

an ongoing community effort. To maximize their value, the data from each of these emerging lines of research must be pulled together and constantly evaluated by asking ‘what is missing?’ and ‘how can we integrate what is known?’ Any member of the malaria community can have a role in bringing these data together, whether by performing the high-throughput research, by carrying out bench-scale research or by contributing insight into how different strains of the disease behave in patients.

The time and money required to generate genomic and, now, postgenomic resources in malaria are substantial; however, the investment is important if progress is to be made. The cost of establishing these systems is not small but they will yield data that will move the field forward faster. As human, anopheline and plasmodial biology becomes better defined, each new step sharpens the resolution of the picture of malaria, increasingly illuminating the key elements of malaria parasite biology that can be exploited as drug and vaccine targets, and bringing solutions to the disease ever closer.

Acknowledgements

The Next Steps in Malaria Research meeting was sponsored by the Burroughs Wellcome Fund and hosted by the Broad Institute. We thank Dan Hartl, David Roos and Dyann Wirth for comments that improved the manuscript, and the researchers involved in laying out these next steps.

References

- Gardner, M.J. *et al.* (2002) Genome sequence of the human malaria parasite *Plasmodium falciparum*. *Nature* 419, 498–511
- Carlton, J.M. *et al.* (2002) Genome sequence and comparative analysis of the model rodent malaria parasite *Plasmodium yoelii yoelii*. *Nature* 419, 512–519
- Holt, R.A. *et al.* (2002) The genome sequence of the malaria mosquito *Anopheles gambiae*. *Science* 298, 129–149
- Hall, N. *et al.* (2005) A comprehensive survey of the *Plasmodium* life cycle by genomic, transcriptomic, and proteomic analyses. *Science* 307, 82–86
- Deitsch, K.W. and Hviid, L. (2004) Variant surface antigens, virulence genes and the pathogenesis of malaria. *Trends Parasitol.* 20, 562–566
- Mehlin, C. *et al.* (2004) Cloning grills: high throughput cloning for structural genomics. *J. Struct. Funct. Genomics* 5, 59–61
- The International HapMap Consortium. (2003) The International HapMap Project. *Nature* 426, 789–796
- Anderson, T.J. *et al.* (2000) Microsatellite markers reveal a spectrum of population structures in the malaria parasite *Plasmodium falciparum*. *Mol. Biol. Evol.* 17, 1467–1482
- Carlton, J. *et al.* (2005) The genome of model malaria parasites, and comparative genomics. *Curr. Issues Mol. Biol.* 7, 23–37
- Bahl, A. *et al.* (2003) PlasmoDB: the *Plasmodium* genome resource. Tools for integrating experimental and computational data. *Nucleic Acids Res.* 31, 212–215
- Ralph, S.A. *et al.* (2004) Metabolic maps and functions of the *Plasmodium falciparum* apicoplast. *Nat. Rev. Microbiol.* 2, 203–216
- Adams, J.H. *et al.* (2000) Malaria Research and Reference Reagent Resource Center. *Parasitol. Today* 16, 89

1471-4922/\$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pt.2005.11.011

Research Focus

Risk factors in the spread of leishmaniases: towards integrated monitoring?

Jean-Claude Dujardin

Institute of Tropical Medicine, Molecular Parasitology, Nationalestraat 155, B-2000 Antwerpen, Belgium

Environmental changes, immune status and treatment failure constitute the three major risk factors for the (re-)emergence and spread of leishmaniases. Except for *Leishmania*-HIV co-infection, these risk factors are not systematically monitored and their interaction is poorly studied and understood. Recently, the multi-disciplinary network Leish-Med was launched to document this issue around the Mediterranean and to promote transborder control strategies.

