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LEPTOSPIROSIS

Diamantis Plachouras

Athens, Greece

Rat disease kills Redgrave's gold medal partner: Rower dead in days from water-borne illness

By MICHAEL SEAMARK

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Olympic rowing champion Andy Holmes, who twice partnered Sir Steve Redgrave to gold medal triumph, has died suddenly from suspected Weil's disease.

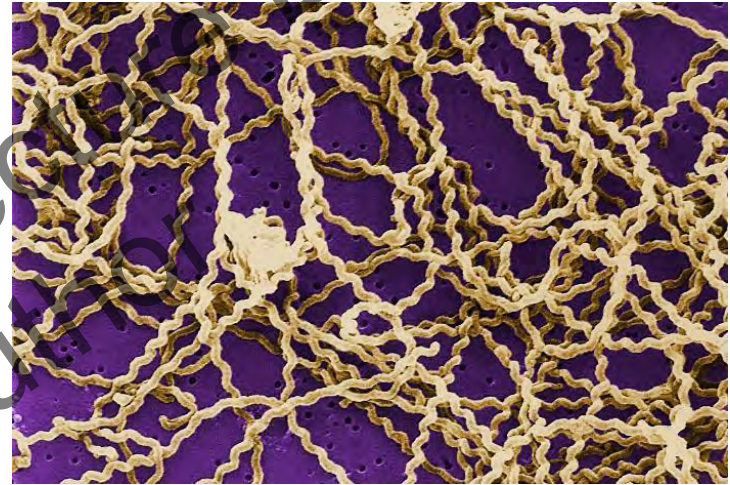
The athlete, who became a father for the fifth time only a month ago, had recently returned to the water after 17 years' break from the sport.

The 51-year-old was said to be in superb physical condition but became unwell after competing in a 200-mile sculling marathon at Becket, Lincolnshire, a couple of weeks ago.



WHAT IS LEPTOSPIROSIS?

- Zoonotic infection
- Caused by spirochaete *Leptospira* spp
- Historically two species
 - *L. interrogans* → pathogenic
 - *L. biflexa* → non-pathogenic
 - Serovars / serogroups
 - >250 serovars
- Today 14 species taxonomy by 16s RNA sequencing
 - e.g. *L. interrogans* (incl. serovars Icterohemorrhagiae, Canicola), *L. borgpetersenii* (incl. Hardjo)
 - Distinct from serologic classification



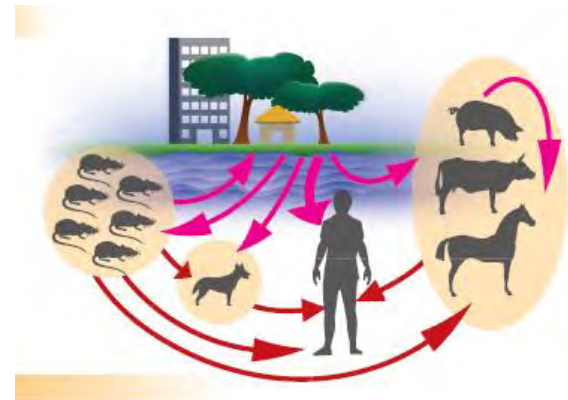
TYPICAL RESERVOIR HOSTS OF VARIOUS SEROVARS

| Reservoir host | Serovar(s) |
|----------------|----------------------------------|
| Pigs | pomona, tarassovi |
| Cattle | hardjo, pomona |
| Horses | bratislava |
| Dogs | canicola |
| Sheep | hardjo |
| Racoon | grippotyphosa |
| Rats | icterohaemorrhagiae, copenhageni |
| Mice | ballum, arborea, bim |
| Marsupials | grippotyphosa |
| Bats | cynopteri, wolffi |



RESERVOIRS - TRANSMISSION

- Excreted in urine of infected animals
- Rodents (rats, mice)
- Other animals
 - Dogs, livestock
- Leptospirae survive in humid environment for months
- Humans get infected by
 - Contact with urine
 - Through skin and mucosa
 - Swallowing contaminated water
 - Contact with infected animal tissues



