Epidemiology of Zoonotic Visceral Leishmaniasis in the European Union

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World distribution of human leishmaniases

World distribution of human leishmaniases

Agents of zoonotic leishmaniases: 13 out of 15

<table>
<thead>
<tr>
<th>Leishmania species</th>
<th>Disease in humans</th>
<th>Geographical distribution</th>
<th>Main vector species</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. donovani</td>
<td>Kala-azar, viscerotis, cutaneous, mucocutaneous</td>
<td>Old World (Europe, Asia, Africa)</td>
<td>Phlebotomus species</td>
</tr>
<tr>
<td>L. major</td>
<td>Chronic mucosal leishmaniasis</td>
<td>New World (South America)</td>
<td>Phlebotomus species</td>
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<tr>
<td>L. tropica</td>
<td>Subcutaneous leishmaniasis</td>
<td>Both</td>
<td>Phlebotomus species</td>
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<tr>
<td>L. braziliensis</td>
<td>Cutaneous leishmaniasis</td>
<td>Both</td>
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<tr>
<td>L. guyanensis</td>
<td>Cutaneous leishmaniasis</td>
<td>Both</td>
<td>Phlebotomus species</td>
</tr>
<tr>
<td>L. infantum</td>
<td>Subcutaneous leishmaniasis</td>
<td>Both</td>
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</tr>
<tr>
<td>L. chagasi</td>
<td>Kala-azar, visceral leishmaniasis</td>
<td>Both</td>
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<tr>
<td>L. panamensis</td>
<td>Cutaneous leishmaniasis</td>
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Phylogenetic tree of Leishmania genus based on zymodeme polymorphism

The specific association

- **PARASITE-RESERVOIR-VECTOR**
- **DISEASE IN MAN** distributed in a given
- **TERRITORY**

NOSOGEOGRAPHICAL ENTITY OF LEISHMANIASIS
Zoonotic Visceral Leishmaniasis (ZVL) by viscerotropic *Leishmania infantum*

Sporadic Cutaneous Leishmaniasis (SCL) by dermatropic *Leishmania infantum*

The canine reservoir of ZVL and SCL

The coevolution of *Leishmania infantum* and the subgenus *Phlebotomus* (Larroussius)

*P. ariasi*  *P. perniciosus*  *P. neglectus*  *P. tobbi*  *P. major*  *P. kandelakii*

*Phlebotomus ariasi*  *Phlebotomus perniciosus*
INCIDENCE OF HUMAN LEISHMANIASIS IN MEDITERRANEAN EUROPE:
INFORMATION SOURCES

Passive notification of any clinical leishmaniasis case
[no distinction for VL vs CL, first episodes vs relapses, endemic vs imported, HIV- vs HIV+ coinfections]

Centralized information system for infectious diseases (CISID)

Yearly incidence of VISCERAL LEISHMANIASIS
[regardless HIV condition; includes first episodes only]: Information from Leishmaniasis Reference Centres

Current drug therapy of VISCERAL LEISHMANIASIS:
Information from Leishmaniasis Reference Centres

BACKGROUND
In the early 1990s*, information on drug efficacy and tolerability of first-line treatment regimens employed for Mediterranean VL, was collected from nine endemic countries of Southern Europe and Northern Africa.

MEGLUMINE ANTIMONIATE was the only drug employed in the Region

*Gradoni et al. 1995. Bull WHO 73, 191-197
Relationship between gross domestic product (GDP) per capita and first-line VL treatment options in Mediterranean countries

- Sb
  - exclusive use of pentavalent antimony drugs
- Sb/Amb
  - both pentavalent antimony and lipid-associated amphotericin B-based drugs are employed but in different patient categories
- Amb
  - predominant use of liposomal amphotericin B

(Northern African and Middle East countries, excluding Israel

Countries and

(Gradoni et al, TM&IH 2008)

Yearly incidence of CUTANEOUS LEISHMANIASIS

A BLACK HOLE !!!

- Benign nature
- Misdiagnosed
- Cases seen at private dermatologists (only complicated forms hospitalized)
- Unreported

Distribution by country of the 1911 Leishmania/HIV co-infection cases in south western Europe by early 2001

CUTANEOUS LEISHMANIASIS by dermatropic L. infantum: HIGHLY POLYMORPHIC

HIV-LEISHMANIA CO-INFECTIONS IN SOUTH EUROPE: AN UPDATE

For the 2001-2005/6 period:

- WHO Collaborating Centre for Leishmaniasis, Servicio de Parasitología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain
- Centre National de Référence des Leishmania, Laboratoire de Parasitologie, Montpellier, France
- Leishmanioses Unit, Instituto de Higiene e Medicina Tropical, Lisboa, Portugal
- Unit of Vector-borne Diseases & International Health, Istituto Superiore di Sanità, Roma, Italy
For the incidence analysis of the 2001-2005/6 period, only new cases (primary infections) were considered:

- Spain: from late 2001 through 2006 → 95
- Portugal: from 2001 through 2006 → 64
- Italy: from 2001 through 2006 → 52
- France: from late 2001 through 2005 → 30

... for a total of 241 new HIV/VL cases.

