Urban epidemic of severe leptospirosis in Brazil

Albert I Ko, Mitermayer Galvão Reis, Cibele M Ribeiro Dourado, Warren D Johnson Jr, Lee W Riley, and the Salvador Leptospirosis Study Group*

Summary
Background Leptospirosis has, traditionally, been considered a sporadic rural disease. We describe a large urban outbreak of leptospirosis.

Methods Active surveillance for leptospirosis was established in an infectious-disease referral hospital in Salvador, Brazil, between March 10 and Nov 2, 1996. Patients meeting case criteria for severe manifestations of leptospirosis were recruited into the study. The diagnosis was confirmed in the laboratory with the microagglutination test and identification of leptospires in blood or urine. Risk factors for death were examined by multivariate analyses.

Findings Surveillance identified 326 cases of which 193 (59%) were laboratory-confirmed (133) or probable (60) cases. Leptospira interrogans serovar copenhageni was isolated from 87% of the cases with positive blood cultures. Most of the cases were adult (mean age 35·9 years [SD 15·9]), and 80% were male. Complications included jaundice (91%), oligaemia (35%), and severe anaemia (26%). 50 cases died (case-fatality rate 15%) despite aggressive supportive care including dialysis (in 23%). Altered mental status was the strongest independent predictor of death (odds ratio 9·12 [95% CI 4·28–20·3]), age over 37 years, and 80% were male. Complications included jaundice (91%), oligaemia (35%), and severe anaemia (26%). 50 cases died (case-fatality rate 15%) despite aggressive supportive care including dialysis (in 23%). Altered mental status was the strongest independent predictor of death (odds ratio 9·12 [95% CI 4·28–20·3]), age over 37 years, renal insufficiency, and respiratory insufficiency were also significant predictors of death. Before admission to hospital, 42% were misdiagnosed as having dengue fever in the outpatient clinic; an outbreak of dengue fever was taking place concurrently.

Interpretation An epidemic of leptospirosis has become a major urban health problem, associated with high mortality. Diagnostic confusion with dengue fever, another emerging infectious disease with a similar geographic distribution, prevents timely intervention that could minimise mortality.

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*Other members listed at end of paper

Gonçalo Moniz Research Centre, Oswaldo Cruz Foundation, Brazilian Ministry of Health, Salvador, Brazil (A I Ko MD); Hospital Couto Maia, Secretary of Health for the State of Bahia, Salvador, Brazil (C M Ribeiro Dourado MD); Division of International Medicine and Infectious Disease, Cornell University Medical College, New York, USA (A I Ko, W D Johnson Jr MD); and School of Public Health, University of California, Berkeley, USA (L W Riley MD)

Correspondence to: Dr Albert I Ko, Centro de Pesquisas Gonçalo Moniz, Fundação Oswaldo Cruz/MS, Rua Waldemar Falcão 121, 40295-001 Salvador, Bahia, Brazil (e-mail: albertko@cpunet.com.br)

Introduction
Leptospirosis is caused by spirochaetes belonging to the genus Leptospira, of which there are over 200 serovars. The infection, acquired through contact with animal reservoirs or an environment contaminated by their urine, produces a wide range of clinical manifestations. The early phase of leptospirosis is characterised by fever, chills, headache, and severe myalgias; however, fever can be the only identifiable symptom in many cases. In 5–15% of clinical infections, the disease progresses to cause severe multisystem complications such as jaundice, renal insufficiency, and bleeding diatheses. Leptospirosis-associated haemorrhagic pneumonitis has been highlighted in studies on the 1995 Nicaragua outbreak and in outbreaks from other geographical locations. Severe forms of the disease are associated with case-fatality rates of 5–40%.

Although leptospirosis has a worldwide distribution, the disease is most common in tropical and rural settings. In developed countries leptospirosis remains a rare disease; when encountered, it has been increasingly associated with recreational activities. However, leptospiral antibodies have been detected in up to 30% of those screened from selected urban populations, indicating that a substantial proportion of inner-city residents may be exposed to the disease. Furthermore, with the report of three cases of leptospirosis from the city of Baltimore, we suggest that leptospirosis is an under-recognised urban problem.

Brazil underwent a dramatic demographic transformation between 1960 and 1996 that has caused a 350% increase in its urban population. One consequence of this change has been the creation of urban slums (favelas) where the lack of basic sanitation favours rodent-borne transmission of leptospirosis. During the rainy season in 1996, a large epidemic of an acute illness associated with jaundice and acute renal failure occurred in the city of Salvador. The same climatic conditions contributed to a concurrent outbreak of dengue fever, the manifestations of which are indistinguishable from those of early-phase leptospirosis. We report the results of active surveillance.

