Annual Report 2010

CRESIB
BARCELONA

Hospital Clínic - Universitat de Barcelona

CRESIB
Annual Report
2010

Hospital Clínic - Universitat de Barcelona

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Foreword

Almost five years after it was founded, CRESIB (Barcelona Centre for International Health Research) has become established as one of the most important research centres in the field of global health at both a national and international level. 2010 has been a year of strengthening our scientific structure with the appointment of new research professors associated with our trustee institutions, such as professors Jordi Vila, Tomàs Pumarola, Toni Trilla and Jaume Ordi. Dr. Ivo Mueller also joined the team through a joint appointment with the Walter and Eliza Hall Institute of Medical Research (WEHI, Australia). This further strengthens the areas of research into viral and bacterial infections, public health and malaria.

The expansion of CRESIB's scientific structure is the result of the implementation of its Strategic Plan for 2010-2013. With this new plan, CRESIB has gone from being a vertical structure with four programs to a matrix structure that encourages multidisciplinary interrelation between the different research areas. The key objective of this structure is to achieve a greater impact on improving the health of the most disadvantaged population groups.

2010 was also a year in which, once again, CRESIB demonstrated its scientific and technical excellence. The centre's

scientific output has grown continuously over the last few years in terms of both volume and the impact factor of its publications. The productivity of our centre has been recognised by the Research and Innovation Coordination Office of the Generalitat of Catalonia (OCRI) which, in its report entitled *Anàlisi comparativa internacional de la producció científica dels agents de recerca de Catalunya: una visió de sistema* (A comparative international analysis of the scientific output of research agents in Catalonia: system overview), considered CRESIB to be the second best research centre in Catalonia in terms of the standardized impact factor in the period under study (2004-2008).

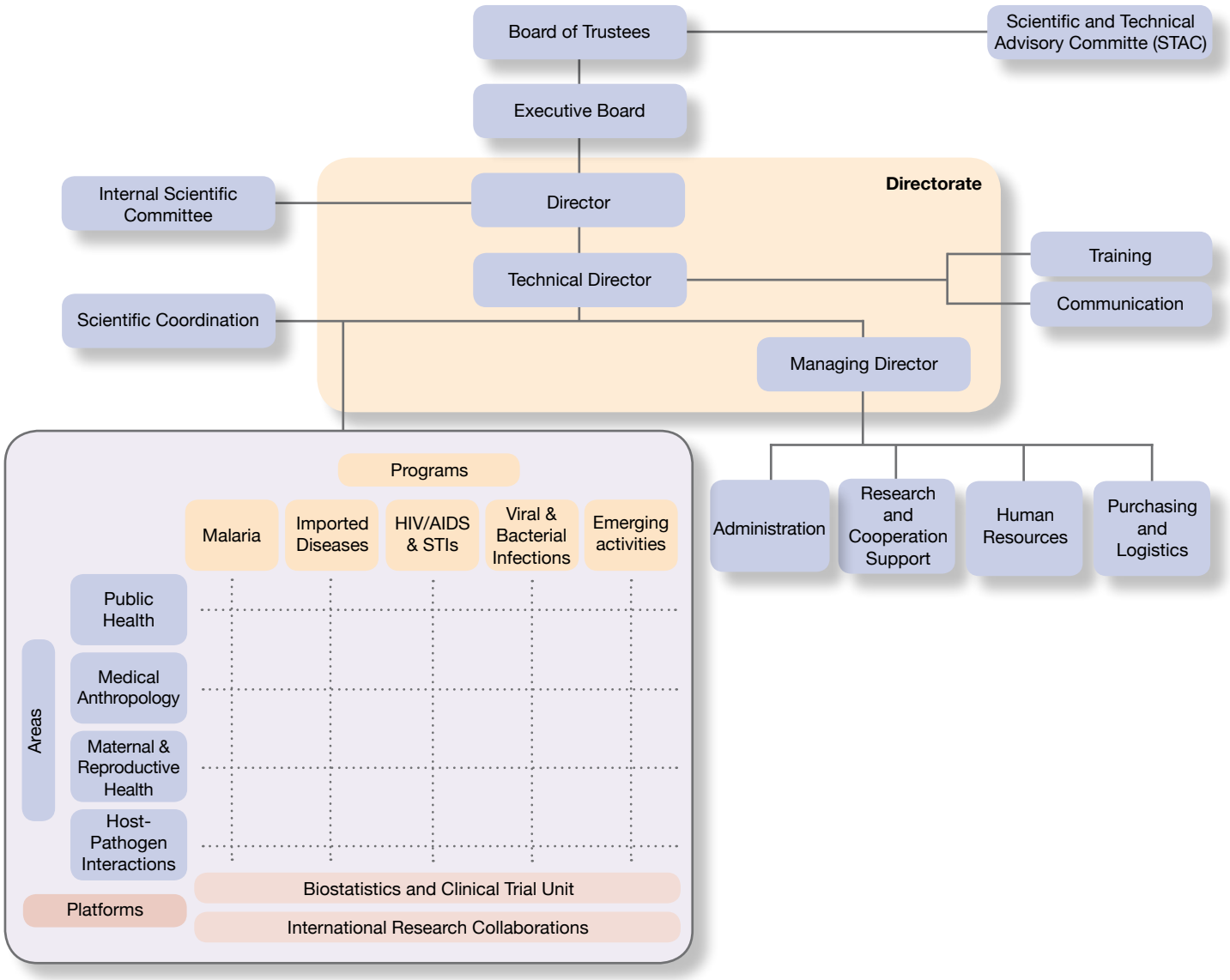
CRESIB already collaborates with more than 100 centres in 40 countries. The knowledge it has generated has made it one of the most important advisory and consultancy bodies on global health issues in Spain and internationally. Amongst other achievements, CRESIB headed up an unprecedented consultative process in 2010 which, under the auspices of the Malaria Eradication Research Agenda (malERA), brought together more than 250 scientists from 36 countries with the aim of identifying the research and tools necessary to potentially eradicate malaria. After more than twenty meetings and far-reaching discussions, the results will be published at the beginning of 2011 in a special issue of the journal *PLoS Medicine*.

2010 also saw the birth of the Institute for Global Health of Barcelona (ISGlobal), a new institution set up by the Spanish government, the Generalitat of Catalonia, the La Caixa Foundation, the University of Barcelona and the Hospital Clínic of Barcelona with the aim of consolidating a centre of excellence in global health, in which CRESIB forms the backbone of the research area. The aim of ISGlobal is to contribute to improving the health and development of the most disadvantaged population groups through the creation, management, transfer and implementation of global health knowledge.

We are looking forward to many challenges in the coming years. The immediate future looks uncertain due to the profound economic crisis and the wave of cutbacks that may reduce resources, forcing institutions to diversify their sources of financing to maintain their lines of research. We trust that CRESIB's notable capacity to attract competitive funding thus far will guarantee the continuity of our project.

Pedro L. Alonso
Director

Organization Chart



Scientific and Technical Advisory Committe (STAC)

Appointed by CRESIB's Board of Trustees and constituted by eleven renowned external researchers and experts in the field of international health, the tasks of this committee include assessment and evaluation of the scientific activities and research programs undertaken by CRESIB, including uptake of strategies, selection of research staff and evaluation of the Strategic Plan.

Members of the STAC

Dr. José Alcamí
Head, AIDS Immunopathology Unit
National Microbiology Centre
Carlos III Health Institute
Madrid (Spain)

Dr. Mariano Esteban
Director
National Biotechnology Centre
Spanish National Research Council (CSIC)
Madrid (Spain)

Dr. María C. Freire
President
Lasker Foundation
New York (USA)

Dr. Federico Gómez de las Heras
Former VP Director (retired)
Drug Discovery Unit for Diseases
of the Developing World
GlaxoSmithKline
Tres Cantos, Madrid (Spain)

Dr. Marie-Paule Kieny
Director
Initiative for Vaccine Research
World Health Organization
Geneva (Switzerland)

Dr. Vicente Larraga
Director
Biological Research Centre
Spanish National Research Council (CSIC)
Madrid (Spain)

Prof. Myron M. Levine
Grollman Distinguished Professor and
Director
Center for Vaccine Development
School of Medicine, University of Maryland
Baltimore (USA)

Prof. David Mabey
Professor of Communicable Diseases
Clinical Research Unit
London School of Hygiene
& Tropical Medicine
London (United Kingdom)

Dr. José Nájera
Ex-Director of the Tropical Disease
Program
(Malaria Program)
World Health Organization
Geneva (Switzerland)

Dr. Regina Rabinovich
Director of Infectious Diseases
Global Health Program
Bill & Melinda Gates Foundation
Seattle (USA)

Prof. Marcel Tanner
Professor and Director
Swiss Tropical and Public Health Institute
Basel (Switzerland)

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- Deputy Director:
  Prof. Dr. Núria Casamitjana Badia
- Economic and Financial Director:
  Ms. Margarita Sala

Internal Scientific Committee (ISC)

The Internal Scientific Committee (ISC) is an internal body that assesses the CRESIB directorate on scientific matters. It is constituted by the Director, the Technical Director, the Research Professors, the Associate Research Professors and the Scientific Coordinator who holds the Secretariat. The main tasks of this Committee are:

- To evaluate research proposals to ensure they are consistent with the objectives of the centre and compatibility with its Scientific Program.

- To participate in the recruitment of research staff by evaluating candidates for posts or scholarships offered by CRESIB.

