.3% (63/169) of our patients with clinically suspected dengue did not have a specific diagnosis, as they were categorized as having neither dengue nor leptospirosis, or because these diseases were not detected by the methodologies adopted in this study or in the routine surveillance services. Therefore, one of this study's limitations was the use of only serology to detect these pathologies; a combination of different techniques would likely increase the diagnostic sensitivity[10,26]. Another limitation was that we did not test dengue-positive patients for leptospirosis, which may have resulted in the exclusion of cases with co-infection.

Several studies have demonstrated that it is difficult to differentially diagnose dengue from other pathologies (e.g., hantavirus, rubella, hepatitis, influenza A infection, or melioidosis), which may account for some of the cases of fever symptoms that were not diagnosed as leptospirosis in this study[17,18,25]. Those studies' findings highlight the importance of using surveillance protocols for fever syndromes, and the implementation of these systems in Brazil may facilitate the early detection of new diseases with similar clinical characteristics, such as chikungunya fever.

Gaining a more realistic view of leptospirosis cases is important and essential to adopt adequate control measures for the reservoirs and provide support for preventive measures. In addition, the adoption of a specific treatment in the leptospirosis cases can directly reduce morbidity and mortality risks associated with the disease. It would be important to implement measures that allow performing tests in a percentage of the negative samples for dengue, as a form of sentinel surveillance for leptospirosis cases.

RESUMO

Uma nova possibilidade de vigilância: identificamos todos os casos de leptospirose?

A leptospirose é doença febril tipicamente subestimada em todo o mundo, principalmente em áreas que a dengue se apresenta de forma endêmica. Desta forma, há limitações importantes na compreensão do número de casos de leptospirose nessas áreas, o que proporciona maior subnotificação. Neste estudo, apresentamos estimativa de possíveis casos de leptospirose a partir de casos de dengue-símile na cidade de Fortaleza, nordeste do Brasil, durante os anos de 2008, 2010 e 2012. Os pacientes foram investigados para dengue e leptospirose utilizando testes imunoezimáticos para detecção do anticorpo, da classe IgM, específicos para cada patologia. Entre os casos suspeitos de dengue, mas que não apresentaram resultado laboratorial positivo, 10,8%; 19,2% e 30,8% foram confirmados como leptospirose nos anos de 2008, 2010 e 2012; respectivamente. Considerando os casos notificados pela vigilância de dengue e que foram, posteriormente, descartados, baseados nos resultados dos testes laboratoriais, estimamos que o número atual de casos de leptospirose pode ser de 26 a 49 vezes mais do que o detectado e notificado pelos serviços de saúde. Além disso, acreditamos que aproximadamente 20% dos casos de dengue-símile podem ser de leptospirose, em áreas onde as duas doenças ocorram de forma endêmica.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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