Methods
Surveillance and data collection
Salvador is a coastal city in northeast Brazil with more than 2 million inhabitants (figure 1). Active surveillance was established at a state-run infectious-disease hospital (120 beds), which serves as the reference centre for leptospirosis in the metropolitan region. Patients were identified by ten emergency room physicians according to a surveillance case definition based on specific findings at physical examinations, or characteristic late-phase manifestations of leptospirosis (conjunctival suffusion, jaundice and serum aminotransferase activities less than 20 times the normal upper limit [>30 U/L], jaundice and abnormally high serum creatinine [>133 µmol/L], or blood urea nitrogen [>26·8 mmol/L of urea]).
All cases admitted to the surveillance hospital between March 10, and Nov 2, 1996, were studied after they had given informed consent. A standardised data-entry form was used to extract demographic and clinical information from the medical records. We used the following clinical definitions: oliguria was defined as a 24 h urine volume of less than 500 mL; respiratory insufficiency as a respiratory rate over 28 per min, or the observation of respiratory distress; and arrhythmia as an irregular rhythm detected on physical examination. The patient's mental status was assessed daily and coded as: oriented (appropriate responses to questions about patient's identity and current month); confused (responsive to auditory stimuli but incorrect responses to any of the above questions); obtunded (responsive only to tactile or exaggerated auditory stimuli); stuporous (responsive only to painful stimuli); or comatose (unresponsive to painful stimuli). Patients were defined as having altered mental status if the level of consciousness met the definition of confusion, obtundation, stupor, or coma. In those patients who died, information on altered mental status, respiratory insufficiency, and arrhythmia was obtained from examinations done more than 12 h before death. A subgroup of patients were randomly selected and interviewed so that we could obtain information about exposures (work-related activities involving contact with sewage or flood water; reported contact with sewage or flood water, or visual sighting of rodents in home or workplace in the 4 weeks before admission to hospital) and outpatient triage before admission to hospital. Blood and urine samples were collected during the hospital admission for serological and bacteriological testing. Convalescent-phase serum samples were obtained more than 2 weeks after collection of acute-phase samples.

Laboratory confirmation
The microagglutination test was done to confirm the diagnosis of leptospirosis serologically.25 Reference serovars were used, which represented 18 pathogenic and two non-pathogenic serogroups: Icterohaemorrhagiae, Javanica, Canicola, Ballum, Pyrogenes, Cynopteri, Autumnalis, Djasiman, Australis, Pomona, Grippotyphosa, Hendomadis, Serjoe, Bataviae, Tarassovi, Panama, Celledoni, Shermani, Semaranga, and Andamana. Leptospires were cultured on a Tween-albumin medium.24 Isolates were serogrouped with heterologous serum prepared against the serogroups represented in the serovar battery described above.24 Monoclonal antibodies (WHO/FAO Collaborating Centre for Reference and Research on Leptospirosis, Amsterdam, Netherlands) were used to identify serovars.25 A laboratory-confirmed case of leptospirosis was defined as the demonstration of a four-fold microagglutination titre rise between paired serum samples, a microagglutination reciprocal titre greater than 800 in one or more serum samples, or leptospires identified in blood or urine cultures by dark-field microscopy. A laboratory-confirmed probable case was defined as having a microagglutination reciprocal titre of more than 100 in one or more serum samples.

Statistical analyses
Information on daily rainfall was obtained from the 4th Meteorological District Station in Salvador. Population estimates for the city of Salvador from the 1991 census12 were used to calculate rates of severe leptospirosis for the epidemic period between March 10 and Nov 2, 1996. Maps showing the distribution of rates were made with Epimap (Version 2). The association of covariates with death was initially examined by univariate analysis. ANOVA and \( \chi^2 \) test was used for comparison of means and proportions. Crude odds ratios and their 95% CIs were calculated with the logit approximation. Statistically significant covariates (in the univariate analyses) and sex, were tested in logistic-regression models. A final model was selected that included significant covariates or covariates deemed to be of biological importance. Statistical analyses were done with SAS for Windows (Version 6.12).

Results
Active surveillance identified 346 clinically defined cases. Of these, 20 (6%) were excluded because laboratory or radiography evidence indicated other diagnoses: obstructive jaundice (five patients); viral hepatitis (four); bacterial sepsis (three); pneumonia (two); endocarditis (two); typhoid fever (two); systemic lupus erythematosus (one); and sickle-cell crisis (one). In analyses of the remaining 326 cases, we found that rainfall had exceeded...
75 mm per week in the 1–4 weeks before each peak in the number of cases (figure 2). Severe flooding occurred during the heaviest period of rainfall between April 21 and April 27. The largest number of cases per week (39) was reported 2 weeks after this event. Cases accounted for 32% (231 of 715) of all admissions to the study hospital during the peak of the epidemic between April 14 to July 31.

