Leishmaniasis emergence in Europe

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Distribution and burden of cutaneous leishmaniasis worldwide

0.7 % NTD DALYs
(0.6 % for Chagas’ disease)

Sporadic SE Europe, caused by *Leishmania tropica*

WHO (2012) [www.who.int/leishmaniasis/leishmaniasis_maps](http://www.who.int/leishmaniasis/leishmaniasis_maps)
Distribution and burden of visceral leishmaniasis worldwide

**Visceral leishmaniasis**
- Incidence: tens of 1,000s p.a.
- 1.9 % NTD DALYs
- Endemic in southern Europe

**Visceral + cutaneous leishmaniasis**
- c. 12 million cases globally
- 2.6 % NTD DALYs
- 73.0 % NTD DALYs for malaria

Most infections caused by *Leishmania donovani* complex

WHO (2012) [www.who.int/leishmaniasis/leishmaniasis/](http://www.who.int/leishmaniasis/leishmaniasis/)
Types of emergence or re-emergence of human leishmaniasis in northern Italy

• Endemic disease: a focus becomes evident
  Example 1. Existing transmission of *Leishmania infantum* changes from hypo- to hyper-endemic
  Example 2. Transmission spreads from the upper to lower slopes of the Apennines in the same region, on the southern edge of the Po Valley

• Exotic disease: infections are introduced by travellers or immigrants from another region
  Example 1. *Le. tropica* enters Emilia-Romagna from (Sicily), N Africa, eastern Mediterranean or Afghanistan
Distinguishing endemic from exotic human leishmaniasis

• Case history: residency, travel history
  Contacts with mammalian (human) reservoir hosts

• Clinical symptoms
  Compatible with cutaneous leishmaniasis
  or visceral leishmaniasis

• Morphology of intracellular parasites
  \textit{Leishmania} identified, but not the species

• Serology
  Leishmaniasis identified, but not the causative species

• PCR, qPCR
  \textit{Leishmania} identified to species, except \textit{Le. donovani}

Turkey & Greece

Includes Italy

“Classical” Kala-azar from Indian sub-continent and East Africa
Zoonotic visceral & cutaneous leishmaniasis of humans and canine leishmaniasis caused by *Leishmania infantum*

- Endemic in southern Europe
- Emerging in North?

**Human disease**
- Mainly rural
- Prevalence: only 100s after better nutrition (cf. Europe in 1940s; N Africa, NE Brazil now)
- Up to 50% of village children infected (skin-test positive); risk of disease emergence

**Canine disease**
- Major veterinary problem
- Seroprevalence often > 20%
- 100% of dogs estimated to become PCR positive some time during life
- Deltamethrin dog collars have potential for community control; now used for individual protection
Establishment of endemic transmission of *Le. infantum* in a new area of Emilia-Romagna

- Establishment depends on $Ro > 1$
  
  $Ro =$ Basic reproduction number

  With or without a supply of new reservoirs? (Quinnell & Courtenay, 2009)

- Establishment depends on transmission mode
  
  Human-to-human by syringe (Drug users, HIV)
  Human-to-human by vector
  Dog-to-human by vector
Aims of leishmaniasis surveillance in Emilia-Romagna

• Rapid detection of human cases
  To optimise response to drugs
  To eliminate high-risk reservoir hosts, such as needle users & those infected with *Le. tropica*

• Targeting preventative measures
  Introducing preventative measures to endemic areas
  Constructing a barrier zone?
  Introducing preventative measures to at-risk areas
Surveillance for the spread of dog reservoirs of ZVL caused by *Leishmania infantum*

- Assess if dogs are the main reservoirs and/or indicators of ZVL
  - Cats (Italy, Spain etc) and hares (near Madrid, Spain)
- Assess the importance of dog-to-dog transmission
  - Congenital and venereal
  - Variation among breeds
- Select the method of dog surveillance
  - Standardized questionnaire distributed to veterinarians (government and/or private practice?)
  - Serology or PCR
- Assess the importance of vectorial transmission
Surveillance of canine leishmaniasis: major challenges

- Sample collection not standardized for PCR
  Conjunctival eye swabs (Di Muccio et al., 2012)
- Parasite loads & distribution and sero-positivity show complex changes during disease progression and cure (Foglia Manzillo et al. et al., 2013)
- PCR tests not standardized
  Cysteine protease B for specificity (Hide & Banuls, 2006)
  Kinetoplast rDNA for sensitivity (Di Muccio et al., 2012)
- Serological surveys have not been standardized for Dog sampling
  Serological tests and cut-offs (Give all results)
- Sentinels: Only way to confirm vectorial transmission?

