Leptospirosis: An emerging disease in travellers

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Summary A recent upsurge in leptospirosis in travellers has prompted the following review of the epidemiology of this infection in humans. The available data from the published literature as well as laboratory surveillance were examined to determine the possible causes of the apparent change in epidemiology.

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Introduction

Leptospirosis is the most common bacterial zoonosis worldwide, caused by spirochetes of the genus Leptospira that are transmitted from animals to humans. There are over 200 of known serovars, divided between 25 serogroups based on antigenic similarities. Many of the serovars circulating in animal reservoirs have been shown to cause disease in humans as well as in other animal species. Infection can be acquired either through direct contact with animals, or through environmental contamination by animal urine. This might occur through ingestion of contaminated food or water, through mucosal surfaces, or through skin contact, particularly if there are breaks in the skin. There is a wide range of animal hosts including rats, other rodents, livestock, and dogs. Infected animals are mostly asymptomatic, act as reservoir hosts to a particular serovar of leptospires, and shed the bacteria through their urine for prolonged periods of time. However, animals can develop illness after infection with a different serovar.1–5

Geographic distribution

Leptospirosis is found throughout the world, particularly in tropical and subtropical regions where environmental conditions favour the survival and transmission of leptospires. Reliable epidemiological data are lacking from many countries, making it very difficult to accurately assess disease burden, but known high-risk areas include India, Sri Lanka, Thailand, Vietnam, Malaysia, China, Seychelles, the Caribbean, Brazil, and the Pacific Islands. Table 1 shows the incidence of leptospirosis in selected high-risk countries where data are available.6–28 Queensland, New Zealand, and Hawaii have some of the highest reported incidences in developed countries.4,6
Clinical presentation

After an incubation period of 2–30 days, the most common symptoms are fever, chills, headache, myalgia, conjunctival suffusion, and jaundice. Although it often presents as a mild influenza-like illness and resolves spontaneously, leptospirosis can be responsible for more serious illness (Weil’s disease) including acute hepatic failure, acute renal failure, pulmonary haemorrhage, myocarditis, and meningencephalitis.

Leptospirosis is often poorly recognised and overlooked as a cause of fever or systemic illness. It is commonly misdiagnosed because of its variable symptoms and nonspecific presentations, and laboratory diagnosis is not always available in less developed countries. There may also be poor disease awareness and a low index of suspicion among clinicians, particularly in countries where leptospiral infection is less common. Clinically, leptospirosis can mimic many tropical infections including dengue, malaria, hepatitis, meningitis, and haemorrhagic fevers.

Risk factors

Risk factors for infection vary significantly between countries, and depend on many cultural, environmental, and ecological variables. In developing countries, infection is mostly related to farming activities, contact with animals (rats, other rodents, and livestock), poor sanitation, urban overcrowding, poor waste disposal, heavy rainfall, and floods. Globally, there have been many reports of epidemics after severe flooding. With climate change, extreme climate events such as flooding are expected to occur with increasing frequency, potentially leading to an increase in general incidence as well as frequency of outbreaks of leptospirosis. Infection has also been associated with recreational activities such as freshwater swimming, rafting, kayaking, canoeing, fishing, hunting, caving, hiking, and trail biking. Other risk factors include walking barefoot, immersion in water, contact with floodwater, drinking river water, and having skin wounds.

Changing epidemiology

The global burden of disease is unknown because of the paucity of data, but incidence estimates range from 0.1 to 1/100,000/year in temperate areas, to over 100/100,000/year during epidemics in the tropics. An estimated 300,000–500,000 severe cases occur each year, with case-fatality reports of up to 30%.

In developed countries such as Australia, leptospirosis has traditionally been an occupationally acquired disease, predominantly affecting males working in farming and livestock industries. However, recreational exposure and international travel have emerged as increasingly important sources of infection over the past decade. Nature-based tourism, outdoor recreation, and wildlife viewing comprise some of the fastest growing sectors in the tourism industry. Athletes are also increasingly looking for more extreme challenges (ultramarathons, triathlons, multisport events, multi-day events) in more remote locations (jungles, mountains, deserts) which can put them at increased risk of unusual infectious diseases including leptospirosis. A national surveillance report of leptospirosis in Australia from 1998 to 2004 revealed a shift in disease epidemiology from occupational to recreational risk, with the latter accounting for 18% of all cases during this period. This trend has continued, and in 2008, approximately 35% of cases reported to the enhanced surveillance system at the WHO Collaborating Centre for Reference and Research on Leptospirosis in Brisbane, Australia, were related to international travel and/or recreation, and approximately 19% were acquired overseas. However, enhanced surveillance in 2008 only captured about a third of the total number of cases in Australia, and it is difficult to accurately determine the true number of cases acquired through recreation and travel. Most of the cases acquired internationally over the past decade were related to travel to Asia, but also to New Zealand, the Pacific Islands, and South America.