Among the 326 clinically defined cases, 193 (59%) laboratory-confirmed or probable cases were identified after the testing of paired (128 cases) and single (122 cases) serum samples in the microagglutination test (table 1), and by leptospirosis culture (38 cases, table 2). Complete serological testing was not possible in 123 (93%) of the 133 unconfirmed cases because paired serum samples were not available.

The predominant serogroup recognised in the microagglutination test was Icterohaemorrhagiae. In 90% (173 of 193) of the laboratory-confirmed and probable cases, the highest agglutination titres were directed against this serogroup. Serogrouping of leptospires isolated from cases confirmed this finding: 13 of the 15 isolates were identified as Icterohaemorrhagiae and one as Canicola; the remaining isolate could not be grouped. All serogroup Icterohaemorrhagiae isolates were serotyped and identified to be serovar copenhagenii.

The rate of severe leptospirosis was 12·5 cases per 100 000 population for the city of Salvador during the epidemic period, based on the 262 (80% of 326) cases admitted to hospital who lived within municipal boundaries. Of the 76 census districts, 15 had incidence greater than 20·0 per 100 000 population and were distributed in the urbanised peripheral region bordering the bay (figure 1). The 15 districts are composed of favelas where 47% of the housing structures (5 0 613 of 21 072) have open sewage systems, compared with 29% (106 049 of 367 803) in the other 61 districts. The relative risk of acquiring severe leptospirosis was 4·0 (95% CI 3·2–5·1) for residents from these 15 districts (population 489 910; 23% of 2 091 129) when compared with those from the other 61 districts.

Most of the cases were adults and 79·8% were male (table 3). Of the 299 cases who were employed, 118 (40%) had occupations in which they had contact with flood or sewage water. Of 162 interviewed, 112 (69%) recalled having contact with flood or sewage water within the 4 weeks before identification of leptospirosis and 125 (77%) reported seeing rodents in the home or workplace.

During the study period, an epidemic of dengue fever occurred in which 22 129 cases were notified from the city of Salvador. Before admission to hospital (mean duration of symptoms 7·5 days [SD 7·4]) many cases reported symptoms characteristic of dengue fever (fever, severe myalgias, headache; table 3). Conjunctival suffusion, a specific diagnostic sign for leptospirosis, was identified in only 21·8% of 326 cases during emergency-room triage. Of 136 interviewed cases, 57 (41·9%) reported a previous outpatient examination during which they received the diagnosis of dengue fever. In 74 interviews, 42 patients initially believed they had dengue fever.

Cases had developed signs of severe leptospirosis by the time they were admitted to hospital (jaundice, renal insufficiency, electrolyte disturbances, and haemorrhages; table 3). Other complications included respiratory insufficiency, arrhythmia, altered mental status, and anaemia. The 326 cases received intravenous antibiotics and intensive supportive care (intraperitoneal dialysis in 23%) during their hospital stay. Despite the aggressive management, there were 50 deaths and the case-fatality rate was 15%.

### Table 1: Serological confirmation of cases of leptospirosis

<table>
<thead>
<tr>
<th>Serological status (MAT)</th>
<th>Number of cases</th>
<th>Paired samples (n=128)</th>
<th>Single acute-phase sample (n=98)</th>
<th>Single convalescent-phase sample (n=24)</th>
<th>Without samples (n=76)</th>
<th>All (n=326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>107 (84%)</td>
<td>15 (15%)</td>
<td>4 (17%)</td>
<td></td>
<td>126 (39%)</td>
<td></td>
</tr>
<tr>
<td>Four-fold rise in titre and single titre &gt;1:1600</td>
<td>56 (44%)</td>
<td>.</td>
<td>.</td>
<td></td>
<td>56 (17%)</td>
<td></td>
</tr>
<tr>
<td>Four-fold rise in titre only</td>
<td>43 (34%)</td>
<td>.</td>
<td>.</td>
<td></td>
<td>43 (13%)</td>
<td></td>
</tr>
<tr>
<td>Single titre &gt;1:1600 only</td>
<td>8 (6%)</td>
<td>16 (15%)</td>
<td>4 (17%)</td>
<td></td>
<td>27 (8%)</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>10 (8%)</td>
<td>35 (36%)</td>
<td>16 (66%)</td>
<td></td>
<td>61 (19%)</td>
<td></td>
</tr>
<tr>
<td>Unconfirmed</td>
<td>11 (9%)</td>
<td>48 (49%)</td>
<td>4 (17%)</td>
<td></td>
<td>76 (100%)</td>
<td>139 (43%)</td>
</tr>
</tbody>
</table>

MAT–microagglutination test.

