Leptospirosis is presumed to be the most widespread zoonosis in the world; it is caused by pathogenic spirochaetes of the genus *Leptospira*. Humans are accidental hosts and usually become infected through contact with water or soil contaminated by the urine of infected animals such as rodents, dogs, cattle, and pigs. Exposure of skin or mucous membranes to leptospires can lead to infection. Clinical signs and symptoms are variable and range from subclinical to potentially fatal manifestations. After an incubation period of 2–20 days, leptospirosis manifests as a biphasic illness consisting of an initial leptospiraemic phase lasting 3–7 days followed by an immune phase lasting 4–30 days. The more common mild, anicteric form of the disease is characterised by non-specific symptoms such as fever, headache, chills, myalgia, nausea, and abdominal pain. The severe, potentially fatal, icteric form of leptospirosis (Weil’s disease) is typically characterised by jaundice, renal dysfunction, and bleeding diathesis. Early diagnosis and prompt treatment of leptospirosis is important as all forms of leptospirosis, whether a mild flu-like illness, anicteric leptospirosis, or Weil’s disease, begin in the same way. At the onset of infection it is not possible to predict the natural course of the illness. This makes early diagnosis—that is, diagnosis before the onset of the immune phase all the more imperative. Although there is still some dispute about the value of antimicrobial therapy for leptospirosis, it is generally believed that antimicrobial agents are effective only if given as early as possible. There are relatively limited data on the clinical manifestations of symptomatic leptospiral infection in children. Reports from the USA, France, Brazil, Cuba, and India are in the form of isolated case reports, descriptions of small outbreaks, and retrospective analysis of case series. In 1996, the International Leptospirosis Society had expressed concern that leptospirosis was often overlooked and under-reported in tropical countries. In India leptospirosis has been reported in adult patients from Chennai (Madras), Kolenchery, Port Blair (Andaman and Nicobar Islands), and Orissa in the past decade. However, the true incidence and prevalence of leptospirosis in India are not known.

Following torrential rains on 12 July 2000, the city of Mumbai (formerly Bombay) was flooded and came to a standstill for two days. About two weeks later an outbreak of leptospirosis was reported in adults admitted to public hospitals, which was confirmed by the National Institute of Communicable Diseases, New Delhi. Initially the public health authorities had suspected the outbreak to be due to dengue fever, and samples from 18 adult patients were sent for testing to the National Institute of Virology, Pune. None of these 18 samples tested positive for dengue. To cope with the outbreak of leptospirosis the Public Health Department of the Municipal Corporation of Greater Mumbai issued a directive to admit all patients reporting to its public hospitals with a history of abrupt onset of fever and investigate for leptospirosis. The present study was conducted to determine whether an outbreak of leptospirosis had occurred in children reporting to our hospital with high fever, to describe the clinical illness, and to identify possible risk factors and prevention strategies.

**PATIENTS AND METHODS**

All consecutive children from 1 month to 12 years of age who came to our outpatient or emergency care department and were suspected to be suffering from acute leptospirosis were admitted and enrolled for the study. The study was
conducted from 24 July to 14 September 2000. Our hospital is attached to a medical college and is situated in close proximity to Dharavi, one of the largest slums in Asia. Our hospital has 111 paediatric beds and approximately 4000 paediatric admissions per year.

The working definition of a “suspected” case of leptospirosis for inclusion into the present study was “a child who had presented to our hospital with a history of abrupt onset of high fever, and the fever was documented to be more than 39°C at the time of presentation”. Other known symptoms of acute leptospirosis such as chills, myalgia, conjunctival suffusion, headache, abdominal pain, diarrhoea, vomiting, cough, skin rash, jaundice, oliguria, reduced level of consciousness, and bleeding diathesis were also kept in mind, but their presence was not necessary for the child to be labelled as “suspected leptospirosis”. Our study was a public health response that did not require review by the research and ethics committee of our hospital. However, all patients had an informed consent form signed by their parents or by a responsible family member.