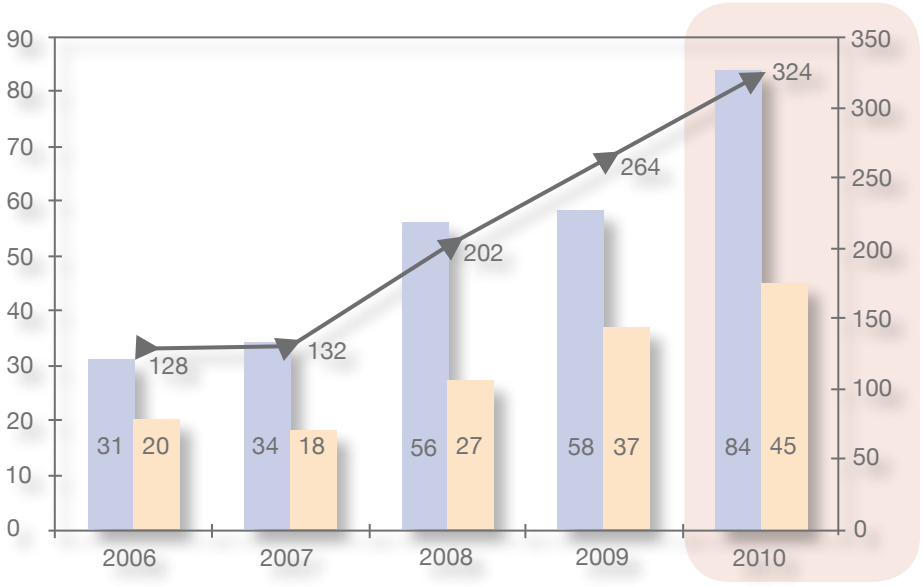
This Committee also serves as a forum for updating and discussing with senior researchers important scientific aspects concerning the centre.

In 2010 the Committee was made up of the following members:

Dr. Pedro L. Alonso, Dr. Núria Casamitjana, Dr. Hernando A. del Portillo (chair until October 2010), Dr. Edward B. Hayes (chair from October 2010), Dr. Joaquim Gascón, Dr. Robert Pool, Dr. Clara Menéndez, Dr. John J. Aponte, Dr. Jordi Vila, Dr. Tomàs Pumarola, Dr. Jaume Ordi and Dr. Antoni Trilla.

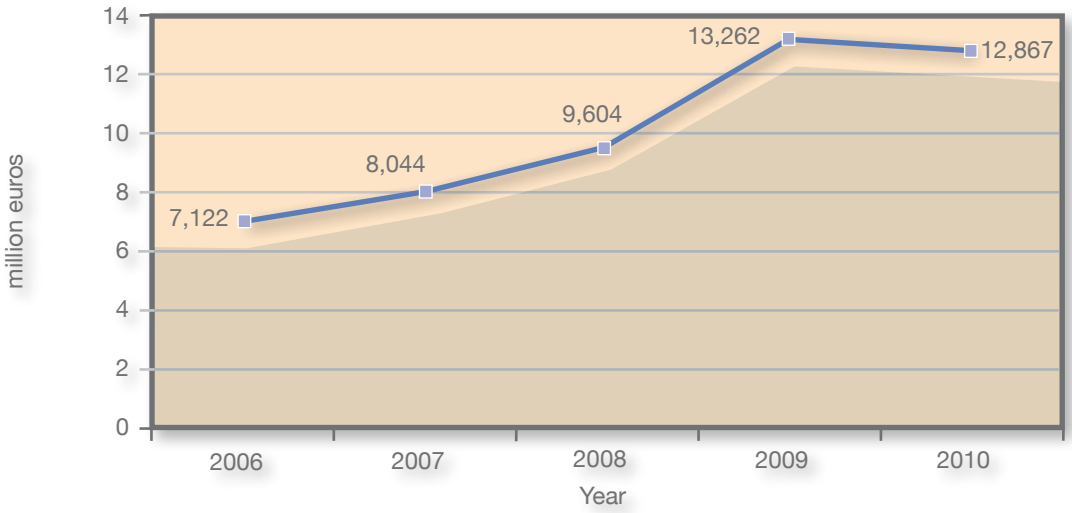
Facts and Figures

CRESIB Publications



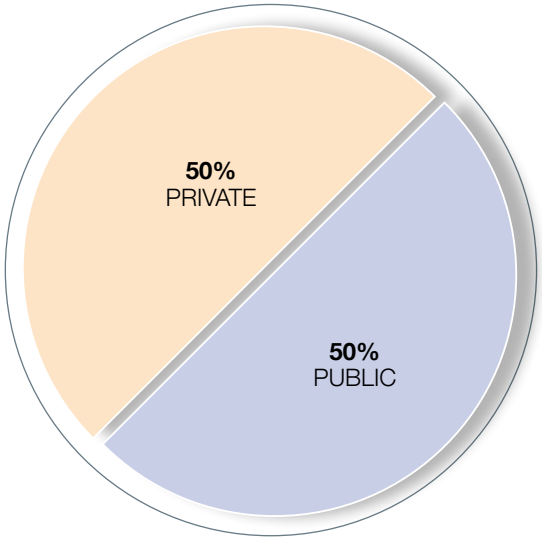
Number of articles, impact factor and articles in the first quartile of the speciality published by CRESIB's researchers since its foundation.
NOTE: This includes papers by researchers attached to CRESIB since January 2010, from founders institutions, regardless of the affiliation indicated by the authors of the paper.

Research Funding



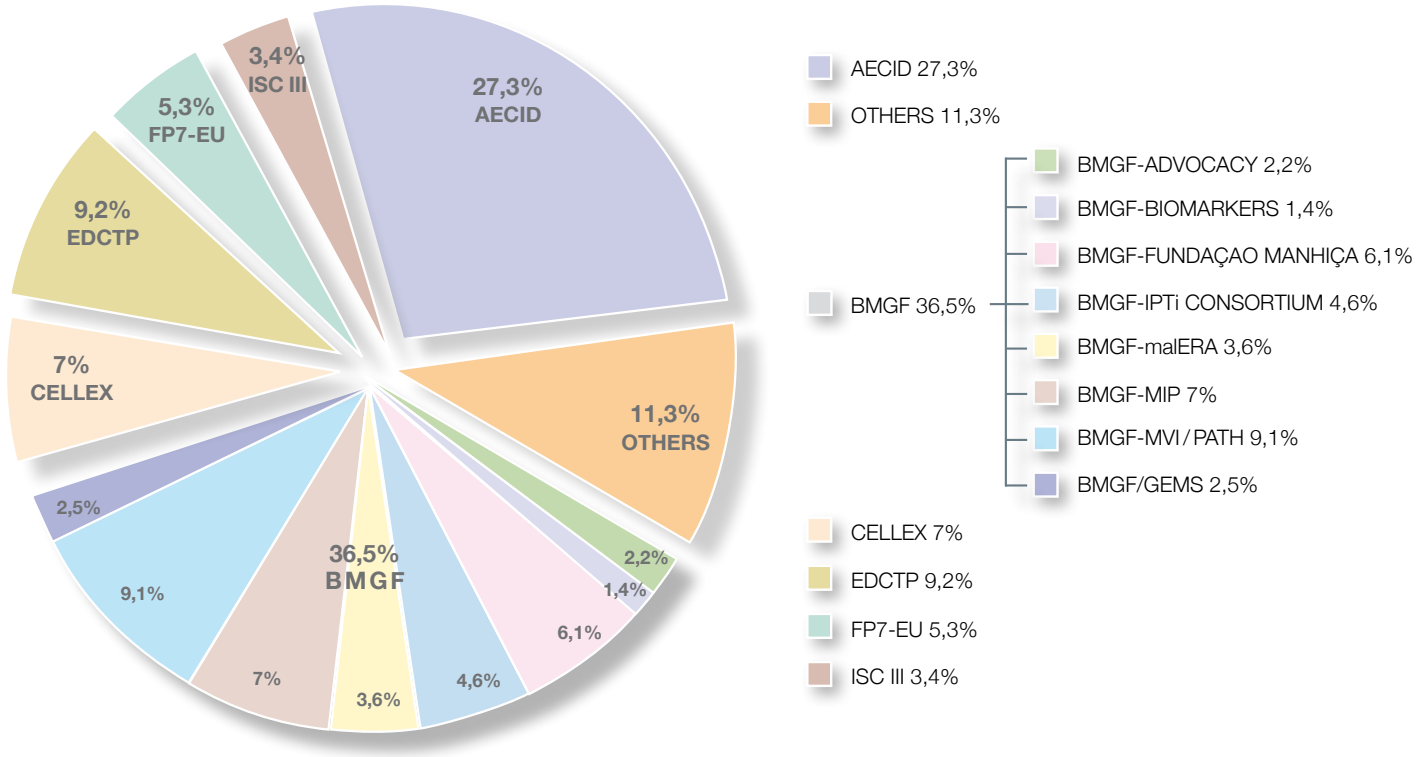
Evolution of CRESIB's annual executed budget since its foundation. The Centre is financed by international health research funds (competitive and structural funds) awarded to CRESIB, its founding institutions (Hospital Clínic de Barcelona, IDIBAPS, University of Barcelona) and the Clinic Foundation for Biomedical Research (FCRB), acting as the organization responsible for managing these funds.
NOTE: Following the audit, there may be changes to the data for 2010.

Sources of funding



Sources of funding (public or private) for project funds and grants active in 2010.