Figure 2: Weekly cases of leptospirosis and rainfall in Salvador, Brazil, between March 10, and Nov 2, 1996.
Table 2: Bacteriological confirmation of cases of leptospirosis

<table>
<thead>
<tr>
<th>Serological status (MAT)</th>
<th>Number of cases Tested</th>
<th>Culture confirmed</th>
<th>Culture unconfirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>19</td>
<td>11 (58%)</td>
<td>8 (42%)</td>
</tr>
<tr>
<td>Probable</td>
<td>5</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Unconfirmed</td>
<td>14</td>
<td>6 (43%)*</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>18 (47%)</td>
<td>20 (53%)</td>
</tr>
</tbody>
</table>

MAT = microagglutination test.
* One case confirmed by culture, among five MAT-confirmed cases with paired serum samples available; the isolate could not be typed with heterologous serum against the reference serovars.
† All had positive blood cultures; four had positive urine cultures.

Table 3: Characteristics of cases, 1996

- **Confirmed or probable cases (n=193)**
  - Mean (SD) or % of group
- **Unconfirmed cases (n=133)**
  - Mean (SD) or % of group
- **Total cases (n=326)**
  - Mean (SD) or % of group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Confirmed or probable cases (n=193)</th>
<th>Unconfirmed cases (n=133)</th>
<th>Total cases (n=326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and epidemiological data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>193</td>
<td>133</td>
<td>326</td>
</tr>
<tr>
<td>Male</td>
<td>133</td>
<td>96</td>
<td>230</td>
</tr>
<tr>
<td>Recent exposure to rodents†</td>
<td>168</td>
<td>113</td>
<td>281</td>
</tr>
<tr>
<td>Occupation with contaminated water contact†</td>
<td>134</td>
<td>96</td>
<td>230</td>
</tr>
<tr>
<td>Recent exposure to contaminated water</td>
<td>110</td>
<td>52</td>
<td>162</td>
</tr>
<tr>
<td>Recent exposure to rodents‡</td>
<td>110</td>
<td>52</td>
<td>162</td>
</tr>
<tr>
<td>Presentation</td>
<td>190</td>
<td>132</td>
<td>322</td>
</tr>
<tr>
<td>Diagnosis of dengue during a previous outpatient visit</td>
<td>95</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Fever</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Myalgia</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Headache</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Conjunctival suffusion</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Jaundice</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Laboratory examinations‡</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Leucocyte count (&lt;10³/L)</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Serum bilirubin (µmol/L)</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Complications during hospital stay</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Oliguria</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Other bleeding diatheses</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Anthrhythm</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Meningeal irritation</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Outcome</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Intraperitoneal dialysis</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Days spent in hospital</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
<tr>
<td>Case-fatality rate</td>
<td>193</td>
<td>41</td>
<td>136</td>
</tr>
</tbody>
</table>

Other significant multivariate predictors of death were age over 36 years, oliguria, serum creatinine greater than 354 µmol/L, blood urea nitrogen of 54 mmol/L, and respiratory insufficiency. Although respiratory insufficiency was a concomitant finding in 12 (20%) of 59 cases with haemoptysis, no deaths were associated with haemoptysis and it could not be assessed in the logistic-regression model. Of indicators of renal insufficiency, oliguria was the strongest predictor in models where combinations of indicators were included (results not shown). T total serum bilirubin, an indicator of hepatic dysfunction, was not a significant predictor of death in univariate or multivariate analyses. The presence of the three strongest predictors in multivariate analyses (altered mental status, oliguria, and age >36 years) had an 82% (18 deaths among 22 cases) positive predictive value for death from leptospirosis.

**Discussion**

When Noguchi and colleagues isolated “Leptospira icteroides” during a 1923 investigation of yellow fever in northeast Brazil, leptospirosis was a sporadic rural disease associated with livestock, sylvatic reservoirs, and cultivating practices. Rural to urban migration and urban population growth have since altered Brazilian cities and created new environments for leptospiral transmission.

This investigation, the largest case series for a single outbreak of leptospirosis, shows that the epidemiology...
and high male to female case ratio, these findings suggest that contact with flood water contaminated by rat urine and exposure to contaminated water were commonly associated with the epidemic. However, case-control investigations are needed to identify the risk associated with these exposures during urban outbreaks.