The spread of leishmaniases

Leishmaniases are serious communicable diseases that are endemic worldwide. They are caused by several species of *Leishmania* and are transmitted through the bite of sandflies. Several clinical forms are encountered, ranging from benign cutaneous leishmaniasis (CL) to

visceral leishmaniasis (VL), which is lethal if untreated. Consolidated data are not frequently available and only estimates have been done [1]: worldwide prevalence of 12 million, 1.5–2.0 million new cases (among which 500 000 are VL cases, 90% of which occur in the Indian subcontinent and Sudan [2]) occurring annually and causing a burden estimated at 2 357 000 disability-adjusted life years (DALYs) and 59 000 deaths. Several conditions are responsible for the (re-)emergence and spread of leishmaniases worldwide, concerning three major risk factors specifically [2]: (i) human-made and environmental changes; (ii) host immune status; and (iii) treatment failure and drug resistance.

Human-made and environmental changes

Human-made and natural changes to the environment can lead to alterations in the range and densities of vectors and reservoirs, thereby increasing human exposure to infected sandflies [3]. For instance, new villages in several

Corresponding author: Dujardin, J.-C. (jcdujard@itg.be).

Available online 21 November 2005

southern Mediterranean countries were developed with inadequate abattoirs that are attractive for semi-domestic and/or stray dogs: a situation that is likely to favour an increase in the population of these animals and, consequently, the sources of *Leishmania infantum* for human infection. In parallel, a high density of susceptible human hosts – populations that have not been exposed to *Leishmania*-free sandfly probing or bloodmeal and/or to *Leishmania* – is also the consequence of human-made changes such as widespread migration from rural to urban areas or fast urbanization. In 2001, an estimated 67 500 cases of CL occurred among the <2 million inhabitants of the city of Kabul (Afghanistan) [4]. Other contributors to increased density of susceptible human hosts are population movements for economic reasons such as the development of agroindustrial projects or the seeking of safe haven from civil unrest. The latter is illustrated best by the recent epidemics of VL in Sudan, where an estimated 100 000 people (out of 300 000) died from VL in Western Upper Nile State [5]. Finally, the disruption of public health systems leads to increasing sandfly density when vector control is compromised and to a higher incidence of leishmaniasis.

Immune status

Leishmania–HIV co-infection has emerged as a result of the increasing overlap among HIV and both *Leishmania donovani* and *L. infantum* in rural and suburban areas. Cases of co-infection have been reported from 36 countries around the world, with most of the cases in southwestern Europe: >1911 in early 2001 (from which 717 new cases occurred between 1996 and 1998; see WHO website in Box 1). Although the incidence of new clinical cases of VL in HIV co-infected individuals has dropped significantly in Europe during the past ten years [6], co-infection

might increase further in several African and Latin American countries (<http://www.who.int/csr/resources/publications/surveillance/Leishmaniasis.pdf>). The risk of co-infected patients – carriers of *Leishmania* in many tissues, including blood – being a source of infection for sandflies or other humans (through syringe sharing among intravenous drug users) has been confirmed [7]. Co-infected patients might become reservoirs of *L. donovani* or *L. infantum*, the causal agents of VL, especially in an urban context [8]. Apart from HIV, there are other immunosuppressive factors that might contribute to the spread of leishmaniasis (e.g. graft-associated treatments [9] or concomitant diseases such as tuberculosis).

Treatment failure and drug resistance

Chemotherapy is crucial for reducing the burden of leishmaniasis and the population of reservoirs of anthroponotic leishmaniasis. Antimonials (SbVs) are the first-line drug for all clinical forms but the increasing failure of SbV-based regimens is a major concern. In some areas of the Bihar focus in India, 60% of VL patients do not respond to SbV-based regimens [10]. New drugs such as miltefosine – an oral drug that has, so far, been relatively effective against VL [11] – constitute a promising alternative and are even considered in eradication programmes such as the one recently launched in the Indian subcontinent (http://www.who.int/tdr/diseases/leish/press_release.htm). However, the use of suboptimal doses might also lead to the development of resistant parasite strains, a phenomenon that occurs quickly in the laboratory [12]. The situation is even more preoccupying when the small number of other drugs currently in the pipeline is considered. Leishmaniasis, as is the case with several other vector-borne diseases, are among the most neglected diseases.