ACTIVITIES ASSOCIATED WITH RISK



CLINICAL PRESENTATION



- Asymptomatic
- Incubation of 2-30 days
- Undifferentiated febrile illness
- Myalgia, severe headache, gastrointestinal symptoms, conjunctival suffusion
- Severe illness (Weil syndrome)
 - 5-15%
 - Renal failure: non-oliguric, hypokalemic
 - Liver failure: hyperbilirubinemia with moderate increase in ALT/AST
 - Thrombocytopenia
 - Shock
 - Mortality: 5-40%
- Pulmonary haemorrhage
- Two phases – not always distinct
 - Initial “septicemic”
 - Second “immune”

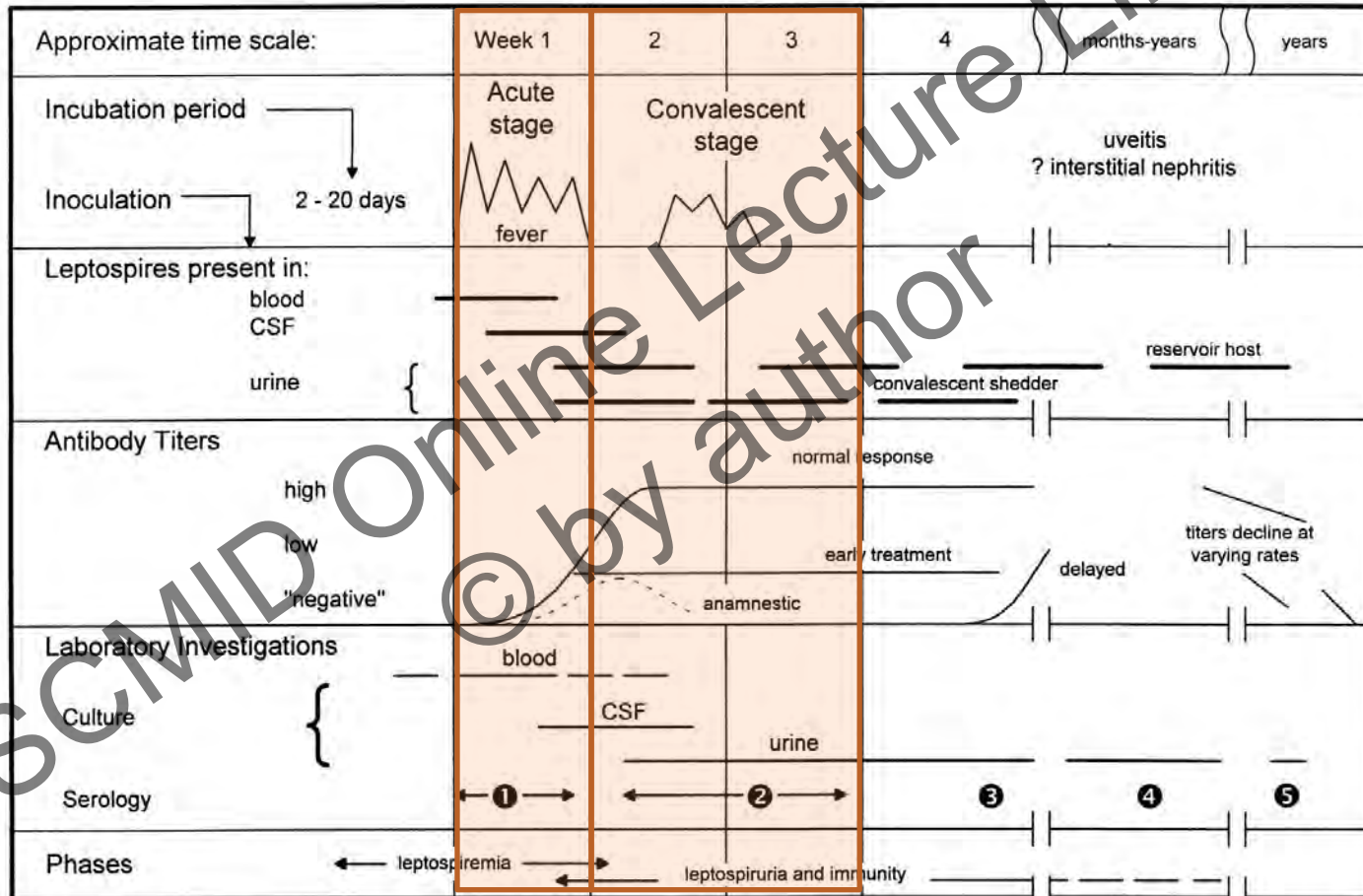


LEPTOSPIROSIS ASSOCIATED PULMONARY HAEMORRHAGIC SYNDROME (LPHS)