Similar social and climatic conditions for epidemic leptospirosis are present in cities throughout Central and South America. Seasonal outbreaks, are a problem in all major urban centres in Brazil. An epidemic occurred in 1997 in the city of Guayaquil, Equador, during heavy rainfall associated with El Niño (G Miño León, personal communication). These reports are additional evidence that leptospirosis is an emerging infectious disease that is spreading from its traditional rural setting to urban centres.

Although many descriptions of severe leptospirosis have been reported, questions about its clinical presentation still need to be addressed. Leptospirosis-associated haemorrhagic pneumonitis, characterised by pulmonary haemorrhage, acute respiratory distress, and high fatality, has been reported in various locations including Brazil. In contrast to reported experience, in the epidemic we report here, no deaths were observed among patients with haemoptysis although respiratory insufficiency by itself was a significant predictor of death. These discrepancies between our study and previous studies may be due to a variety of factors associated with host, strain, and inoculum and show the importance of doing detailed investigations in each epidemiological setting.

Altered mental status was the strongest independent predictor of death in patients admitted to the hospital during the epidemic. To avoid non-causal associations, altered mental status was defined to exclude positive findings identified within the 12 h before death. In logistic-regression models, the association was unaffected by factors attributable to uraemia, hepatic dysfunction, or other disease processes associated with severe leptospirosis. The presence of altered mental status alone had a positive predictive value for death of 47% (34 deaths among 73 cases). As a result of these analyses, patients with altered mental status now receive detailed neurological assessments at the study hospital.

The strength of these associations suggests that a central nervous system process directly contributed to death. In the only other investigation of death-related risk factors, 68 cases (12 deaths) identified during a 5-year period, neurological manifestations, including altered mental status, were not significantly associated with death in multivariate analyses. However, over 90 cases have been reported which show that leptospirosis is a cause of encephalitis, cerebral infarct and haemorrhage, and M.oyamoya disease. Our observation suggests that current tertiary-care treatment options may not be sufficient in addressing the underlying processes that led to death in Salvador.

Case fatality was 15% during the Salvador epidemic even though patients received intravenous antibiotics and aggressive supportive care (including intraperitoneal dialysis). These tertiary-care costs represent a substantial burden on the public sector whose annual health expenditure per head is US$19-74. Antibiotic therapy is generally believed to provide the greatest benefit when it is started early in the illness, and prompt outpatient diagnosis is therefore essential.

However, leptospirosis continues to be misidentified because of its variable and often non-specific clinical presentation. Certainly in the 1995 N icaragua outbreak, an initial suspicion of dengue fever delayed the final identification of leptospirosis. During the same period as the outbreak of leptospirosis in Salvador, the first
epidemic of dengue fever in 50 years had broken out and
was due to a single serotype, DEN-1.5 The clinical case
presentation was that of classic dengue fever. Its
manifestations of fever, headache, and myalgia, overlap
with those of early-phase leptospirosis. M ore than 40% of
leptospirosis patients were diagnosed with dengue fever
during their previous outpatient visit. By the time they
presented to the surveillance hospital, cases had
developed characteristic severe manifestations of late-
phase leptospirosis, such as jaundice and acute renal
failure, which enabled the leptospirosis to be
differentiated from dengue fever. In Central and South
America, where epidemic dengue fever and leptospirosis
are emerging as infectious diseases associated with similar
patterns of urbanisation, poverty, and climatic conditions,
the rapid differentiation of these two disease becomes
ever more critical.

Early case identification requires a diagnostic test that
is rapid and easy to carry out. Current methods are the
same as those used 70 years ago1 and are inadequate for
clinical decision-making and local epidemiological
surveillance. During the Salvador epidemic, the diagnosis
of 40 of the 50 patients who died could not be laboratory-
confirmed because complete serological testing requires
convalescent-phase serum samples. PCR methods have been developed24,25 but their application in the outpatient-
clinic setting is questionable. Serological diagnosis has
been complicated by the large antigenic diversity among
pathogenic leptospires. However, serotyping of isolates
from the Salvador epidemic shows that a narrow range of
serovars are involved in urban leptospirosis. Validation
of newly developed tests such as IgM-ELISA26 and dipstick27
techniques will be a critical step in the response against
this emerging urban disease.

The Salvador leptospirosis study group

Contributors

Albert Ko designed and coordinated the epidemic investigation and
analysis of the data. Mitermayer Galvão Reis supervised the laboratory
investigation. Cibele Dourado Ribeiro supervised the hospital study team.
Warren Johnson Jr and Lee Riley provided scientific guidance during the
epidemic investigation. Cibele Dourado Ribeiro supervised the hospital study team.

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