Similar observations in changes in leptospirosis epidemiology have been noted in other developed countries. Hawaii has a high incidence of locally acquired leptospirosis, and cases attributed to recreation have risen from 0% in the 1970s to 50% in the 1990s. In California, 59% of reported cases of leptospirosis from 1982 to 2001 were due to recreational exposure, increasing to 85% in the 1997–2001 period, with rising numbers being seen in returned

| Table 1 Selected regions with reports on leptospirosis incidence. |
|--------------------------|-----------------|----------|
| Country or region        | Incidence/100,000/year | Ref.   |
| Seychelles              | 101              | 7        |
| Andaman Islands         | 50               | 6        |
| Guadeloupe, French      | 41               | 12       |
| West Indies             |                  |          |
| Vanuatu                 | 40               | 13       |
| Antilles, Guyana        | 23               | 86       |
| Reunion, Mayotte        | 12               | 86       |
| Kerala, India           | 11.4             | 15       |
| China                   | 7.1              | 11       |
| New Caledonia           | 2.1–30           | 16–18    |
| Thailand                | 4.1–40           | 19,20    |
| Sri Lanka               | 11               | 21       |
| French Polynesia        | 11               | 6        |
| Portugal, Azores Islands| 11               | 10       |
| Cambodia                | 7.7              | 22       |
| Costa Rica              | 6.7              | 6        |
| Hawaii                  | 3.3              | 23       |
| New Zealand             | 2.8              | 24       |
| Cuba                    | 2.5              | 6        |
| Queensland              | 2.1              | 25       |
| Croatia                 | 1.8              | 26       |
| Brazil                  | 1.7              | 27       |
| Argentina               | 1.0              | 6        |
| Australia               | 0.52             | 25       |
| Italy                   | 0.13             | 8        |
| Germany                 | 0.06             | 9        |
| Israel                  | 0.05             | 28       |
travelers from tropical destinations.48 More than half of the leptospirosis cases diagnosed in the United Kingdom are now acquired abroad,49 mostly from tropical and subtropical destinations. In Israel, 42% of all leptospirosis cases from 2002 to 2008 were diagnosed in returned travelers, most of whom had acquired their infection in Southeast Asia, and the majority had participated in water-related activities.50 In Germany, international travel is now the single most important exposure risk factor for leptospirosis, accounting for 16% of all cases.9 Shifts from occupational to recreational and travel-related risk have also been noted in the Netherlands, Italy, Portugal, and Bulgaria.8,10,51–53

Travel medicine perspective

In 2008, there were an estimated 922 million international tourist arrivals around the world, and this number is expected to increase to 1.6 billion by 2020.54 Most post-travel cases of leptospirosis were acquired in Southeast Asia, the Caribbean Islands, and Central and South America. These areas represent some of the most significant foci of leptospirosis worldwide (Table 1), and include many popular travel destinations where tourism numbers are forecast to rise significantly.11,41,54

With the unprecedented scale of international travel for recreation and commerce, the diagnosis of leptospirosis requires an astute clinician with awareness of the disease, its varied presentations, and knowledge of its risk factors and geographical distribution.

Many of the areas with a high incidence of leptospirosis are popular destinations for domestic and international travelers. With the increasing popularity of ecotourism and outdoor adventure activities, travelers are likely to become increasingly exposed to leptospirosis through activities that involve contact with freshwater, soil, and animals. Large leptospirosis outbreaks have occurred during outdoor adventure events around the world.9,41,55 The Eco-Challenge-Sabah was a 10-day multi-sport endurance competition held in Borneo in 2000, involving 304 athletes from 26 countries and 29 states of the USA. Activities included jungle trekking, caving, outrigger sailing, kayaking, climbing, scuba diving, mountain biking, and swimming in rivers in the jungle. The leptospirosis attack rate for competitors in the event was 42% among 189 interviewed athletes (62% of all participants), with 36% of these requiring hospital admission despite being young and extremely fit.56

Many outbreaks of leptospirosis have also been described in military personnel during deployments and training exercises, where they are often exposed to extreme outdoor environments.57–60 Although no data are currently available, other subgroups of travelers might potentially be at higher risk of leptospirosis because of the nature of their activities, e.g. humanitarian aid workers,61 mining workers,62 exploration geologists, and research scientists involved in fieldwork. Chemoprophylaxis with doxycycline may be of benefit in high-risk groups, although there is no conclusive evidence regarding its effectiveness.63,64

Travellers visiting families and relatives in developing countries are known to be at substantially higher risk of most infectious diseases compared to tourist travelers,65 and this increased risk might also apply with leptospirosis.