Three countries presented a similar trend:

- Spain: from late 2001 through 2006
- Portugal: from 2001 through 2006
- Italy: from 2001 through 2006

All VL cases from 1987 to 2005:
- No: 1296
- Pediatric cases: 41.7%
- Adult cases: 58.3%

Patients with concomitant/underlying clinical conditions other than HIV:
- No: 68 = 5% of total VL cases, 12% among adults

HIV positives:
- No: 179 = 14% of total VL cases, 31% among young adults
Concomitant/underlying conditions (no: 23)
Single in 54 patients, double in 14 patients

Patients without concomitant/underlying clinical conditions
No: 1049 = 81% of total VL cases

PREVALENCE OF ASYMPTOMATIC LEISHMANIASIS IN MEDITERRANEAN EUROPE

1974
First description of asymptomatic cases of VL in Southern Europe
1975 – 2010
Several reports from Italy, France, Spain and Greece
Methods
Leishmanin skin test (LST)
Serology (Western blot, ELISA, IFAT)
Blood culture
Blood PCR
Prevalence range (%)
All age groups: 9.7 – 46.8 (LST)

First demonstration of viable cultured parasites

Occurrence of Leishmania infantum Parasitemia in Asymptomatic Blood Donors Living in an Area of Endemicity in Southern France

1981
2005
Quantitative relationship between human and canine leishmaniasis in a typical ZVL focus

Importation and risk for the introduction of “EXOTIC” LEISHMANIA AGENTS

“HISTORICAL EXAMPLE” OCCURRED FOR LEISHMANIA INFANTUM

Great Britain
Sand flies: NO; Risk for introduction: NO

HOLLAND
San flies: NO; Risk for introduction: NO

GERMANY
Sand flies: YES (*Perniciosus, 1 sre). Risk of introduction:

<table>
<thead>
<tr>
<th>Period</th>
<th>Human leishmaniases</th>
<th>Canine leishmaniasis</th>
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<tr>
<td></td>
<td>VL, CL and MCL</td>
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<tr>
<td>1996-2007</td>
<td>32</td>
<td>47</td>
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<tr>
<td>1989-1993</td>
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<td>1993-1995</td>
<td></td>
<td>236</td>
</tr>
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</table>

QJM, 2004; EID, 2006; Vet Parasitol, 2009

Bti Health, 2010; Acta Vet Scand, 2002

Tierarztl Prax 1997; EID, 2003; Forschh Rex 2008
1999: first 4 sandflies ever collected (P. mascittii, an unproven but suspected *L. infantum* vector)

2001: first collection of *P. perniciosus*

From 1991 to present:

11 cases of leishmaniasis in man, dog, cat and horse, which were confirmed as autochthonous or likely to have been of indigenous origin

**ITALY**

Sand flies: 6 vector species; Risk for introduction: YES

Agent identification at ISS

Mainly passive detection

Poor monitoring of CL cases

**Importation** — **Introduction of exotic *Leishmania***

Monitoring is difficult in countries already endemic for other entities of leishmaniasis

**Clinical forms of human and canine leishmaniasis imported and, in case, introduced may be identical to the autochthonous ones**

**In the absence of etiological identification, new agents can remain unnoticed for long time thus allowing establishment of new biological cycles**

**Competent sand fly species other than Phlebotomus (*Larroussius*) species found endemic in: Spain, Italy and Southern France**

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<th>Species</th>
<th>Specificity</th>
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<tr>
<td><em>P. papatasi</em></td>
<td><em>L. major</em></td>
</tr>
<tr>
<td><em>P. sergenti</em></td>
<td><em>L. tropica</em></td>
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**Phlebotomus sergenti/Leishmania tropica**

In endemic areas the association *Ph. sergenti/L. tropica* causes *Anthroponotic Cutaneous Leishmaniasis* in urban areas (patients with chronic lesions are the reservoir host)
The Sicilian population of *P. sergenti* is genetically very similar to the Northern African populations competent for *L. tropica* transmission.

### Risk for the introduction of *Leishmania tropica* in Sicily

THE NORTHWARD SPREAD OF LEISHMANIASIS

Major climatic zones in Italy

Boundaries of endemic leishmaniasis in Italy through 1990

CanL in continental Italy: analysis of literature before 1993


47 clinical index cases; 106 seropositives/5442 asymptomatic (2%)
Autochthonous human cases recorded (passive detection)

Phlebotomine vectors in continental Italy: 2009

Cross-sectional evaluation - A puzzling pattern of conditions disclosed by LONGITUDINAL evaluation

Longitudinal evaluation - Exposure
Low-titre IFAT serology → Negative

3-6 months

Longitudinal evaluation - Subpatent infection
BM n-PCR, Low-titre IFAT → Negative → Positive → Negative etc

2-4 years

Longitudinal evaluation - Progressive infection leading to disease
BM n-PCR → LN culture/smear → IFAT serology → Clinical signs

0-22 months
0-3 months
3-14 months

31/05/2011
Commune territories with presence of autochthonous canine leishmaniasis

Period: 2005-2010
Samples: 500,000 sera
PRESENCE/ABSENCE