Main Funders

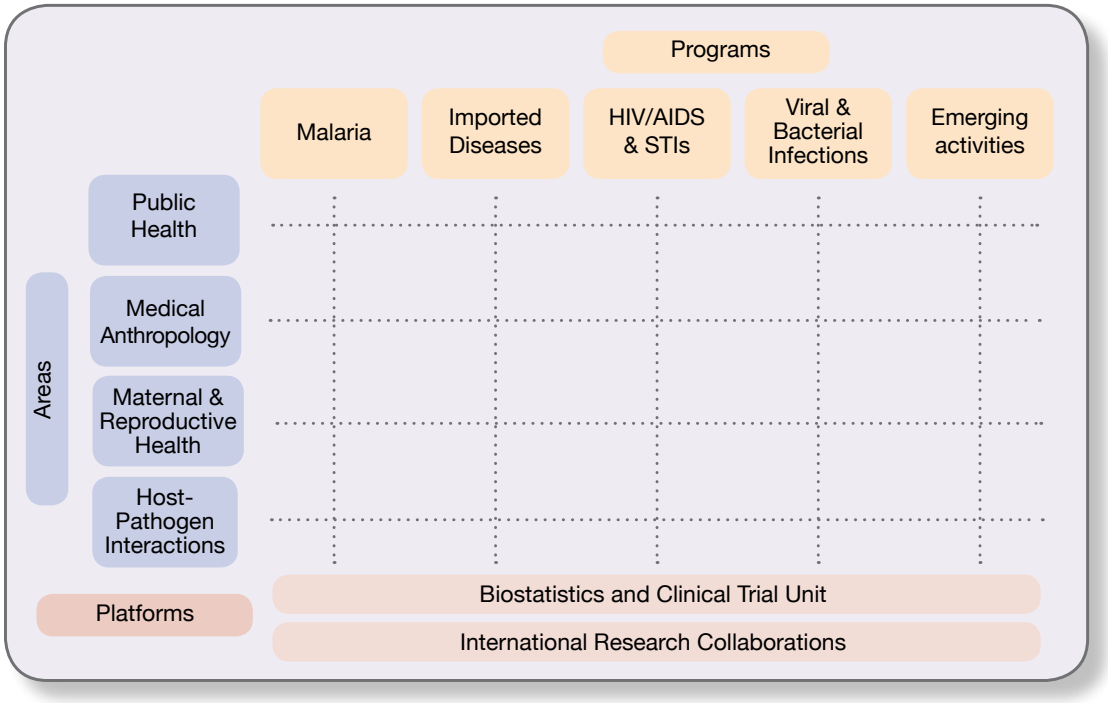


CRESIB's main funders, taking into account project funds and grants active in 2010. As in the Research Funding graph, these include international health research funds awarded to CRESIB, to its founding institutions (Hospital Clínic, IDIBAPS, University of Barcelona) and to the Clinic Foundation for Biomedical Research (FCRB). (AECID, Spanish International Development Cooperation Agency; BMGF, Bill and Melinda Gates Foundation; EDCTP, European and Developing Countries Clinical Trials Partnership; EU, European Union; ISCIII, Carlos III Health Institute; IPTi Consortium, Intermittent Preventive Treatment in Infants Consortium; malERA, Malaria Eradication Research Agenda; MiP, Malaria in Pregnancy Consortium; MVI/ PATH, Malaria Vaccine Initiative/ Program for Appropriate Technology in Health; GEMS, Global Enteric Multi-Centre Study; FP7 EU, Framework Program 7 European Union).

Research Organization

Four years after its creation, the Barcelona Centre for International Health Research (CRESIB, Hospital Clínic – University of Barcelona) has implemented in 2010 a new organizational model which is a more faithful reflection of the multidisciplinary and cross-cutting nature of the Centre's research and contributes better to achieving its mission: To improve global health through research and training.

CRESIB has been re-organized into a matrix organization to maximize interaction between researchers and to better coordinate and promote multidisciplinary, translational and cross-cutting research, as shown in the following chart:



CRESIB's new scientific matrix organization

This matrix contains:

Areas as disciplines focused on health systems or health problems of relevant population groups:

- Public Health (Effectiveness and Safety of Preventive Interventions)
- Medical Anthropology
- Maternal and Reproductive Health
- Host-Pathogen Interactions

Programs focusing on diseases or particular groups of diseases:

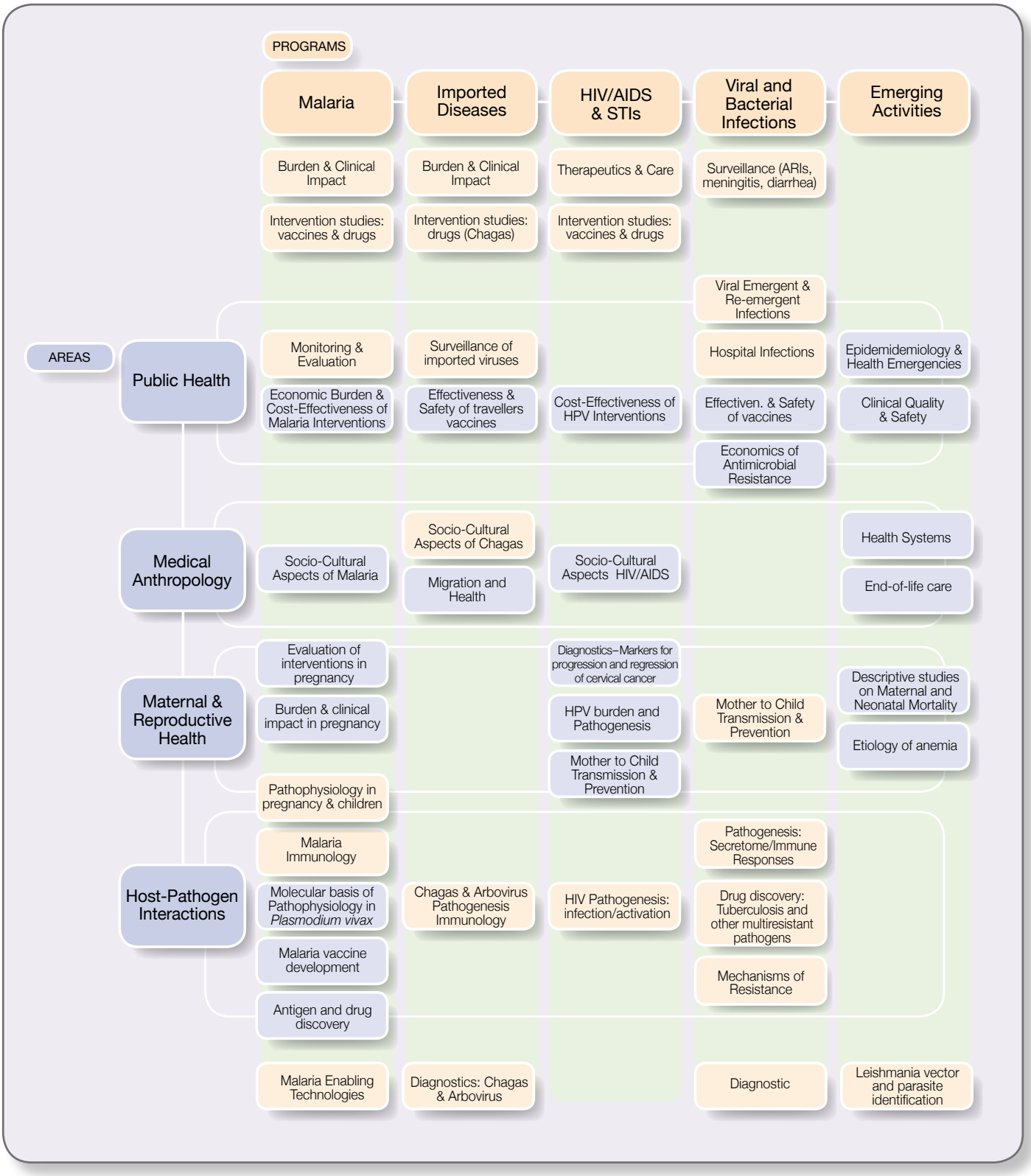
- Malaria
- Imported Diseases
- HIV/AIDS and Sexually Transmitted Infections
- Bacterial and Viral Infections

Platforms providing specific research support services that can have their own (methodological) research:

- Biostatistics and Clinical Trial Unit
- International Research Collaborations

Specifically, each research program or area has its own lines of research which can include researchers from different disciplines, as shown in the following chart, where the colour indicates where the principal researcher is based. The "Emerging Activities" program has been added to include those projects/lines which are not cross-cutting and whose track record does not yet allow them to be considered as programs or areas.

CRESIB's lines of research by programs and areas.



The lines of research include:

Malaria

- **Malaria Enabling Technologies:** development of technologies or methodologies to improve malaria research.

Malaria/ Host-Pathogen Interactions

- **Antigen and drug discovery:** aims at discovering new antigens for the development of *Plasmodium* vaccines and new drugs against malaria.

- **Malaria vaccine development:** focused on the development of a subunit vaccine and platform against *Plasmodium vivax* malaria.

- **Malaria Immunology:** aims at describing the naturally-acquired humoral and cellular immune responses associated with protection from clinical malaria in children and pregnant women and at describing the mechanisms of humoral and cellular immune responses induced by the RTS,S malaria vaccine in children.

- **Molecular basis of pathophysiology in *Plasmodium vivax*:** focused on the role of adherence and variant proteins in the pathology associated with infections of *Plasmodium vivax.*

Malaria/ Maternal and Reproductive Health

- **Pathophysiology in pregnancy and children:** focused on the pathophysiology of malaria in pregnancy and its immune mechanisms, on the parasite factors of severe *Plasmodium falciparum* malaria, and on resistance to antimalarials.

- **Burden and clinical impact in pregnancy:** description of the burden and clinical impact of malaria on pregnancy outcomes in different epidemiological settings.

- **Evaluation of interventions in pregnancy:** currently focused on evaluating alternative drugs for intermittent preventive treatment for malaria in pregnancy (IPTp).

Malaria/ Medical Anthropology

- **Socio-cultural aspects of malaria:** description of the broader social and cultural context of malaria in pregnancy and its influence on the acceptability and implementation of different malaria in pregnancy treatment and prevention strategies.

Malaria/ Public Health

- **Economic Burden & Cost-Effectiveness of malaria interventions:** cost-effectiveness studies of preventive interventions of malaria in pregnancy and estimate of the economic burden of malaria in pregnancy in areas of both high and low transmission.