- Also Severe Pulmonary Haemorrhage Syndrome (SPHS)
- Recently identified as a distinct syndrome
- Can accompany severe infection or occur in isolated form
- Nicaragua outbreak in 1995
- High mortality (up to 50%)
- Pathogenesis: Vascular endothelial damage



CLINICAL AND LABORATORY COURSE OF LEPTOSPIROSIS



LONG-TERM SEQUELAE

- 10 year follow-up of patients in the Netherlands
- 27% of patients
- Myalgias, back pain, tiredness, headache
- 11% serious complaints lasting > 1yr or requiring referral to physician
- Uveitis



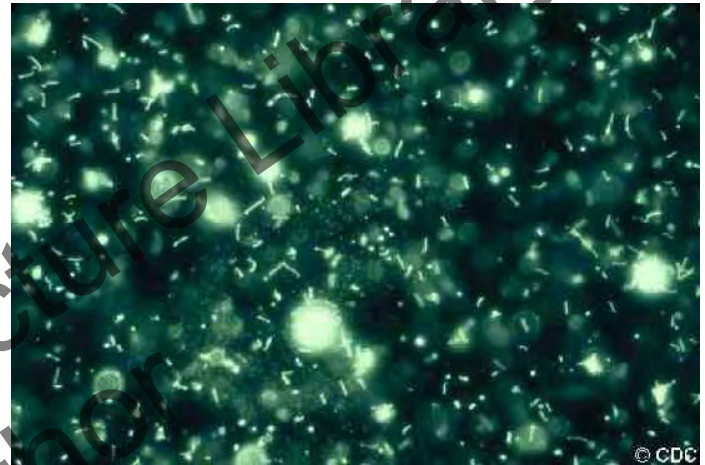
PATHOGENESIS

- Unclear
- Initially haematogenous dissemination
 - Mild manifestations: low binding of LPS to TLR-4
- Severe disease: Immune phase
 - HLA-DQ6 risk factor for severe disease
 - Superantigen
 - Surface lipoproteins (e.g. LipL32) → immune system activation



DIAGNOSIS

- Direct detection
 - Microscopy
 - Dark field
 - Specific stains (e.g. silver stain)
 - PCR
- Isolation
 - Culture (EMJH medium)
- Indirect detection
 - Serology
 - Microscopic agglutination test (MAT)
 - IgM ELISA
 - Rapid tests (Lateral flow test)



COMPARISON OF DIAGNOSTIC TESTS

| | Sensitivity | Specificity | Cost | Note |
|---------------------------------|-------------|-------------|------|--|
| Culture | 5-50 | 100 | 20 | Slow and difficult |
| Microscopy | | Low | 1 | Quick and early but unreliable |
| MAT (microscopic agglutination) | 90 | 90 | 160 | Serology, gold standard but difficult |
| IgM ELISA | 90 | 88-95 | 9-48 | Cost effective and quick |
| Lateral flow test | 81 | 96 | 1-5 | Quick, cost effective, point of care method but needs confirmation |
| PCR | 100 | 93 | 100 | Requires expertise and equipment |