To illustrate the extra dimension that international travel can add to the epidemiology of leptospirosis, cases diagnosed in Australia over the past decade include Australians who acquired the infection locally; Australians who acquired the infection overseas through recreational, occupational, or military exposure; international visitors who acquired the infection in Australia through recreation or occupational exposure; international visitors who acquired the infection in their home country, but presented with the clinical illness in Australia; and international visitors who acquired the infection in transit countries between their home and Australia, e.g. European backpackers who spent weeks to months in Southeast Asia before arriving in Australia.

Illness in returned travellers

Fever is one of the most common presentations of illness in returned travelers. The most likely diagnoses include malaria, respiratory illness, diarrhoeal illness, and dengue fever. However, significant numbers of post-travel febrile illnesses are undiagnosed. A recent international multi-centre survey of the causes of fever in returned travellers showed that 22% of 6957 cases did not have a specific diagnosis, with 10% of these requiring hospital admission.66

The etiology of fever in local populations may provide insight into the likely causes of fever in returned travelers from these destinations. Recent surveys in various tropical areas have shown that leptospirosis is a significant cause of acute febrile illness, as well as acute hepatitis and acute renal failure. A study in Cambodia in 2007 found that leptospirosis was the most likely cause of fever presenting to health centres, accounting for 14% of all cases, and more common than dengue, malaria, influenza, or typhoid.67 Another study in the Thai–Myanmar border area found that 17% of fevers were due to leptospirosis, the second most common diagnosis after malaria.68 In a survey of acute undifferentiated febrile illness in the Ecuadorian Amazon from 2001 to 2004, 13.2% of cases were diagnosed with leptospirosis. Although leptospirosis had never been detected in the study area previously, it was responsible for more cases than malaria or dengue.69 Table 2 illustrates the large number of leptospirosis cases diagnosed during studies of the causes of fever, jaundice, hepatitis, and renal failure around the world, particularly in Southeast Asia and the Indian subcontinent.29,67–79 These studies indicate that leptospirosis is widespread in many countries, is responsible for significant morbidity, and is also likely to contribute to acute febrile illness in returned travelers.

Of the cases reported to the enhanced surveillance system at the WHO Collaborating Centre for Reference and Research on Leptospirosis in Brisbane, Australia, about a third of international visitors who acquired leptospirosis in Australia over the past decade were young European travelers who had worked in the fruit growing industries of Northern Queensland. Clinicians in other countries should include leptospirosis in the differential diagnosis of acute febrile illnesses in travelers who have recently been in areas of high endemicity, including Australia, particularly if
they were involved in agricultural work or had contact with recreational waters.

Co-infection with leptospirosis and malaria may also occur, and can complicate clinical diagnosis and management. A study of acute febrile illness in Egypt found that 12.4% of cases had more than one infection. Out of 167 patients with 2 or more concurrent infections, 83% had leptospirosis as one of their diagnoses.

Diagnostic and laboratory challenges

There are a wide variety of diagnostic tests for leptospirosis, and their availability can vary significantly between laboratories. These include:

- **Blood culture.** A positive culture provides definitive proof of diagnosis, but leptospires can take many weeks to grow. This test is only useful in the first 10 days of illness, after which leptospires begin to disappear from the blood, and serodiagnosis should be used.

- **Nucleic acid testing (PCR).** This test is only useful in the first 7 days of the illness, when it can rapidly confirm a diagnosis of leptospirosis during the bacteraemic phase. However, it is not readily available in all laboratories.

- **Serology for EIA IgM.** This is used as a screening test, and can produce false positive results. Diagnosis should be confirmed with the microscopic agglutination test if possible.

- **Microscopic agglutination (MAT) test.** This is considered the “gold standard” test, with its high specificity being the major advantage. However, a panel of live leptospires are required to perform this test, and it is not available in all laboratories. In order to detect infection from a specific serogroup, the panel needs to include a representative serovar from that serogroup. Cross-reaction occurs between serovars within each serogroup, and further testing might be required to identify the specific serovar responsible for the infection.