- **Monitoring and Evaluation:** monitoring and evaluation of malaria burden and interventions, including assessment of the effectiveness of malaria control tools and monitoring of antimalarial drug efficacy and resistance.

Malaria

- **Intervention studies: vaccines and drugs:** assessment of the safety, efficacy and effectiveness of malaria vaccines, new antimalarial treatments and drug combinations in children or adults. It also includes the development of statistical methodology in the evaluation of clinical trials, including how to estimate the duration of the protection provided by malaria prevention tools.

- **Burden and clinical impact:** description of the burden, clinical presentation and epidemiological features of malaria in different epidemiological settings as a baseline for intervention studies.

Imported Diseases

- **Diagnostics: Chagas and Arboviruses:** studies aimed at discovering new tools for the diagnosis of Chagas and Arboviral diseases.

Imported Diseases/ Host-Pathogen Interactions

- **Chagas and Arboviruses: Pathogenesis/ Immunology:** studies aimed at understanding the molecular, physiopathological mechanisms and immunological responses of *Trypanosoma cruzi* and/or Arboviral infections, including the discovery of new biomarkers.

Imported Diseases/ Medical Anthropology

- **Migration and Health:** studies on the pathological and socio-cultural aspects related to migrants' health and studies on the full migration cycle in relation to the health systems in Europe and Latin America in order to suggest general and specific (disease-driven) policies to address the priority aspects of ill-health of the migrant population.

- **Socio-cultural aspects of Chagas:** medical anthropological studies on Chagas diseases such as the accessibility of the Catalan health system to Chagas patients.

Imported Diseases/ Public Health

- **Surveillance of imported viruses:** epidemiological surveillance of imported viruses such as dengue and chikungunya.

- **Effectiveness and Safety of travellers vaccines:** focused on the safety and immunogenicity of yellow fever vaccine in special populations and the monitoring of safety of commercially available vaccines through participation in the Brighton Collaboration (www.brightoncollaboration.org) and episodic consultations.

Imported Diseases

- **Intervention studies: drugs (Chagas):** clinical development of drugs for the treatment of Chagas disease and other imported diseases.

- **Burden and Clinical Impact:** description of the burden, clinical presentation and epidemiological features of imported diseases as a baseline for intervention studies.

HIV/AIDS and Sexually Transmitted Infections/ Host-Pathogen Interactions

- **HIV Pathogenesis: infection/activation:** study of factors related to HIV entry and to pathogenesis of early immune activation.

HIV/AIDS and Sexually Transmitted Infections/ Maternal and Reproductive Health

- **Diagnostic-Markers for progression and regression of cervical cancer:** studies to improve the tools for diagnosing cervical cancer by looking for biomarkers for the progression and regression of cervical cancer.

- **Mother-to-child transmission and prevention:** study of strategies to prevent mother-to-child transmission and the impact of maternal HIV infection on child outcomes.

- **HPV burden and pathogenesis:** assessment of the burden of cervical cancer and Human Papilloma Virus (HPV) infection in different epidemiological settings in Africa as a baseline for studying the safety and effectiveness of HPV vaccine in adolescent girls. It also includes the study of the role of HPV in the pathogenesis of human cancer.

HIV/AIDS and Sexually Transmitted Infections/ Medical Anthropology

- **Socio-cultural aspects of HIV/AIDS:** studies on the feasibility and acceptability of microbicides and of future HIV vaccine trials.

HIV/AIDS and Sexually Transmitted Infections/ Public Health

- **Cost-Effectiveness of HPV interventions:** assessment of the cost-effectiveness of implementing Human Papilloma Virus vaccinations.

HIV/AIDS and Sexually Transmitted Infections

- **Intervention studies: vaccines and drugs:** focused on capacity-building and raising baseline information to conduct future HIV vaccine trials in Mozambique, on studies on the safety and effectiveness of HPV vaccines in adolescent girls and on the assessment of the safety and efficacy of co-administration of antimalarials and antiretroviral drugs in HIV-infected individuals.

- **Therapeutics and care:** studies on the evaluation of the impact of highly active antiretroviral therapy (HAART) on morbidity, mortality and interactions with co-infections.

Viral and Bacterial Infections

- **Diagnostic:** identification and characterization of biomarkers to discriminate between pneumonia and malaria in poor resource settings, as well as the development of new microbiological techniques in the etiological diagnosis of pneumonia and bacteraemia.

Viral and Bacterial Infections/ Host-Pathogen Interactions

- **Mechanisms of resistance:** studies on the mechanisms of resistance to antibiotics and their correlation with virulence.

- **Drug Discovery: tuberculosis and other multiresistant pathogens:** focused on the *in vivo* evaluation of new fluoroquinolones and on drug discovery for multiresistant bacteria.

- **Pathogenesis: Secretome/immune responses:** studies on the proteins secreted by the bacterial pathogens and their correlation with virulence.

Viral and Bacterial Infections/ Maternal and Reproductive Health

- **Mother-to-child transmission and prevention:** studies on the epidemiology of maternal bacterial and viral carriage and its relation to premature delivery and early neonatal sepsis.

Viral and Bacterial Infections/ Public Health

- **Hospital Infections:** focused on improvements in the prevention and control of hospital infections.

- **Viral Emergent and re-emergent infections:** virological surveillance of emergent and re-emergent viruses, including the identification of circulating viruses, molecular epidemiology studies, studies on virulence factors, antiviral resistance genotypes, seroprevalence, seroprotection and on the presence in the reservoir or vector.

- **Economics of Antimicrobial Resistance:** cost-effectiveness of interventions for the prevention and treatment of viral and bacterial infections and estimates of the associated economic burden.

- **Effectiveness and safety of vaccines:** studies on the safety and effectiveness of vaccines to prevent viral and bacterial infections.

Viral and Bacterial Infections

- **Surveillance (ARIs, meningitis, diarrhea):** studies on the burden of disease, etiology and antibiotic susceptiblity of Acute Respiratory Infections (ARIs), diarrhea and meningitis as a tool to prioritize Public Health Interventions.

Emerging Activities

- ***Leishmania* vector and parasite identification:** studies on the ecoepidemiology of *Leishmania* and its diagnostic and drug susceptibility.

Emerging Activities/ Maternal and Reproductive Health

- **Etiology of anaemia:** description of the etiology of anaemia in infants, the contribution of malaria, and the evaluation of the safety and efficacy of prophylactic iron supplementation in African children.

- **Descriptive studies on maternal and neonatal mortality:** studies on the causes of maternal and neonatal mortality in different settings in Africa to evaluate whether maternal and neonatal death can be significantly reduced by implementing prevention tools.

Emerging Activities/ Medical Anthropology

- **End-of-life care:** studies on the positive diversities of European priorities for research and measurement in end-of-life care culture and home-based care in Africa.

- **Health Systems:** development of ethnographic studies with a focus on understanding health systems and their contexts.

Emerging Activities/ Public Health

- **Clinical Quality and Safety:** studies to improve quality and safety in clinical practice.

- **Epidemiology and Health Emergencies:** local epidemiological studies and studies to improve the management of health emergencies.

Malaria

Program Leaders: Pedro L. Alonso and Hernando A. del Portillo

Researchers working on the program:

Clara Menéndez
Ivo Mueller
Jaume Ordi
Robert Pool
John J. Aponte
Carlota Dobaño
Alfredo Mayor
Azucena Bardají
Quique Bassat
Carmen Fernández-Becerra
Xavier Fernàndez-Busquets
Caterina Guinovart
Luis Izquierdo
Ruth Aguilar
Francisco Javier López
Lorena Martín
Arantza Meñaca
Gemma Moncunill
Pilar Requena
Edmilson Rui
Elisa Sicuri
Juan José Valle
Raquel González
Miguel Lanaspa
Joseph Joe Campo
Christopher Pell
Pedro Aide
María Bernabeu
Mireia Ferrer
Ariel Magallón
María Nelia Manaca
Ernest Moles
Laura Moro
Diana Quelhas
Eduard Rovira
Patrícia Urbán
Laura Puyol
Josep Astola
Diana Barrios
Pau Cisteró
Alfons Jiménez

Introduction

The WHO estimated 225 million malaria cases and 781,000 deaths due to malaria in 2009, the highest burden being focused in Sub-Saharan Africa and among children under five years of age and pregnant women. Despite decreases in the malaria burden observed in most endemic regions in recent years, there is still a long way to go to achieve WHO and Roll Back Malaria (RBM) Partnership targets for 2015 (reduce the number of malaria cases and deaths recorded in 2000 by 75% or more by 2015) and even further to eventually reach the goal of malaria eradication.

Malaria burden is mainly caused by two different parasite species, *Plasmodium falciparum* and *Plasmodium vivax*, with *Plasmodium vivax* historically being the most neglected one. The recent call for malaria eradication has highlighted the importance of doing research on both parasites if eradication is to be achieved. CRESIB's malaria program includes a comprehensive research portfolio with a translational view (from discovery through development to delivery) on both species, *Plasmodium falciparum* and *Plasmodium vivax*. This program is also fed from research in the areas of maternal and reproductive health, medical anthropology and host-pathogen interactions.

Malaria is one of the strongest programs at CRESIB, which has contributed to the clinical development of new tools for the prevention and treatment of malaria including Intermittent Preventive Treatment strategies for both infants and pregnant women, proof-of-concept studies involving infants and children of the GlaxoSmithKline RTS,S malaria vaccine candidate (currently the most clinically advanced) and new artemisin-based combination treatments. CRESIB's malaria program also includes

research on naturally acquired and experimentally-induced immunity, on the pathophysiology of the disease and on antigen and drug discovery.

CRESIB is firmly engaged with the long-term goal of malaria eradication and has held the secretariat of the Malaria Eradication Research Agenda (malERA) initiative which aimed to identify the knowledge gaps and tools needed for malaria eradication.