TREATMENT

- Antibiotics are recommended

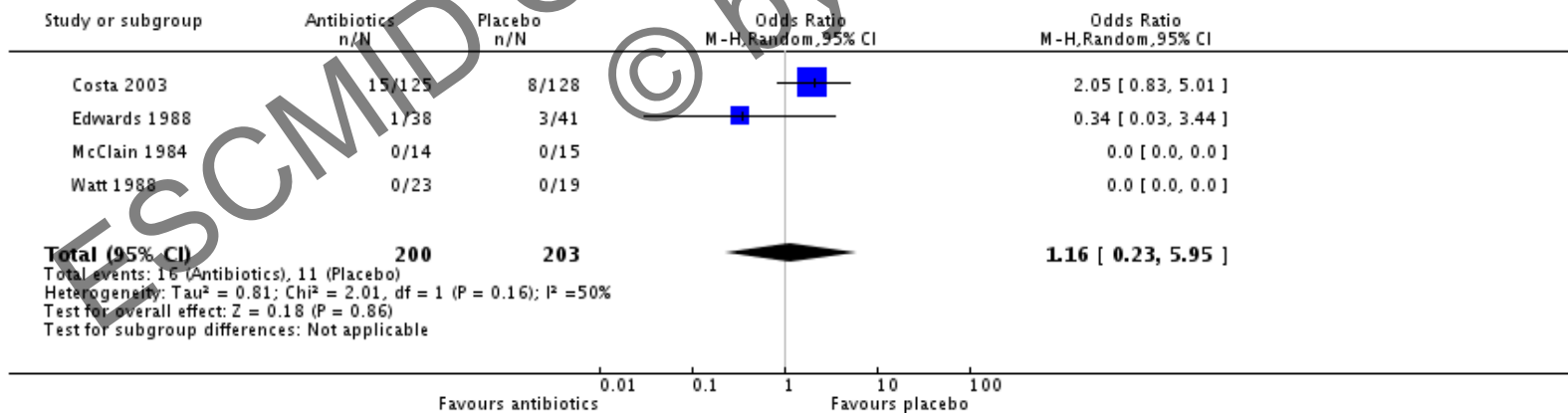
| Prophylaxis | |
|--------------------|-------------|
| Vibramycin | 200 mg/wk |
| Treatment | |
| Mild | |
| Doxycyclin | 100 mg bid |
| Ampicillin | 500 mg qid |
| Moderate to severe | |
| Penicillin | 1.5 MIU q6h |
| Ceftriaxone | 1g iv q24h |



TREATMENT

- Systematic review of treatment with antibiotics
- 7 trials
 - 4 penicillin against placebo
 - 3 comparing antibiotics (penicillin, cephalosporin, tetracycline)
- No effect in mortality
- No difference between antibiotics

Review: Antibiotics for leptospirosis
 Comparison: 1 Antibiotics versus placebo
 Outcome: 1 Death



PREVENTION

- Protective equipment
- Vaccine against *Icterohaemorrhagiae* available in France for high-risk groups
 - Needs booster every 2 years
 - Serogroup specific
- Pre- and post-exposure prophylaxis with tetracycline
- Rodent control
- Herd control for domestic animals
 - Vaccination
 - Treatment



EPIDEMIOLOGY – GLOBAL BURDEN OF DISEASE

- The commonest zoonosis worldwide with an estimated 500,000 severe cases per year
- 0.1-1:100,000 in temperate climates
- 10:100,000 in tropical climates
- >100:100,000 in outbreaks



A (RE)EMERGING DISEASE?

- Worldwide outbreaks
 - Sri Lanka, Nicaragua, Philippines
- Urban areas affected
 - Baltimore, Tokyo, Brazil
- Potential factors affecting apparent increase in incidence
 - Increase in rat populations
 - Re-emergence of canine leptospirosis
 - Increasing international travel
 - Popularity of fresh water recreational activities
 - Urbanisation
 - Increased flooding – climate change



AN URBAN OUTBREAK IN BRAZIL

- 326 cases of severe leptospirosis in Salvador, March-November 1996
- *Leptospira interrogans* ser. Copenhageni
- Jaundice 91%
- Renal failure 35%
- Fatality rate 15%
- 45% misdiagnosed initially as dengue fever



A NEGLECTED DISEASE OF THE 21ST CENTURY

- Lacking notification systems
- Mild cases present with undifferentiated febrile syndrome
- Laboratory diagnosis is laborious and unavailable in many areas with high incidence
- Only a proportion of severe cases is correctly diagnosed
- Vicious circle of under-diagnosis → underreporting → lack of awareness → neglect