A call for attention

No regular global surveillance exists for leishmaniasis, even though they are notifiable in 33 of the 88 countries in which they occur. The only systematic and structured monitoring system concerns *Leishmania*–HIV co-infection (Box 1). The surveillance system for *Leishmania*–HIV co-infection began in 1993, and coverage of areas that are at risk is still incomplete. At present, most of the surveillance is carried out in Europe (where 17 of the 28 surveillance institutions are located), although it is feared that the problem of co-infection will rise in other regions (see earlier). Other risk factors (e.g. drug resistance and environmental changes) are not monitored systematically and their interaction is poorly understood. Nevertheless, their synergy might contribute towards a ‘critical mass’ and lead to severe epidemics. For instance, urbanization of leishmaniasis and ruralization of AIDS might lead to an increased number of HIV–*Leishmania* co-infected patients that is difficult to treat and prone to constituting a reservoir for the emergence and spread of drug-resistant parasites. Thus, existing surveillance networks should be expanded in terms of geographical coverage, extended to other risk factors and should provide an integrated risk assessment. Obviously, control programmes should follow the same trend.

Box 1. Transborder surveillance of leishmaniasis: selection of web resources

(i) <http://www.leishmed.net>

Site of the Leish-Med consortium that presents the aim and context of the initiative, the 22 participating institutions and the links with EU, World Health Organization (WHO) and other networks. It will be updated with reports of the different workshops, training sessions and pilot surveillance activities, uploads of publications, technical manuals and guidelines for health authorities.

(ii) <http://www.who.int/csr/resources/publications/surveillance/Leishmaniasis.pdf>

A report published by WHO (Department of Communicable Disease Surveillance and Response) that is based on data from 1990 to 1998 regarding the surveillance system of *Leishmania*–HIV co-infection. An updated report was published in 2003 [13].

(iii) <http://eden.cirad.fr>

Emerging Diseases in a Changing European Environment (EDEN) is an integrated project of the European Commission that aims to identify and catalogue the European ecosystems and environmental conditions that can influence the spatial and temporal distribution and dynamics of human pathogenic agents, one of them being *Leishmania*.

(iv) <http://www.leishnatdrug.org>

Site of the Leishnatdrug-R consortium: an EU-funded project that monitors treatment failure and drug resistance in Peru, Bolivia and Nepal. There are plans to transform this site into a general one in which worldwide information with respect to treatment failure and drug resistance would be gathered.

Leish-Med

In this context, a Euro–Mediterranean multidisciplinary consortium funded by the European Union [EU (Sixth Framework Programme, INCO-MED)] was recently launched to document in an integrated way the main risk factors involved in the spread of leishmaniasis around the Mediterranean and to promote transborder control strategies (Box 2). Currently available data might suggest that some of the risk factors mentioned earlier are not as important in this region, but under-reporting might have a major role in this. Thus, the consortium will perform pilot attempts at integrated surveillance – in the Euro–Mediterranean region – of new risk factors such as drug resistance, concomitant diseases (other than AIDS), human behaviour and, in collaboration with another EU-funded network (EDEN; Box 1), environmental changes. Leish-Med should enable the launch of the bases for global surveillance of leishmaniasis around the Mediterranean and could constitute a model for other regions that are endemic for these diseases.

Launching the bases for integrated surveillance requires multidisciplinary expertise and, most of all, extensive interaction of the experts. To promote these features, a risk–technological-procedure matrix was implemented. The matrix has three vertical axes – the three major risk factors (environmental changes, immune status and treatment failure) – and three horizontal axes: (i) the different surveillance activities necessary to document each risk factor; (ii) the main tools necessary to support each surveillance activity; and (iii) the major control activities. Partners were chosen on a qualitative basis to fill all boxes of this table, and this structure will be used for all activities of the consortium. In the workshop and training session about molecular epidemiology, for

example, applications to parasites, vectors and reservoir will be considered and highlighted in the context of surveillance of the three risk factors and assessment of the respective control activities. The same multidisciplinary and integrated spirit will characterize the five opinion and review articles that will be produced by each workshop and that will be published so that the international community can follow the progress of the initiative.