Objectives

- To discover new antigens and potential drug targets to prevent and treat malaria and develop nanovectors for targeted drug delivery
- To discover biomarkers of immunity and susceptibility to malaria in individuals exposed to *Plasmodium* infection, including immuno-pathological markers of severe malaria and placental malaria
- To understand the impact of malaria control tools in the development of naturally-acquired immunity and the immunity induced by the RTS,S malaria vaccine candidate
- To establish the burden of disease and the epidemiology of malaria in different epidemiological settings as a baseline for interventions
- Clinical development of new and improved control tools
- To monitor and evaluate malaria and the effectiveness of malaria control tools
- To develop a multidisciplinary global R&D agenda for malaria eradication

Summary of main results in 2010

Along the continuum from discovery through development to delivery, CRESIB's malaria program develops and/or validates new enabling technologies that offer significant improvements for research on malaria and other fields[1]. In 2010, a multiplex assay to measure naturally-acquired IgG antibodies against merozoite surface protein 1 (PvMSP1) of *Plasmodium vivax* was validated. This assay was the first to measure naturally-acquired humoral IgG antibody responses against a *Plasmodium vivax* antigen and the first one to study IgG subclasses in malaria. Prospective comparative longitudinal cohort studies in different endemic regions using the BioPlex assay can now be envisaged to look for associations against infection and clinical protection, having clear implications in antigen discovery and vaccine development for *Plasmodium vivax*.

In addition, a duplex quantitative real time PCR (qPCR) assay was developed and validated for the detection of all four *Plasmodium* species (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*). This diagnostic method has the added advantage of quantification of parasite densities and a less laborious workflow and performed well in field samples. Furthermore, due to its high throughput capacity, it is suitable for large scale epidemiological studies and could be of greatest value for monitoring malaria control programs.

For the discovery of new antigens and potential drug targets it is very important to understand the pathophysiology of the disease. In 2010, a significant contribution was made for *Plasmodium vivax* by describing a novel immune spleen evasion mechanism. The group findings revealed remodelling of the spleen and adherence to this organ in Balb/c mice infected with the reticulocyte-prone non-lethal *Plasmodium yoelii* 17X strain, suggesting that structural remodelling of the spleen might have a role in chronic infection as it is somehow related to delay in the onset of precrisis and prevention of host death. A similar mechanism is postulated to occur

1 - See the host-pathogen interaction area for further information

in *Plasmodium vivax*, a reticulocyte-prone non-lethal human malaria parasite, as cytoadhesion has been reported to occur in cells expressing endothelial receptors in a study in which CRESIB researchers also collaborated.

With regard to the development and delivery of malaria control tools, CRESIB's malaria program continued to make important contributions. CRESIB's research on malaria prevention tools focuses on Intermittent Preventive Treatment (IPT) against malaria in pregnant women (IPTp) and infants (IPTi), on the development of the RTS,S malaria vaccine and on Indoor Residual Spraying (IRS).

Intermittent Preventive Treatment involves delivering treatment doses of an antimalarial drug at specified times during pregnancy (IPTp) or during routine Expanded Program on Immunization (EPI) visits (IPTi), regardless of *Plasmodium* infection status.

In 2010, results showed that IPTp with sulfadoxine pyrimethamine (SP) reduces neonatal mortality and is highly cost-effective in both the prevention of maternal malaria and the reduction of neonatal mortality in Mozambique. In addition, the program reported an IPTp-associated reduction in antibodies in HIV-infected women but not in HIV-uninfected women, which did not translate into an enhanced risk of malaria-associated morbidity in mothers and infants. This result may reflect a higher efficacy of the IPTp intervention in preventing malaria among HIV-positive mothers.

Regarding IPTi, a cost-effectiveness analysis has been done showing that IPTi delivered alongside the EPI is a highly cost-effective intervention against clinical malaria with a range of drugs in a range of malaria transmission settings in Sub-Saharan Africa. In addition, building on previous acceptability studies undertaken in Sub-Saharan Africa, CRESIB's researchers from the Medical Anthropology area have investigated the acceptability of IPTi in Papua New Guinea. Their results show similar findings to those reported in Sub-Saharan Africa and Papua New Guinea: IPTi fits in well with local health cultures, appears to be easily accepted and has little impact on attitudes towards the Expanded Program of Immunization (EPI) or malaria prevention. These results reinforce evidence indicating that IPTi could be rolled out in a range of social and cultural contexts.

One of the landmarks of CRESIB's malaria program has been the clinical development of the GSK's RTS,S malaria vaccine candidate in infants and children from the early proof-of-concept trials. In 2010, the group showed that the RTS,S/AS02D malaria vaccine administered to infants has a good safety profile and remains efficacious

over fourteen months. In addition, for the first time a strong association between anti-CS antibodies and risk of clinical malaria has been described. The results also suggest a decrease of both anti-CS antibodies and vaccine efficacy over time. Currently CRESIB, together with its partners at the *Centro de Investigação em Saúde de Manhiça* (CISM), is leading the Phase III clinical trial in Mozambique, which has also been undertaken in ten other sites in seven African countries.

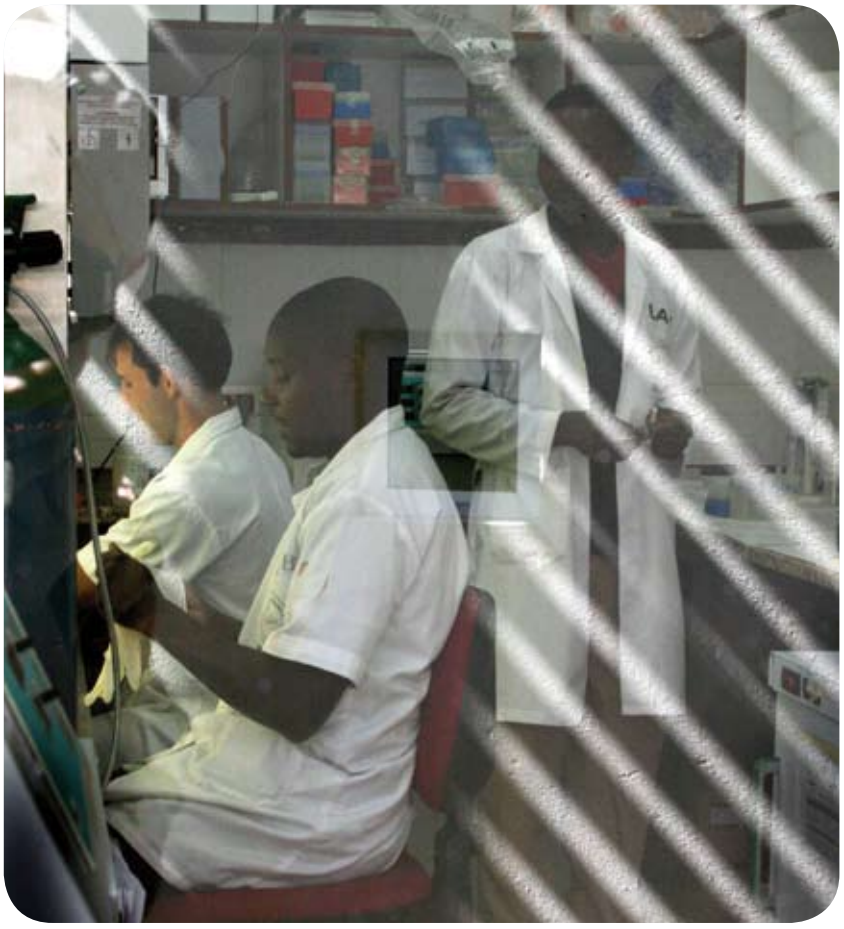
Finally, indoor residual spraying (IRS), a primary vector control intervention for reducing malaria transmission, has been shown to be broadly acceptable despite very low levels of perceived efficacy and duration of effect in Manhiça, Mozambique.

With regard to malaria treatment, program researchers participated in a study to evaluate the effect of food intake on oral lumefantrine bioavailability in African children with malaria receiving artemether-lumefantrine (AL). The study showed that AL was highly efficacious and that concomitant food intake increased lumefantrine absorption in children with malaria.

In a different study, the influences that determine treatment-seeking behaviour for malaria in Papua New Guinea were analysed, concluding that simply bringing health services closer to where people live may not always result in a greater use of formal health care facilities. Aspects such as within-country variation in treatment-seeking behaviour and the role of traditional healers should be taken into account as well as ensuring that the community fully understands the potential implications of not seeking treatment for illnesses such as malaria at a formal health care facility.

CRESIB endorses the re-establishment of malaria eradication as a long-term goal brought up at the Malaria Forum convened by the Bill & Melinda Gates Foundation in 2007, and has held the secretariat of the Malaria Eradication Research Agenda (MalERA) initiative. This initiative consisted of a rigorous scientific consultative process involving more than 250 scientists to identify current knowledge gaps and new tools needed for malaria eradication. The outcomes of the process have been compiled in twelve reviews that will be published in *PLoS Medicine* in January 2011.

Photo: Kim Manresa



Imported Diseases

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Introduction

Due to the increase in international flights, migratory flows, international trade and climate change, the epidemiology of many infectious diseases has experienced significant changes in the last few years. In this respect, some of the biggest challenges facing modern-day societies include: the emergence of diseases in new geographic zones; the transfer of vectors from one area to another; and the reintroduction of diseases that had previously been eradicated. From the perspective of health care, the challenge lies in providing a health system that is capable of tackling the diagnosis of unusual and hence unfamiliar diseases and being open to the implementation of new prevention and control strategies.

Taking advantage of the research tools currently available and the networking possibilities available today at an international level, CRESIB's imported diseases program aims to contribute to improving knowledge of the diseases which for many years, because they have tended to affect disadvantaged people in developing countries, have not warranted the attention of either funders nor, on many occasions, the scientific community.

