



## Leptospirosis among patients presenting with dengue-like illness in Puerto Rico

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### Abstract

Leptospirosis is difficult to distinguish from dengue fever without laboratory confirmation. Sporadic cases/clusters of leptospirosis occur in Puerto Rico, but surveillance is passive and laboratory confirmation is rare. We tested for leptospirosis using an IgM ELISA on sera testing negative for dengue virus IgM antibody and conducted a case–control study assessing risk factors for leptospirosis, comparing clinical/laboratory findings between leptospirosis (case-patients) and dengue patients (controls). Among 730 dengue-negative sera, 36 (5%) were positive for leptospirosis. We performed post mortem testing for leptospirosis on 12 available specimens from suspected dengue-related fatalities; 10 (83%) tested positive. Among these 10 fatal cases, pulmonary hemorrhage and renal failure were the most common causes of death. We enrolled 42 case-patients and 84 controls. Jaundice, elevated BUN, hyperbilirubinemia, anemia, and leukocytosis were associated with leptospirosis ( $p < .01$  for all). Male

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sex, walking in puddles, rural habitation, and owning horses were independently associated with leptospirosis. Epidemiological, clinical, and laboratory criteria may help distinguish leptospirosis from dengue and identify patients who would benefit from early antibiotic treatment.

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## 1. Introduction

Leptospirosis is a zoonotic disease of worldwide distribution caused by spirochetes of the genus *Leptospira* (Farr, 1995; Tappero et al., 1999). Human infection results from exposure to water, soil, or mud contaminated by infected animal urine or other body fluids (Acha and Szyfres, 1987). In the 1990s, several leptospirosis outbreaks in the Americas were associated with flooding or increased rainfall, including an outbreak in Puerto Rico in 1996 following flooding from hurricane Hortense (CDC, 1996, 1998; Morgan et al., 2002; Sanders et al., 1999; Trevejo et al., 1998). While this and other clusters have been reported in Puerto Rico, the burden of leptospirosis in Puerto Rico is unknown. Early clinical signs and symptoms of leptospirosis are non-specific and similar to other febrile illnesses in the tropics, such as dengue fever (Zaki and Spiegel, 1998). Both leptospirosis and dengue fever have well recognized severe forms of disease, which may manifest with hemorrhage (Faine, 1998; Halstead, 1992). Definitive diagnosis of leptospirosis requires confirmation by culture, serology, polymerase chain reaction (PCR), or immunohistochemistry (IHC). Many of these laboratory tests are labor intensive, have variable sensitivity, and are available only at reference centers (Tappero et al., 1999). Antibiotic therapy has been demonstrated to be effective in the treatment of leptospirosis (Watt et al., 1988). The ability to distinguish acute leptospirosis from dengue fever is important because early antibiotic therapy may improve outcome in leptospirosis.

The Center for Disease Control and Prevention (CDC) has had a surveillance system for dengue fever in Puerto Rico for over 25 years. Because signs and symptoms of dengue fever may be similar to those of leptospirosis, we used this system to identify cases of leptospirosis among persons testing negative for dengue fever. Our objectives were to estimate the incidence of leptospirosis among patients presenting with febrile illness suspected to be dengue fever, identify

risk factors for leptospirosis, and examine clinical features that may assist in distinguishing leptospirosis from dengue fever in this population.

## 2. Materials and methods

### 2.1. Study population and surveillance review in Puerto Rico

Puerto Rico is a Caribbean island with a population of 3.8 million residing in 78 municipalities. Surveillance for dengue fever in PR is performed jointly by the Puerto Rico Department of Health (PRDH) and the CDC Dengue Branch (CDC-DB). The CDC-DB receives serum specimens obtained from suspected dengue patients seen at public health and private hospitals and clinics throughout the island (Rigau-Perez et al., 1994). A suspected case of dengue fever was defined as any case with clinical features consistent with dengue fever (as determined by the local physician) from whom a diagnostic sample was submitted to the CDC-DB for dengue testing. A laboratory-positive case of dengue fever was defined as any suspected case that has been confirmed by viral isolation or enzyme-linked immunosorbent assay (ELISA). Serum samples collected less than 6 days after onset of illness were either processed for virus isolation in C6/36 mosquito cell cultures or inoculated into *Toxorhynchites amboinensis* mosquitoes. Dengue viruses were identified by the use of serotype-specific monoclonal antibodies in an indirect fluorescent antibody test on virus-infected cell cultures or tissues from inoculated mosquitoes (Gubler et al., 1984; Rosen and Gubler, 1974). Convalescent serum specimens collected 6 or more days after onset of symptoms were tested for anti-dengue immunoglobulin M (IgM) by the IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) (Burke et al., 1982). Persons who tested negative by MAC-ELISA were defined as dengue-negative cases. Cases were defined as indeterminate

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