Building bridges

Multidisciplinary work is the unique way to establish bridges between the tremendous knowledge accumulated in a postgenomic era and the increased demand from patients and health sectors. However, this is often difficult because of the hyperspecialization of the particular disciplines. Communication platforms such as Leish-Med in which specialists of extreme disciplines gather regularly and learn to find a ‘common’ language might help to catalyse this dialogue.

Acknowledgements

As coordinator of the Leish-Med consortium, I thank all members for their enthusiastic support; this coordinated action receives support from EC-FP6/INCO-MED (contract INCO-CT-2004–509086).

References

- Croft, S. and Coombs, G. (2003) Leishmaniasis, current chemotherapy and recent advances in the search for novel drugs. *Trends Parasitol.* 19, 502–508
- Desjeux, P. (2001) The increase in risk factors for leishmaniasis worldwide. *Trans. R. Soc. Trop. Med. Hyg.* 95, 239–243
- Peterson, A.T. and Shaw, J. (2003) *Lutzomyia* vectors for cutaneous leishmaniasis in Southern Brazil: ecological niche models, predicted geographic distributions, and climate change effects. *Int. J. Parasitol.* 33, 919–931
- Reithinger, R. *et al.* (2003) Anthroponotic cutaneous leishmaniasis, Kabul, Afghanistan. *Emerg. Infect. Dis.* 9, 727–729
- Zijlstra, E.E. and el-Hassan, A.M. (2001) Leishmaniasis in Sudan. Visceral leishmaniasis. *Trans. R. Soc. Trop. Med. Hyg.* 95 (Suppl. 1), S27–S58
- Lopez-Velez, R. (2003) The impact of highly active antiretroviral therapy (HAART) on visceral leishmaniasis in Spanish patients who are coinfecting with HIV. *Ann. Trop. Med. Parasitol.* 97 (Suppl. 1), 143–147
- Alvar, J. and Jimenez, M. (1994) Could infected drug-users be potential *Leishmania infantum* reservoirs? *AIDS* 8, 854
- Ritmeijer, K. *et al.* (2001) Ethiopian visceral leishmaniasis: generic and proprietary sodium stibogluconate are equivalent; HIV coinfecting patients have a poor outcome. *Trans. R. Soc. Trop. Med. Hyg.* 95, 668–672
- Fernandez-Guerrero, M.L. *et al.* (2004) Visceral leishmaniasis in immunocompromised patients with and without AIDS: a comparison of clinical features and prognosis. *Acta Trop.* 90, 11–16
- Sundar, S. *et al.* (2000) Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. *Clin. Infect. Dis.* 31, 1104–1107
- Sindermann, H. *et al.* (2004) Miltefosine (Impavido): the first oral treatment against leishmaniasis. *Med. Microbiol. Immunol. (Berl.)* 193, 173–180
- Perez-Victoria, F.J. *et al.* (2003) *Leishmania donovani* resistance to miltefosine involves a defective inward translocation of the drug. *Antimicrob. Agents Chemother.* 47, 2397–2403
- Desjeux, P. and Alvar, J. (2003) *Leishmania*/HIV co-infections: epidemiology in Europe. *Ann. Trop. Med. Parasitol.* 97 (Suppl. 1), 3–15

Box 2. The Leish-Med initiative

Leish-Med is a multidisciplinary network that links European partners with South and East Mediterranean partners to document the main risk factors involved in the spread of leishmaniasis around the Mediterranean and to promote transborder control strategies. This three-year project was launched in December 2004.

Objectives

To review, assess and inform on current scientific knowledge regarding the epidemiology and control of leishmaniasis around the Mediterranean.

To coordinate existing research on surveillance and control of leishmaniasis.

To disseminate and standardize relevant tools and good practice arising from research.

To advise national, regional and international health authorities on the most effective transborder control measures.

To identify the gaps in current knowledge and expertise.

To define future multidisciplinary research to remedy the situation through coordinated action.

Expected deliverables

The major activities of the Leish-Med initiative centre around three workshops combined with training sessions (molecular epidemiology, diagnosis and epidemiology, and geographical information system and environmental control), two workshops on control with drugs and vaccines, one final conference for broader dissemination of the findings, a website, and a series of articles and guidelines for health authorities.