Objectives

The imported diseases program aims to evaluate the impact of imported pathologies on health systems as well as improving clinical and physiopathological knowledge about them in order to provide better care for patients. However, some lines of research which started off based on imported diseases have now expanded their focus to include research on their impact on endemic countries, an example being the research on Chagas disease.

The main line of research is currently focused on Chagas disease, supporting epidemiological and clinical research on Chagas disease in both Barcelona and Cochabamba (Bolivia):

- Planning joint studies and Ibero-American collaborations to obtain new tools to improve the comprehensive management of Chagas disease.
- Characterization of patients with chronic Chagas disease with digestive conditions in endemic (Cochabamba) and non-endemic areas (Barcelona).
- Investigate the role of echocardiography and different markers of cardiac disease in patients with Chagas at the indeterminate and early cardiac phases.
- Search of prothrombotic and cellular markers of the progression/cure of Chagas disease.
- Describe the profile of adverse events due to Benznidazol treatment in patients with chronic Chagas disease.
- Study *Trypanosoma cruzi* infection among adult migrants originating from continental Latin America in a Primary Health Care Centre of Barcelona.

But there are also collaborations and projects on other imported pathologies with an important line of research developing on the study of full cycle migration in relation to health systems:

- To provide an in-depth insight into priority health-related aspects of Latin American migration (together with the Medical Anthropology area).
- Epidemiological surveillance of imported diseases, mainly in collaboration with the European network TropNetEurop.

Summary of main results in 2010

One of the achievements in 2010 was to strengthen epidemiological and clinical research on Chagas disease in both Barcelona and Cochabamba, Bolivia, thanks to the creation of a Joint Research, Training and Health Care Platform in Cochabamba (Bolivia) with the NGO CEADES and the Higher University of San Simón. In addition, plans were implemented for the Ibero-American network NHEPACHA, which encompasses twelve Ibero-American research centers with the aim of sharing experiences and planning joint studies on new tools for caring for Chagas patients. These synergies have allowed the continuation of studies on curative/progression markers in Chagas disease and together with the Drugs for Neglegted Diseases Iniciative (DNDi) a clinical trial was planned with the drug E1224, which will be starting soon.

With regard to improved diagnoses and therapeutic management of Chagas disease, this research group treated an immunosuppressed Chagas patient for the first time with posaconazol, for whom benznidazol treatment had failed, with excellent results. This case was an incentive for speeding up research with new drugs. The side effects of benznidazol on a series of patients treated with this drug were also described, and a calculation was made of the percentage of patients who had abandoned their treatment due to these effects. At the same time, in a joint study with the Cardiology Service, it was found that measurement of the diastolic function by echocardiography shows the cardiac involvement of Chagas patients with more precision than other parameters, and that this involvement coincides with high BNP values (Brain Natriuretic Factor). These findings could improve the classification of patients in the chronic phases of the disease as well as the decision-making process in terms of the treatment and monitoring of patients.

It is also important to emphasize the funding of the consortium COHEMI (coordinating resources to assess and improve health status of migrants from Latin America) by the FP7 program this year. Within the consortium the CRESIB Imported Diseases Program coordinates the work package on neglected parasitic diseases while the medical anthropology area coordinates the work package on the social and cultural context of health-seeking behaviour of Latin American migrants in Europe.

An analysis was made of a series of patients affected by *Strongyloides stercoralis*, a nematode with the ability to autoinfest and prone to causing hyperinfestation in patients with immune deficiencies. A preventive strategy in cases with eosinophilia was discussed.

A collaborative project with TropNetEurop allowed the team to calculate the risk of malaria with different parameters to the usual ones (local transmission of malaria) in travellers to South East Asia, and to propose a policy of anti-malarial prophylaxis for travellers visiting these areas that more closely matches their genuine needs.

HIV/AIDS and Sexually Transmitted Infections

Program Leader: Denise Naniche

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Introduction

The UNAIDS/WHO estimated number of people living with HIV worldwide reached 33.4 million in 2009, and Sub-Saharan Africa (SSA) remains the region most heavily affected, accounting for 67% of HIV infections worldwide. SSA also bears a high burden of co-infections, including sexually transmitted infections (STI).

The prevalence of HIV in pregnant women exceeded 30% in certain regions of southern Africa, reflecting the gravity of the situation in the population as a whole, as well as the potential impact of maternal HIV infection on infants. Rates of mother-to-child transmission of HIV in SSA vary from 10-50% depending on the prevention available both at delivery and during breastfeeding.

Innovative prevention strategies or combinations of existing strategies are of the utmost importance to slow the spread of HIV in Sub-Saharan Africa. There is also an urgent need to better adapt antiretroviral therapy to the African context both for prevention as well as for optimization of treatment management.

The overarching aims of the HIV/AIDS and STI research program at CRESIB include aspects related to the development of innovative HIV prevention strategies, the impact of HIV infection on infants and the adaptation of HIV clinical management to the African context. The HIV/AIDS and Sexually Transmitted Infections program concentrates on HIV/AIDS in developing regions of the world and specifically in Mozambique, a country representative of the Sub-Saharan African AIDS epidemic. CRESIB has a longstanding collaboration with the Centro de Investigaçao em Saude de Manhiça (CISM) located in southern Mozambique where a great part of its research is conducted.

Objectives

The HIV/AIDS and STI research program at CRESIB encompasses numerous disciplines, including epidemiology, immunology, clinical science, molecular biology and anthropology.

The current research program aims to expand knowledge in the following areas:

- The key epidemiological and sociocultural determinants in the development of HIV prevention tools.
- Epidemiology of sexually transmitted diseases.
- Impact of maternal HIV infection on infant health.
- Implementation of clinical management strategies for decreasing early morbidity and mortality associated with antiretroviral therapy.

Summary of main results in 2010

In the area of epidemiology, studies were performed in both acute HIV infections and community HIV prevalence. Acute HIV infection (AHI) corresponds to the initial phase of HIV infection in which the virus is actively replicating but seroconversion has not yet occurred. In a prospective observational study at the Manhiça District Hospital in Mozambique it was shown that among the HIV seronegative patients, 3.3% were found to have AHI and showed extremely high levels of plasma HIV-1 RNA. These individuals may be hypertransmitters and could be targets for the positive prevention of sexually-transmitted HIV. Regarding the

community prevalence of HIV in Manhiça, Mozambique, in the context of the African European HIV Vaccine Development Network (Afrevacc), fieldwork for determining age-specific community HIV prevalence in Manhiça, Mozambique, has been completed and the data is under analysis.

The study of sociocultural determinants for the development of HIV prevention tools has been led from the area of Medical Anthropology which completed a study on the use of microbicides as an HIV prevention tool. The study suggests that current definitions and conceptual frameworks do not adequately account for the range of meanings that women attribute to microbicide gel, implying the need to move beyond limited notions of acceptability and consider how microbicides fit into a more holistic picture of women's and men's sexuality and sexual health.

Studies in Sexually Transmitted Infections has led to the identification of the relationship between squamous cell carcinoma of the vagina and human papillomavirus. Studies in Spain showed that 80% of vaginal carcinomas are caused by HPV, and that HPV 16 is the most frequent type. In addition, the risk of progression in HPV-positive women with minor or no cervical lesions has been assessed, showing that they have a similar risk of progression, regardless of the cytological result or colcoscopy findings and should benefit from the same follow-up strategies. The conjunctive interpretation of p16(INK4a)-stained cells in cervical biopsies could significantly improve the routine interpretation of cervical histopathology.

A study reported in Maternal and Reproductive Health has analyzed the preval- ence and etiology of STIs and cervical neoplasia in women in a rural area of Mozambique, showing a very high rate of STIs as a whole, approaching 80% (trichomoniasis, gonorrhea, chlamydia, syphilis, etc.).

In the area of HIV impact on infant health, field work has been completed for a study comparing haematological, immunological and health indicators between HIV-uninfected children born of HIV-positive women and those born of HIV-negative women.

With regard to the implementation of clinical management strategies for decreasing early morbidity and mortality associated with antiretroviral therapy, the Immune Reconstitution Inflammatory Syndrome (IRIS) is thought to be one of the determinants of early mortality in Sub-Saharan Africa. The characterization of IRIS in Manhiça, Mozambique revealed a prevalence of 26% in patients initiating antiretroviral therapy (ART) at the Manhiça district hospital. Risk factors for IRIS were a low baseline CD4 (<50 cells/mm^3) count and low body mass index (<18.5).

A specific study of Kaposi's Sarcoma (KS) associated IRIS in Mozambique identified risk factors in human herpesvirus-8 (HHV-8) and HIV co-infected patients initiating ART. A baseline HIV viral load >100,000 copies/ml, a baseline haematocrit >30%, the presence of detectable HHV-8 DNA in plasma at baseline, and previous clinical KS independently predicted KS-IRIS development in Manhiça. Work on KS-IRIS led to a multi-site study including cohorts from Sub-Saharan Africa and the UK, assessing the differences between resource-rich and resource-limited settings. The analysis showed that KS-IRIS incidence was two-and-a-half times fold higher in Sub-Saharan Africa than in the UK, and KS-IRIS mortality was restricted to the Sub-Saharan Africa cohorts. The work on KS-IRIS will be expanded through future collaborations in the context of the International Network for the Study of HIV-Associated IRIS (INSHI).

Viral and Bacterial Infections

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Introduction

One of the most important features of viruses and bacteria is their dynamic evolution and adaptation. In this sense, an interesting group of viruses is the arbovirus group. A comprehensive understanding of host-virus interactions and how they shape both host-specific and virus specific evolutionary pressures is needed to fully evaluate the factors that govern the potential for host shifts and geographic expansions.