Leptospirosis acquired during international travel can pose diagnostic challenges because serovars vary between geographic locations. Many laboratories use MAT panels that only represent the serovars or serogroups found locally. False-negative results will therefore occur if a traveller is infected with a foreign serovar that is not found domestically. In order to diagnose serovars that were acquired internationally, samples might need to be sent to a reference laboratory that carries a wider panel of serovars. Clinicians should therefore be aware that a negative MAT does not completely exclude the diagnosis of leptospirosis if the infection was not acquired locally. A clinical diagnosis will sometimes have to be made based on the patient’s screening test result, clinical presentation, travel history, and exposure risk factors. The first human case of serovar Batavia infection diagnosed in Australia was seen in a traveller arriving from Ghana, and laboratory diagnosis was unable to be confirmed until six weeks after hospital admission.

Leptospiral infection in returned travellers can also result in the discovery of new serovars, particularly if laboratory diagnosis is not readily available in the source country.

### Table 2

Leptospirosis is a significant cause of fever and jaundice in local populations around the world, indicating that travellers to these areas are also at risk.

<table>
<thead>
<tr>
<th>Country or region</th>
<th>Year</th>
<th>Presentation</th>
<th>Sample size</th>
<th>% due to leptospirosis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia Laos Vietnam</td>
<td>1993–1997</td>
<td>Jaundice (non-hepatitis A to E)</td>
<td>577</td>
<td>17</td>
<td>70</td>
</tr>
<tr>
<td>Irian Jaya</td>
<td>1997–2000</td>
<td>Acute non-malarial fever</td>
<td>232</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>Cambodia</td>
<td>1999–2001</td>
<td>Non-dengue haemorrhagic fever</td>
<td>194</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2007</td>
<td>Fever</td>
<td>1336</td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td>Thai-Myanmar border</td>
<td>1999–2002</td>
<td>Fever</td>
<td>613</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>Thailand</td>
<td>1994–1999</td>
<td>Non-dengue fever in children</td>
<td>64 (semirural)</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Thailand</td>
<td>2001–2002</td>
<td>Fever (mostly agric workers)</td>
<td>378 (Bangkok)</td>
<td>1.6</td>
<td>71</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1984</td>
<td>Fever</td>
<td>1629</td>
<td>6.8</td>
<td>72</td>
</tr>
<tr>
<td>Kathmandu, Nepal</td>
<td>2001</td>
<td>Fever</td>
<td>876</td>
<td>4.1</td>
<td>73</td>
</tr>
<tr>
<td>Kolkata, India</td>
<td>2003</td>
<td>Acute jaundice</td>
<td>42</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>Delhi, India</td>
<td>2004</td>
<td>PUO</td>
<td>16.6</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Assam, India</td>
<td>2008</td>
<td>Fever (total)</td>
<td>536</td>
<td>22.6</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In males</td>
<td>53</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In females</td>
<td>483</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Mumbai, India</td>
<td>2000</td>
<td>Fever in children</td>
<td>53</td>
<td>34</td>
<td>77</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2001</td>
<td>Non-dengue fever</td>
<td>359</td>
<td>18</td>
<td>78</td>
</tr>
<tr>
<td>Ecuadorean Amazon</td>
<td>2001–2004</td>
<td>Acute febrile illness</td>
<td>533</td>
<td>13.2</td>
<td>69</td>
</tr>
<tr>
<td>Egypt</td>
<td>1999–2003</td>
<td>Fever</td>
<td>886</td>
<td>16</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute hepatitis</td>
<td>392</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>
described following infection in a mining worker who acquired leptospirosis in Indonesia, and diagnosed with the previously unknown serovar following his return to Australia.

Conclusion
Recreation and international travel are emerging as significant risk factors for leptospirosis in developed countries. With the growth of adventure tourism and travel, these trends are likely to strengthen and continue. Travellers should be advised about preventative measures to reduce their risk of infection such as avoiding flood waters, wearing protective clothing and boots, and covering up cuts and abrasions on their skin when engaging in outdoor activities. They should also be aware of the importance of seeking prompt medical attention if they develop a febrile illness on return.

Given the changing demographics of people being affected by leptospirosis, it is important for clinicians to change their perceptions of the population at risk, and to maintain an index of suspicion even if the patient does not fit the classical profile of a male agricultural worker.

Leptospirosis is likely to be an under-diagnosed cause of fever in adventure seekers and returned travellers. It should be considered as a differential diagnosis of undifferentiated fever and other leptospirosis related syndromes, particularly in those who have travelled to high-risk areas or participated in high-risk activities. Early recognition, diagnosis, and treatment will reduce the incidence of severe illness and deaths.

Ongoing surveillance and research are essential in order to monitor the ecological and epidemiological changes that may redirect both clinical and public health interventions for leptospirosis.

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Conflict of interest
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