A standardised data entry form was used to document demographic and epidemiological data (age, sex, socioeconomic status, type of residence with address, contact with contaminated flood water), and clinical information for each patient. As a screening test in every child with “suspected leptospirosis”, blood dark field microscopy was performed to detect leptospires at the time of admission. Also in every child, anti-Leptospira IgM antibodies were quantitatively estimated using an IgM anti-leptospiral enzyme linked immunosorbent assay (ELISA), which will be further referred to as the IgM-ELISA test. This ELISA kit (Serion ELISA classic for leptospira IgM, quantitative) is available commercially (Institut Virion Serion, Wurzburg, Germany). As per manufacturer’s specifications, the sensitivity, specificity, positive predictive value, and negative predictive value of this kit are 96%, 97%, 90%, and 99%, respectively. The assays were performed and interpreted in strict compliance with the manufacturer’s instructions. It was mandatory that the blood sample for the IgM-ELISA test was to be collected only after a minimum five days of onset of fever. This was necessary as it takes at least two days for anti-Leptospira IgM antibodies to start developing after onset of fever. A positive blood dark field microscopy report in a child presenting with a history of high fever of less than five days duration was an indication to field microscopy report in a child presenting with a history of high fever, and the fever was documented to be more than 39°C at the time of presentation. Also in every child, anti-Leptospira IgM antibodies were quantitatively estimated using an IgM anti-leptospiral enzyme linked immunosorbent assay (ELISA), which will be further referred to as the IgM-ELISA test. This ELISA kit (Serion ELISA classic for leptospira IgM, quantitative) is available commercially (Institut Virion Serion, Wurzburg, Germany). As per manufacturer’s specifications, the sensitivity, specificity, positive predictive value, and negative predictive value of this kit are 96%, 97%, 90%, and 99%, respectively. The assays were performed and interpreted in strict compliance with the manufacturer’s instructions. It was mandatory that the blood sample for the IgM-ELISA test was to be collected only after a minimum five days of onset of fever. This was necessary as it takes at least two days for anti-Leptospira IgM antibodies to start developing after onset of fever. A positive blood dark field microscopy report in a child presenting with a history of high fever of less than five days duration was an indication to start treating this child with “suspected leptospirosis” with intravenous crystalline penicillin.

Simultaneously, a complete blood count, urine routine and microscopy, peripheral blood smear examination for malarial parasites (both thick and thin smear), clot culture, and Widal test were done in every child to screen for urinary tract infection, malaria, and enteric fever. If required, further tests were carried out: urine culture, chest x ray, liver/renal function tests, cerebrospinal fluid examination, and computed tomography scan brain.

A “confirmed case” of leptospirosis was a child who had an anti-Leptospira IgM antibody titre greater than 20U/ml. All confirmed cases of leptospirosis were treated with parenteral crystalline penicillin (200 000 units/kg of body weight/day intravenously divided in six doses) for seven days. Paracetamol was started for the complaints of fever and myalgia.

The data obtained were analysed using the Statistical Package for Social Sciences (SPSS) software program. Wherever appropriate, with bivariate analysis the odds ratio (OR) was calculated and 95% confidence interval (CI) was estimated around the OR. The χ² test was used and p values less than 0.05 were considered significant. The sensitivity, specificity, and positive and negative predictive values for the clinical features significantly associated with leptospirosis were calculated.

**RESULTS**

Fifty three children (32 male, and 21 female) were admitted with suspected leptospirosis. Of these, 18 (34%) were confirmed as cases of leptospirosis by IgM-ELISA test. Four children with leptospirosis had presented with a history of high fever of less than five days duration. In all of these four leptospirosis cases, blood dark field microscopy was negative for leptospires. The remaining 14 children with leptospirosis had presented with a history of fever of more than five days duration. Only four of these 14 leptospirosis cases were blood dark field microscopy positive for leptospires. Table 1 shows the final diagnosis of cases in the study. In the 35 (66%) cases that were leptospirosis negative, the commonest diagnosis was malaria. Table 2 shows the age and sex distribution. While three (16.7%) of the leptospirosis cases were in the age group 1–5 years, 15 (83.3%) were more than 5 years old. Gender was not significantly associated with leptospirosis (p = 0.938). The male:female ratio was 1.6:1 in the leptospirosis group and 1.5:1 in the leptospirosis negative group. All 53 children resided in the slums of Dharavi, Sion Koliwada, and Wadala near our hospital.

Figure 1 shows that the incidence of leptospirosis cases was highest in the first week of August and the outbreak ended by the last week of August. Table 3 shows the difference in the clinical features present on admission, between patients enrolled and found to have leptospirosis and those who were not. Epidemiological data obtained from parents’ information, indicated that contact with contaminated flood water was significantly associated with the diagnosis of leptospirosis (18/18 x 16/35, p ≤ 0.0001). The children had either played in the flood water or waded through it while going to school, and in some cases the flood water had even entered their homes.