Predicting the distribution of canine leishmaniasis in southwest Europe based on environmental variables

947 sero-prevalence surveys analysed
Risk map: Predicted presence of canine leishmaniasis
- Predicts well the low prevalence category (< 5 %) in Italy
- Requires surveys in more environments outside main foci
Vectorial transmission

- Perhaps there is no vector, as in northwest Europe and North America?
- Can it be assumed that the vector is a phlebotomine sandfly?
  Could it be a Ceratopogonid biting midge, as in Australia?
- What determines if a sandfly is a biomedically important vector of *Leishmania* species?
  Certainly not presence and abundance alone
What determines whether a sandfly is a vector of *Leishmania*?

**Vector competence**
- Sandfly permits production of infective forms and regurgitation plug of *Leishmania* after parasite survival, attachment, transformation in midgut
- Sandfly saliva helps produce optimal immunopathogenic response in mammalian host
- Well funded research to develop vaccines

**Ecological associations**
- With humans
- With any reservoir hosts
- Less-well funded research, often descriptive

**Vectorial capacity**
- Biting rates and other biological aspects ensure establishment of endemic transmission
- Ro and other mathematical modelling of transmission urgently required to identify vectors of biomedical importance
Worldwide: 62 sandfly species are incriminated or suspected vectors of 16 *Leishmania* species

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of incriminated or suspected sandfly vectors</th>
<th>Number of <em>Leishmania</em> species infecting humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe, Africa and Asia</td>
<td>27 <em>Phlebotomus</em> species (out of c. 120)</td>
<td>5 species of <em>Leishmania</em> subgenus</td>
</tr>
<tr>
<td>Americas (mostly Latin America)</td>
<td>35 <em>Lutzomyia</em> species (out of c. 400)</td>
<td>12 species of <em>Leishmania</em> and <em>Viannia</em> subgenera</td>
</tr>
</tbody>
</table>

Ecological associations: often Landscape epidemiology
Theory: most vectors, hosts & pathogens are tied to landscape, as environmental determinants control their distribution & abundance
(Pavlovsky, E.N. 1966. *Natural Nidality of Transmissible Diseases, With Special Reference to the Landscape Epidemiology of Zooanthroponoses*. University of Illinois Press, Urbana)

From descriptive accounts to transmission models
Sandfly vectors of zoonotic/anthroponotic leishmaniasis occur in diverse peri-domestic, semi-natural and natural landscapes
Criteria for incriminating phlebotomines as vectors of leishmaniasis

OLD

• Infections typed from unambiguously identified wild female flies more than once
• *Leishmania* (infective) forms seen in anterior midgut
• Fly species attracted to and bites humans & any reservoirs
• Ecological associations of fly, humans & any reservoir hosts
• Experimental transmission after xenodiagnosis

NEW

• Mathematical modelling using retrospective data: fly species maintains transmission
• Mathematical modelling based on planned control: disease incidence decreases significantly after decrease in biting rate of a fly species

Integrated Mapping of Establishment Risk for Emerging Vector-Borne Infections: a Case Study of Canine Leishmaniasis in Southwest France

Ro of a disease defined as: expected average number of secondary cases caused by one infectious individual placed in a naïve population

Conclusions:
First analysis combining a vector abundance prediction model, based on remotely-sensed variables, with a fully mechanistic process-based temperature-dependent Ro model

Lack of standardized methods for estimating vector biting rates – must relate sandfly densities in (light) traps to biting rates on specific hosts
Schematic overview of the $R_0$ approach

How to estimate biting rates on hosts?

Effects of temperature required **temporally** as well as spatially
Integrated control of leishmaniasis, not associated with other disease control

• A WHO Expert Committee (2010) recently stressed how leishmaniasis control could be much improved by better application of existing tools (drug combinations; insecticides: Indoor Residual Spraying, nets (ITN), deltamethrin dog collars)

• However, the careful application of existing tools has rarely been shown to reduce significantly leishmaniasis incidence or sandfly biting rates in disease foci (Ready, 2010; Stockdale & Newton, 2013)

• Long-term community interventions will probably rely on vaccines, and these could include sandfly salivary antigens

• Basic research on vector biology needs to be prioritized to meet the needs of integrated surveillance and control (Ready, 2013)
Integrated surveillance and control of leishmaniasis and WNV?

- Environments of the two diseases are likely to show only a small overlap
  True or false?
- However, there might be substantial overlap where the Apennine foothills meet the lowlands of the Po Valley
  True or false?
- Surveillance for canine leishmaniasis in the southern Po Valley could establish the unsuitability of these lowlands for ZVL, and reduce control measures there
  Surveillance by veterinarian questionnaires (clinical signs in dogs) and sentinel dogs (commercial support)?
  Gravid traps for co-surveillance of sandflies and mosquitoes?
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