Antimicrobial resistance of human pathogens is an increasing problem and it has limited the effective lifespan of newly-developed antimicrobial compounds. In addition, new effective antimicrobials are unlikely to be developed at a sufficient rate. This is posing a major challenge to find alternative ways of combating bacterial pathogens – or find ways to delay resistance development. The intention is to combine expertise in bacteriology, molecular biology, microbial epidemiology, and mathematical modeling to study the evolution and adaptation of antimicrobial resistance in bacterial populations. This will be useful for predicting the appearance of new resistance problems, guiding intervention strategies for the future, and leading to new and improved treatment strategies. Furthermore, the knowledge obtained might also lead to the industrial development of new biotechnologies based on evolutionary concepts.

Objectives

The Viral and Bacterial Infections research program at CRESIB embraces numerous disciplines, and is very closely related to the areas of Public Heath and Host-Pathogen Interactions. This is reflected in the following objectives:

- To improve treatment regimes and procedures for the management of infections caused by multidrug resistant bacteria by:
  - Knowledge of the initial processes of evolution to antimicrobial resistance.
  - Investigation of the molecular bases of antimicrobial resistance and dissemination.
  - Design and evaluation of new drugs.
  - Establishment of an African Antimicrobial Resistance Surveillance Network.
- Surveillance of diarrhoeal and respiratory viral diseases as well as arbovirosis in Africa.
- To identify and characterize new biomarkers to diagnose infectious diseases such as pneumonia.

- To investigate early and late neonatal sepsis and the pathogenesis of neonatal sepsis caused by *Escherichia coli*.
- To improve clinical quality and safety in hospitals in developing countries.

Summary of main results in 2010

During the past year, the research group of the Department of Clinical Microbiology at the Hospital Clinic at CRESIB has become fully consolidated. The main findings of the research conducted over the last year have been in the area of antimicrobial resis-tance. Several new mechanisms of resistance to multiple antimicrobial agents have been and continue to be investigated; for instance, the characterization of a new efflux pump which contributes to resistance to different classes of antibiotics. In addition, the evolution of antimicrobial resistance in enterotoxigenic *Escherichia coli* responsible for travellers diarrhea has shown that there has been a significant increase in the resistance to quinolones in these microorganisms, causing diarrhea in travellers to India. This trend has also been studied in pathogens isolated in Mozambique and it has been reported in the increase of resistance to the most commonly-used antimicrobial agents, such as ampicillin or chloramphenicol. The link between antimicrobial resistance and virulence has been investigated, establishing a relationship between decreased cell invasion and quinolone resistance in *Salmonella spp*. and *Yersinia enterocolitica*. The role of procalcitonin and reactive-C-protein as a marker for bacterial pneumonia diagnosis has been studied, showing that these markers may be used to differentiate viral and bacterial pneumonia in a malaria-endemic area. Finally, an interesting line of research on yellow fever has been initiated, as reported in the area of Public Health.

Photo: Pau Fabregat

Public Health

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Introduction

While all of CRESIB's research is broadly applicable to public health, its strategic plan includes an area of research that is directly focused on public health action and response.

Within the vast field of public health, CRESIB researchers are focusing on the prevention of emerging infectious diseases with an emphasis on evaluating opportunities for the use of vaccines to reduce the infectious disease burden. The Public Health Area has completed work on the safety of yellow fever vaccines, cost-effectiveness evaluations related to malaria and HIV interventions, assessment of the need for rotavirus vaccination in Catalonia, preparedness for the introduction of emergent arboviruses into Catalonia, evaluation of the risk of vector-borne diseases among travellers, and response to pandemic influenza. Explorations have begun into initiating or expanding work on improving healthcare safety, and new strategies for the prevention of leishmaniasis.

Objectives

The Public Health Area has the following objectives:

- To evaluate the effectiveness of established preventive interventions such as commercially available vaccines.
- To monitor the safety of preventive interventions.
- To evaluate the economic effectiveness of such interventions.
- To improve and inform public health decisions that will optimize the implementation of effective disease prevention strategies in the public health context.

Summary of main results in 2010

Embracing a global perspective on health, the area evaluated the risk of vector-borne diseases from a novel perspective by considering risk among travellers to the United States and strategies to reduce such risk. Millions of travellers and immigrants enter the United States each year, and the highest number of travellers arrive during months of peak vector-borne disease transmission. Travel advice should focus on preventing Lyme disease, anaplasmosis and babesiosis in the northeast and north central States, West Nile virus disease in western plains States, and Rocky Mountain spotted fever and tularemia in the southeast; other diseases and itineraries requiring particular attention were described. All travellers to the United States should be advised to practice personal protection against arthropod bites, including appropriate use of insect repellents, especially when visiting rural and suburban areas during the warm months.

Yellow fever is one of the great infectious disease scourges of humankind. An inexpensive live attenuated vaccine (the 17D vaccine) against yellow fever has been effectively used to prevent yellow fever

for more than seventy years. Interest in developing new inactivated vaccines has been spurred by recognition of rare but serious, sometimes fatal, adverse events following live virus vaccination. CRESIB researchers participated in the international Brighton Collaboration process to develop a case-definition for viscerotropic disease as an adverse event after vaccination. The area also analyzed the utility of a newly developed inactivated yellow fever vaccine. A safer inactivated yellow fever vaccine could be useful for vaccinating people at higher risk of adverse events from the live vaccine, but could also have broader global health utility by lowering the risk-benefit threshold for assuring high levels of yellow fever vaccine coverage.

Recent studies have indicated that flaviviruses might persist in humans for longer periods of time than previously expected. A study was completed to evaluate possible persistence of yellow fever vaccine viral RNA in urine. Evidence of persistence of the vaccine virus might help elucidate mechanisms of long-lasting immunity conferred by the vaccine.

CRESIB worked with Catalan health officials to help plan preparedness for arboviral disease emergence in Catalonia. The risk of autochthonous dengue and chikungunya transmission remain a concern due to the infestations of the mosquito vector *Aedes albopictus*, the so-called "tiger mosquito", in many areas of Catalonia.

CRESIB also contributed to the development of a strategic plan to control dengue in Mesoamerica.

In 2009, the H1N1 influenza pandemic became a major public health issue. The CRESIB group prepared a case-detection protocol and data collection instrument for evaluating outcomes of pregnancies complicated by maternal influenza. This established a base for detecting the effects of any future outbreaks of influenza or other emerging viral diseases. In addition, the group reported an outbreak of 2009 H1N1 influenza among travelling medical students. The results showed markedly higher influenza attack rates among students on the trip than among their household contacts upon return to Barcelona, and suggested that secondary spread of influenza could be limited through practical hygiene recommendations.

Rotavirus is the most common cause of severe gastroenteritis among young children in Spain and worldwide. The CRESIB researchers estimated the frequency of community and hospital-acquired rotavirus gastroenteritis (RVGE) and related costs in children under 5 years old in Catalonia, Spain. According to analyses, immunisation would result in health system cost savings if the cost of the vaccine was 0.19 € or less, concluding that at current vaccine prices (187 €), rotavirus vaccine does not appear to provide cost savings in Catalonia.

Respiratory and diarrhoeal diseases are leading causes of childhood mortality worldwide. Researchers from the area collaborated in setting up studies to determine the burden of vaccine preventable causes of pneumonia and diarrhoea among children under five years of age at Hôpital d'Enfants de Rabat, Morocco. Two multiyear studies are now underway.

Medical Anthropology

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Introduction

Medical anthropology is important in public and international health and essential in the development of culturally acceptable healthcare. In addition to being effective, interventions need to be culturally sensitive and address local needs. Medical anthropological research takes into account the insider perspectives of the local communities that are the target of public health interventions.

Objectives

The Medical Anthropology Area at CRESIB encompasses numerous themes such as malaria, imported diseases and HIV/AIDS, focusing on the socio-cultural factors of health and disease with the following objectives:

- Implementing world-class independent social science research on the major issues in international and global health.
- Contributing social science expertise to multi-disciplinary collaborations aimed at researching and developing interventions in the field of international health.
- Developing innovative approaches and methodologies for studying the socio-cultural factors of health and disease.

Summary of main results in 2010

One of the lines of research with the most significant results in 2010 has been the Microbicides Development Program. This program completed its MDP301 Phase III trial of a candidate microbicide, which included a social science component led by CRESIB. The medical anthropology analysis undertaken in South Africa, Zambia, Tanzania and Uganda suggests that current definitions and conceptual frameworks do not adequately account for the range of meanings that women attribute to microbicide gel, implying the need to move beyond limited notions of acceptability and consider how microbicides fit into a more holistic picture of women's and men's sexuality and sexual health. The program also involved the development of an innovative mixed-

methods model for studying adherence and sexual behaviour. This model generated more accurate data than conventional Case Record Form (CRF) questionnaires and revealed major inaccuracies in the data collected using CRFs.

This Area also made some major contributions to understanding the acceptability of malaria interventions. First, Indoor Residual Spraying (IRS) was found to be broadly acceptable despite very low levels of perceived efficacy and duration of effect. The involvement of local governmental leaders in the intervention appears to have led many people to accept spraying as part of their civic duty, as decreed by the post-war decentralization policy in rural areas in Mozambique. Second, the degree of similarity between findings from acceptability studies undertaken in various Sub-Saharan African countries and Papua New Guinea allows for some generalization with regard to the implementation of intermittent preventive treatment of malaria in infants (IPTi). IPTi was found to fit in well with local health cultures, appears to be accepted easily and has little impact on attitudes towards the Expanded Program on Immunization (EPI) or malaria prevention. The evidence indicates that IPTi could be rolled out in a range of social and cultural contexts.