Table 3 shows that the commonest complaints in the enrolled patients at presentation were chills, generalised myalgia, headache, and vomiting. However, for these complaints, there was no significant difference between patients found to have leptospirosis, and those who were leptospirosis negative. Table 3 shows that the signs and symptoms significantly associated with leptospirosis were conjunctival suffusion (p = 0.007), abdominal pain (p = 0.005), and skin rash (p = 0.007). The conjunctival suffusion could be described as reddening of the eye surface due to dilatation of the conjunctival vasculature with or without subconjunctival haemorrhage. It only involved the bulbar conjunctiva. Chemosis and inflammatory exudates were absent. The abdominal pain was mild and could be described as the abdomen being diffusely tender, without guarding or rebound tenderness. This diffuse tenderness was elicitable on superficial palpation of the abdomen or on pinching the abdominal muscles, and was not localised to

<table>
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<tr>
<th>Table 1: Final diagnosis of cases in the study</th>
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<tbody>
<tr>
<td>Final diagnosis</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Enteric fever</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pyogenic meningitis</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Viral fever</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>All</td>
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</table>
any particular area. Ultrasoundographic examination and erect x-ray of the abdomen were normal. There was no abdominal wall causalgia. No child had intra-abdominal pathology (for example, toxic dilatation of gall bladder), nor was the pain severe enough to suggest pancreatitis or an acute surgical abdomen. The abdominal pain was in the form of a localised myalgia; it subsided totally a few days after starting crystal-line penicillin and paracetamol. The skin rash was maculo-papular, erythematous, and covered the entire body. It was most prominent on the truncal area and disappeared within a week.

For further analysis of our data, we termed these four clinical features—contact with flood water, conjunctival suffusion, abdominal pain, and skin rash—which were significantly associated with leptospirosis, as clinical risk factors for leptospirosis. As the number of risk factors present in a child increased, the chances of having leptospirosis also increased significantly (p<0.0001). Without a single risk factor being present no child had leptospirosis. Of 24 children who had a single risk factor present, only five had leptospirosis. Of 10 children who had two risk factors present, eight had leptospirosis. All four children who had three risk factors present had leptospirosis. Only one child had all four risk factors present and had leptospirosis.

Table 4 shows that a history of contact with flood water had a sensitivity and negative predictive value of 100% for identifying children with leptospirosis. The presence of conjunctival suffusion had a high specificity of 97% and a high positive predictive value of 83% for identifying leptospirosis. The presence of abdominal pain had a high specificity of 90%, 100%, and 100%, respectively; and high positive predictive values of 80%, 100%, and 100%, respectively.

There was no difference in the outcome, in terms of survival, between enrolled patients found to have leptospirosis and patients who were leptospirosis negative. All 18 children with leptospirosis were started on intravenous penicillin; they responded well to the treatment and were discharged after 10–12 days in hospital. All 35 children who were leptospirosis negative received treatment for their illnesses and went home.

DISCUSSION

The present study confirms that in the year 2000, an outbreak of leptospirosis did occur in children who were admitted to our hospital, following heavy rainfall and flooding. Since in the early phase of leptospirosis abrupt onset of fever can be the only identifiable symptom in many cases, we restricted the inclusion criterion to “only fever” for our study. Active surveillance for leptospirosis has rarely been conducted. A Medline literature search revealed three reports documenting similar studies using fever as an entry criterion. In these studies conducted in Thailand, Trinidad, and Nicaragua, the percentage of patients diagnosed as having leptospirosis was 15%, 4.9%, and 6.1%, respectively. The Thailand, Trinidad, and Nicaragua studies had surveyed all age groups. The present study was restricted to the paediatric age group; 34% were diagnosed to have leptospirosis.

Early diagnosis of leptospirosis is difficult clinically as other illnesses such as malaria, enteric fever, dengue, and viral hepatitis have a similar presentation. In the present study we have identified four clinical features which can help a physician to strongly suspect leptospirosis. All four clinical features were present at the time of admission. The presence of any of these four features in a child, who presents with a history of abrupt onset of high fever, should alert the physician to investigate for leptospirosis. In the present study, localised myalgia in the form of tenderness of the abdominal muscles, and presenting as abdominal pain was one of the features significantly associated with leptospirosis. Such selective involvement of certain muscle groups is known to occur in leptospirosis, though the reasons remain unexplained. The presence of more than one significant feature in a child should make the suspicion of leptospirosis even stronger. Whether these four risk factors associated with leptospirosis were specific only for our paediatric population, setting, and time, or whether they can be useful even in the future to diagnose leptospirosis early, especially in Mumbai, will require further research.