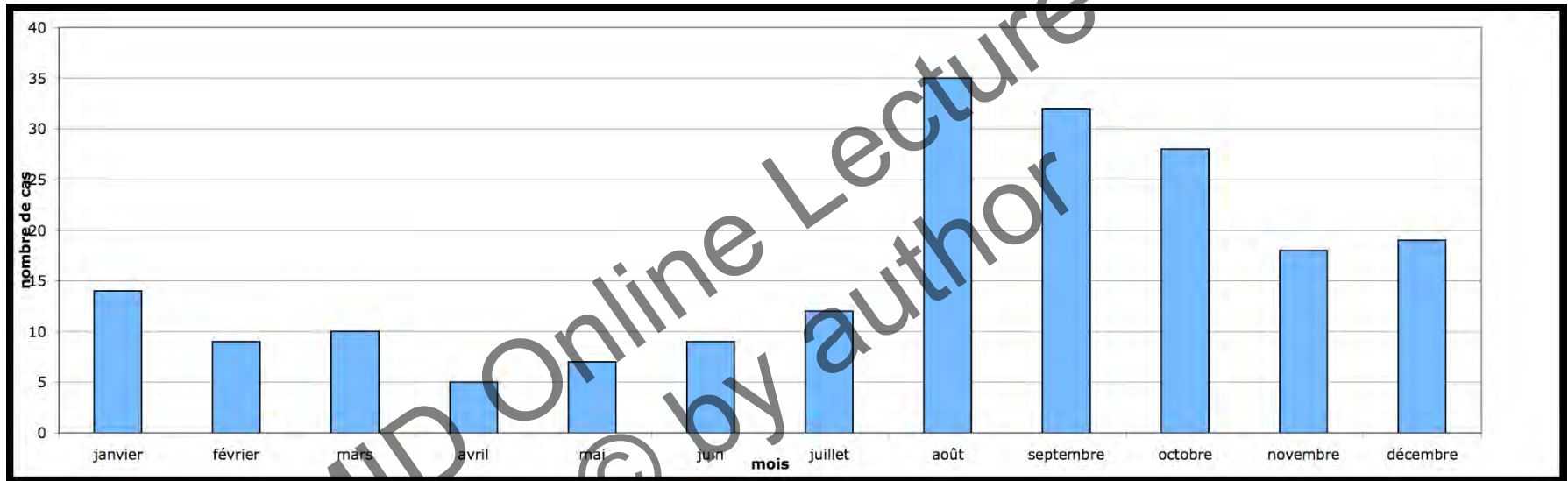


LEPTOSPIROSIS IN EUROPE



- No. of cases reported per country in 2009

SEASONALITY



Monthly distribution of cases in metropolitan France - 2009





Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid



Strikes, flooding, rats, and leptospirosis in Marseille, France

Cristina Socolovschi^a, Emmanouil Angelakis^a, Aurélie Renvoisé^a, Pierre-Edouard Fournier^a, Jean Lou Marié^b, Bernard Davoust^b, Andreas Stein^c, Didier Raoult^{a,*}