In the present study, leptospirosis was not associated with high rates of complications such as jaundice, myocarditis, bleeding diathesis, or renal failure. In all the 18 cases, the illness was relatively mild and anicteric. The treatment outcome was gratifying, with all 18 children responding well to intravenous penicillin. Penicillin was started promptly after receiving the IgM-ELISA test results within a few hours of admission. Another reason for the mild illness in our study

Table 2 Distribution of cases in the study according to age and sex grouping

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. children</th>
<th>Confirmed leptospirosis</th>
<th>Leptospirosis negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>1–11 months</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1–5 years</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>6–12 years</td>
<td>8</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>All</td>
<td>11</td>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

Figure 1 Temporal distribution of confirmed leptospirosis and leptospirosis negative cases in Mumbai (Bombay), India, 24 July to 14 September 2000.
An observational study to detect leptospirosis

We found only four reports describing anicteric mating skin rashes with gangrenous extremities, impaired suspicion of this illness accounts for its alleged rarity. Most presentation of leptospirosis coupled with a low index of heart failure due to myocarditis, and renal failure. She died of the complications of Weil's disease: congestive the form of crystalline penicillin, but it was probably too late. Meßlichich was also treated as a case of viral hepatitis. A diagnosis of leptospirosis treated as a case of viral hepatitis. A diagnosis of leptospirosis was thought of only after the outbreak was suspected. IgM-ELISA test was positive. By then, however, her clinical condition had worsened. She did receive antibiotic therapy in ELISA test was positive. By then, however, her clinical condition had worsened. She did receive antibiotic therapy in the form of crystalline penicillin, but it was probably too late. She died of the complications of Weil's disease: congestive heart failure due to myocarditis, and renal failure.

There are relatively few reports of paediatric leptospirosis in the medical literature. The diverse and non-specific presentation of leptospirosis coupled with a low index of suspicion of this illness accounts for its alleged rarity. Most of the reports of leptospirosis in children are of Weil's disease, 5 with complications such as acalculous cholecystitis; pancreatitis; abdominal causalgia; desquamating skin rashes with gangrenous extremities; impaired renal function; meningitis; and bleeding dia- phoresis. We found only four reports describing anicteric leptospirosis in children. A report from Cuba has described an outbreak of leptospirosis in six children (aged 8–13 years) who developed the illness after bathing in the Cimarron Channel. The illness had a meningoencephalitic presentation in four children. Fever, arthralgia, and myalgia were the other complaints. A report from rural Illinois (USA) described an outbreak in five children who developed an acute febrile illness, which was associated with swimming in a pond and was confirmed as leptospirosis by serological tests. An unusual case of leptospirosis in an 11 year old girl following a rat bite at home has been reported from Honolulu (USA). She presented with fever, vomiting, myalgia, severe headache, and neck pain due to aseptic meningitis. Recently, a report from Cuba has retrospectively analysed a large case series of 253 children diagnosed with leptospirosis from 1982 to 1995. Isolated cases prevailed over those occurring in outbreaks, with the 10–14 years age group being predomin- ant. Fever, headache, and myalgia were the symptoms and signs more frequently reported, and 92% of cases showed no icterus. Possible sources of infection involving a large number of cases were contact with low terrains and bathing in rivers, ponds, and lakes.

A temporal association between heavy rainfall and human leptospirosis has been reported in India from Chennai, and Orissa and also in other tropical countries. Flooding after heavy rains is particularly favourable to leptospirosis. It prevents animal urine from being absorbed into the soil or evaporating, so leptospires pass directly into the surface waters or persist in mud. Following the 12 July deluge the slums near our hospital, which are constructed on low lying

<table>
<thead>
<tr>
<th>No. of risk factors present</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>100</td>
<td>54</td>
<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Flood water contact +ve</td>
<td>28</td>
<td>97</td>
<td>83</td>
<td>72</td>
</tr>
<tr>
<td>Conjunctival suffusion</td>
<td>50</td>
<td>86</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28</td>
<td>97</td>
<td>83</td>
<td>72</td>
</tr>
<tr>
<td>Skin rash</td>
<td>61</td>
<td>90</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Two</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>Three</td>
<td>5</td>
<td>100</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>Four</td>
<td></td>
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areas, were waterlogged for 6–8 days (fig 1). The children in whom leptoepioirsis was diagnosed resided in these slums. Prolonged exposure of the skin to contaminated water provides an opportunity for invasion by leptospirae.1, 2, 3, 4, 5, 6 Although we did not aim to identify the source of infection, it is conceivable that the flood water was contaminated by the urine of infected animals. In urban areas, domestic rats (Rattus norvegicus)7, 8 and stray dogs8, 9 are known to be the predominant sources of pathogenic leptospirae. In the distant past, isolated cases of leptoepioirsis in adults due to exposure to rat urine have been reported in Mumbai.10 In the slums of Mumbai there are a large number of rodents and stray dogs. Also the sewerage and drainage facilities are inadequate. In recent years outbreaks of leptoepioirsis occurring in urban areas have been reported.11, 12 A retrospective analysis (1989–95) of 43 children, 4–14 years of age, with leptoepioirsis and living in an urban area in Sao Paulo, Brazil had shown that the source of infection in most cases (88%) was exposure to contaminated water during floods.13 Another recent report from Salvador, Brazil14 has described a large urban outbreak of leptoepioirsis in 193 adults from March to November 1996. The adults at highest risk for leptoepioirsis were the urban poor living in slums; contact with flood water contaminated by rat urine was the probable mode of transmission.15, 16

The Glasgow (quantitative) test is a sensitive and specific test for diagnosing patients in the acute phase of leptoepioirsis.17, 18, 19, 20 IgM antibodies become detectable during the first week of illness, allowing the diagnosis to be confirmed and treatment initiated while it is likely to be most effective.1, 2, 3, 4, 5, 19 The test is easy to perform, rapid, and permits the use of a single serum sample. A Medline literature search revealed three recently published studies wherein the diagnosis of leptoepioirsis was similarly confirmed using the IgM-ELISA test.19, 20, 21 Availability of this test has eliminated the shortcomings of the reference standard serodagnostic test—the microbiologic agglutination test (MAT)—which is not sensitive enough to guide the diagnosis in time to influence the treatment of an individual case.1, 2, 3, 4, 5, 6, 22, 23 MAT requires paired serum samples which delays diagnosis, is time consuming, and requires both significant expertise and the maintenance of a panel of live antigens. In the year 2000, in India, standardised MAT facility was available only at the National Reference Laboratory in Port Blair, the capital city of the Andaman & Nicobar Islands. Due to transport constraints, we could not send the sera to Port Blair. The courier services are not permitted to accept biological samples which need to be delivered by air mail. MAT can be performed, for a period of up to six months, on sera stored at −20°C.1 Fortunately, this problem for sending sera samples to Port Blair could not be resolved, within the time period. Since the IgM-ELISA test detects genus specific antibodies we were unable to identify the serogroups/serovars involved. Only MAT could have given this epidemiological data; this is a limitation in our study.

Outbreaks of dengue fever occur in similar climatic conditions as leptoepioirsis in urban slums.24, 25 Dual infection can occur.26, 27 A recent report from Barbados detected that two (8%) of 25 patients with confirmed leptoepioirsis had simultaneously acute primary dengue infection.28 We were not able to test our patients for dengue virus infections.

Our results suggest that leptoepioirsis may be an emerging infectious disease in Mumbai and therefore laboratory testing for its diagnosis should be considered part of the routine work up of febrile children with a history of contact with flood water. To prevent future outbreaks of leptoepioirsis, rodent control measures and improvement in sewerage and drainage facilities are necessary. At present in Mumbai, there is a raging controversy whether stray dogs (estimated number 50 000–400 000) could be a reservoir of infection.29 There seems to be insufficient evidence, at the moment, that stray dogs are more likely to transmit leptoepioirsis in Mumbai than domestic/licensed dogs. This controversy needs to be resolved by doing serological studies in stray dogs. During flooding, parents should ensure that their children avoid playing in the flood water.

ACKNOWLEDGEMENTS

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SK initiated and designed the study, directed the data analysis, and wrote the manuscript; he will act as guarantor for the paper. MB and AK monitored patients, collected the data, performed the literature review, and helped in drafting the manuscript. MK helped in designing the study, discussed the core ideas and analysis, and edited the manuscript. AD and AV helped design the study, performed the IgM-ELISA, tests and edited the manuscript.

The Municipal Corporation of Greater Mumbai paid for the IgM-ELISA kits used in the study.

REFERENCES


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