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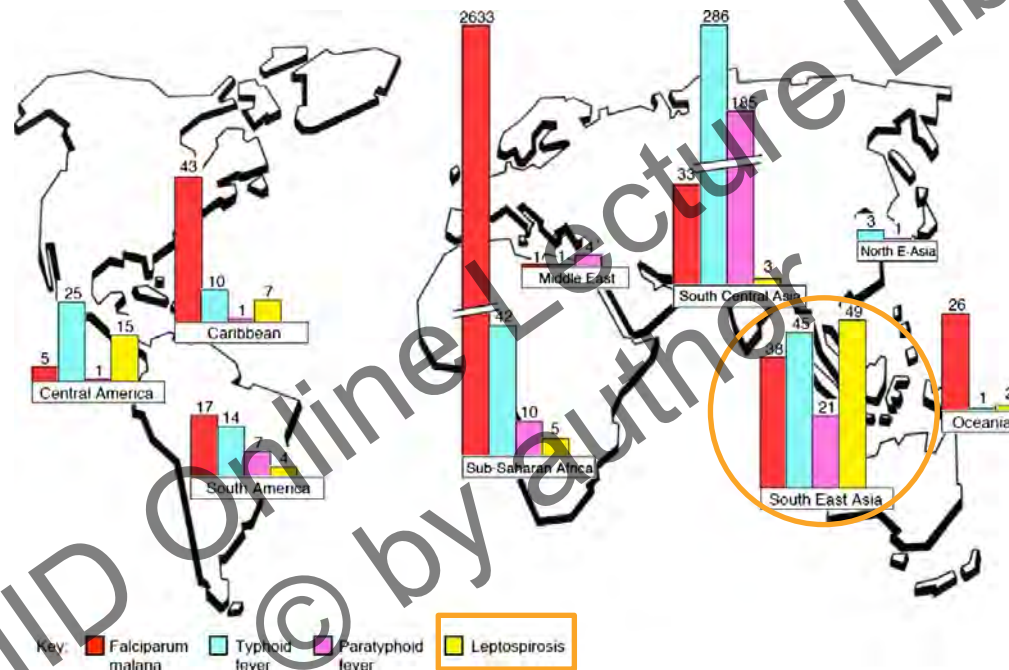
^b Direction Régionale du Service de Santé des Armées de Toulon, Toulon, France

^c Service des Maladies Infectieuses, Hôpital de la Conception, Marseille, France

- 3 cases of Leptospirosis in Marseille in 2009
- Association with
 - Increased rainfall
 - Garbage-collectors strikes

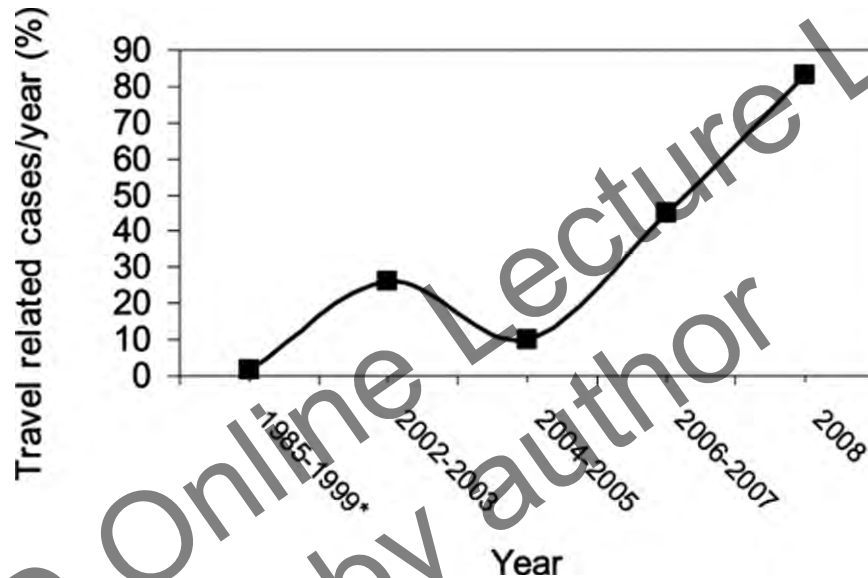


LEPTOSPIROSIS IN RETURNING TRAVELLERS



- 3rd commonest acute or life-threatening disease in returning travelers
- 2.4% of cases (88) compared to: Malaria 77% and Enteric fever 18%
- Mostly from **Southeast Asia**
- **82% tourists**, 9% business, 4% VFR
- 82% male and 50% hospitalised
- Geosentinel data: 1996-2011
 - 82,825 ill travellers
 - 3,866 patients with acute and potentially life-threatening disease

LEPTOSPIROSIS IN RETURNING TRAVELLERS IN ISRAEL



- 20 patients (2002-2008)
- 15 (75%) from South East Asia
- 18 (90%) males
- 89% water related activity
- Mortality 0%
- 1.78:100,000 in travellers compared to 0.06/100,000 in general pop
- Relative risk: 29

CONCLUSIONS

- Leptospirosis is a widely underdiagnosed and underreported zoonosis
- Incidence is expected to increase due both climatic change and anthropogenic factors
- Epidemiology is changing with an emergence in urban areas
- Insufficient evidence for treatment but generally recommended

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