In 2010 the FP7 program funded the COHEMI Consortium (coordinating resources to assess and improve the health status of migrants from Latin America). The team is leading the work package on the social and cultural context of health-seeking behavior of Latin American migrants in Europe in close collaboration with researchers from the Imported Diseases program who are leading the work package on neglected parasitic diseases.

Finally, in 2010 the FP7 PRISMA project on culture and end-of-life care also completed its final year, culminating in an international conference in Vic on 17-18 May organized jointly with the University of Vic and the Institut Català d'Oncologia (Catalan Oncology Institute) and attended by more than 200 people from over ten countries.

Maternal and Reproductive Health

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Introduction

Approximately 250,000 African women die every year during pregnancy, delivery or puerperium. In Africa, maternal mortality ratios (MMR) are more than 100 times higher than those in the developed world. Reduction of MMR by 2015 is one of the targets of the Millennium Development Goals, but little progress has been achieved in this objective, and in Sub-Saharan Africa MMR figures have remained unchanged for the last twenty years. A major handicap in achieving this goal is that efforts to reduce MMR in the region are not evidence-driven. Malaria in pregnancy (MiP) is one of the main causes of maternal and infant mortality in endemic areas. Research should be targeted towards safe, cost-effective control tools. The epidemiology and clinical impact of infection by *Plasmodium vivax* in pregnancy is largely unknown. Filling this gap in knowledge will provide guidance for implementing control policies of *Plasmodium vivax* malaria for pregnant women. HIV/AIDS is another important cause of poor maternal and reproductive health in many developing areas. There is an urgent need to understand the mechanisms of vertical HIV transmission and maternal infection to reduce this dramatic burden.

The goal of the area is to improve the health of women of reproductive age and reduce the maternal death toll. The Maternal and Reproductive Health research area at CRESIB is focused on the evaluation of interventions in pregnancy, descriptive studies of the burden and clinical impact of infectious diseases on pregnancy outcomes, and understanding the causes of anemia, a major health problem in women and children, to help reduce its frequency and impact.

Objectives

The Maternal and Reproductive Health research area at CRESIB focuses on some of the most urgent health issues affecting this vulnerable population group in low income countries. It aims to do so by encompassing numerous disciplines, ranging from epidemiology and social sciences to molecular biology. The current research program includes such geographically distinct areas as Latin America, Africa, India and the Pacific. The objectives of the main research programs during 2010 were the following:

- To evaluate the safety and efficacy of mefloquine as Intermittent Preventive Treatment for malaria in pregnancy (IPTp) as an alternative drug to prevent malaria among pregnant women.
- To estimate the burden of *Plasmodium vivax* malaria during pregnancy and its impact on pregnancy outcomes in

different epidemiological settings in Latin America, India and Papua New Guinea, and study the pregnancy-specific immune responses and the characterization of parasites in the placenta both genotypically and phenotypically.

- To describe the main causes and preventable factors of anemia among infants in Mozambique.
- To determine the burden and risk factors of mother-to-child HIV transmission in Mozambique.
- To establish the causes of maternal mortality in Sub-Saharan African women.

Summary of main results in 2010

Using as a framework the completed clinical trial on the efficacy of Sulfadoxine-Pyrimethamine as an IPTp, several studies have assessed the immune response to malaria infection in pregnancy and the effect of HIV infection, suggesting a higher efficacy of the intervention in preventing malaria among HIV-positive mothers. In addition, an economic analysis on the cost-effectiveness of IPTp with SP to prevent malaria in pregnancy was carried out, showing that it is highly cost-effective for both the prevention of maternal malaria and the reduction of neonatal mortality.

During the last year, the consortium coordinated by CRESIB that is assessing new antimalarial drugs as IPTps to prevent malaria in pregnancy (MiPPAD consortium) has been consolidated, with the organization of several scientific and managerial meetings. The study's recruitment drive has achieved half of the target sample size with more than 3,500 pregnant women recruited.

The multicentre descriptive study on the epidemiology and clinical impact of *Plasmodium vivax* malaria during pregnancy (PregVax consortium), coordinated by CRESIB, has nearly reached its target sample size with more than 8,000 women recruited, and most of the follow-up completed. Immunological assays in study samples were initiated, and the management team started working on a timeline to accomplish all the project's goals and allow the first results of the study to be available by the end of 2011.

Moreover, the field activities of a case control study of the etiology of anemia in children in Mozambique were completed at the end of last year. Laboratory analyses will be completed soon and the results are expected for next year.

Finally, a study has analyzed the prevalence and etiology of Sexually Transmitted Infections (STIs) and cervical neoplasia in women in a rural area of Mozambique, and has revealed a very high rate of STIs as a whole, approaching 80% (trichomoniasis, gonorrhea, chlamydia, syphilis, etc.). The highest prevalence was found in the group of women of fertile age, with some of the STIs being diagnosed most often in pregnant women. With regard to cervical neoplasia, this was diagnosed in 12% of the 262 participants. These results underline the urgent need to set up STI control programs to reduce their incidence, including HIV and cervical neoplasia.

Host-Pathogen Interactions

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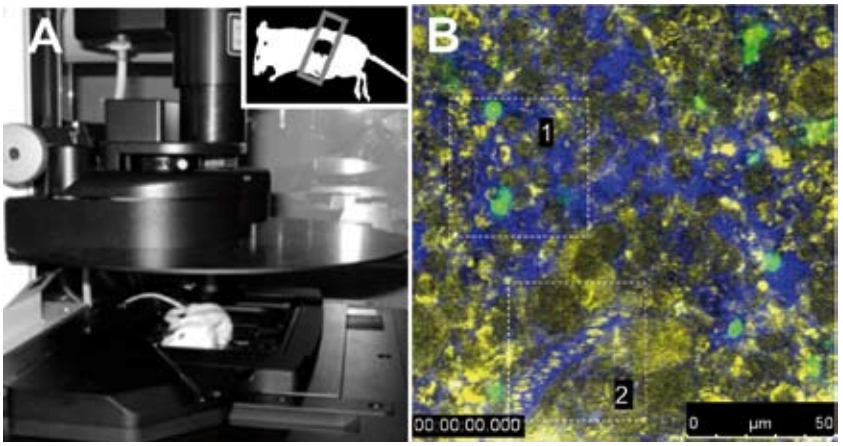
Introduction

Infectious diseases result from the interaction between pathogenic microorganisms and the hosts they infect. The ability of a pathogen to damage the host, together with the ability of the host to respond to the pathogen, will determine the appearance and severity of the disease. Therefore, studying the interaction between the host and the pathogen is crucial to understand what triggers the outcome of an infection.

Host-Pathogen Interactions is a newly created area of CRESIB which aims to boost the existing research on host-pathogen interactions within each program (malaria, imported diseases, HIV/AIDS and STIs, and viral and bacterial infections) with a more multidisciplinary approach. Within each program report you will find more information on the study of the different pathologies, including pathophysiology and immunity in malaria, molecular markers of the progression and cure of Chagas disease, pathogenesis of HIV infection and mechanisms of antimicrobial resistance.

An important feature for this area in 2010 has been the opening of the communal laboratories at the Esther Koplowitz Centre (CEK) with outstanding laboratory facilities and research support platforms. CRESIB's groups from different programs engaged in benchwork now have an open lab space which facilitates researcher interactions.



Intravital microscopy of the spleen in a rodent malaria model.

A. Leica TCS-SP5 confocal microscope with one mouse placed on the stage of the microscope. The mouse has the inferior part of the spleen exposed and sealed with a cover-slip.

B. 25x image of a representative area of the spleen of a non-infected animal injected with FITC-labelled RBCs and Cy5 to visualize the vasculature. Reflection (yellow), Cy5 (blue) and FITC-RBCs (green) are shown. Image produced by Mireia Ferrer, Lorena Martin-Jaular and María Calvo.

Objectives

The Host-Pathogen Interactions research program at CRESIB embraces numerous disciplines, and aims to create an environment where common platforms can be developed both at the molecular level and at studying responses to the human host. Specific objectives are:

- To study the *in vivo* pathogenesis of the spleen in relation to experimental and natural malaria infections.
- To study the ligand and receptors involved in cytoadherence of *Plasmodium vivax* malaria.
- To study the expression of the *var* gene repertoire of *Plasmodium falciparum* in natural isolates elicited by different clinical syndromes.
- To study the molecular basis of cytoadherence to placental tissues.
- To study the invasion mechanisms of bacteria into the amniotic membrane.
- To study host-pathogen interactions in co-infections between different infectious diseases.
- To develop common enabling technologies to study host-pathogen interactions.

Summary of main results in 2010

This is a newly-created area which so far has mainly focused on the creation of synergisms among different research groups with the ultimate goal of having collaborative projects that take advantages of complementary knowledge and expertise in the area of host-pathogen interactions.

Within the area, in 2010 the bulk of results have been in developing and validating enabling technologies for the study of host-pathogen interactions. Intravital and magnetic resonance imaging have been developed, in collaboration with Drs. María Calvo and Anna Planas from Hospital Clínic, for *in vivo* studies of pathogenesis in rodent models and human patients. As a result, a novel immune spleen evasion mechanism in malaria has been described, explained in greater detail under the malaria program.

A reverse genetic approach for generating knock-out and knock-in of genes in malaria and bacteria has been established and a global transcriptional analysis to determine genes involved in different host-pathogen interactions is under development.

In addition, a small-scale High Throughput (HPT) system for soluble expression of malaria proteins in the wheat germ system has been developed, which represents an important step forward towards validation of ligands for functional assays.

Different amniotic cell lines are being developed and knock-out bacterial strains are being produced to determine the role of different coding genes in the translocation of the amniotic membrane.

Research Support Platforms

The Research Support Platforms offer CRESIB's researchers the most advanced scientific technology to develop cutting-edge research.

In addition to CRESIB's own platforms (Biostatistics and Clinical Trial Unit and International Research collaborations), there are a set of platforms developed by CRESIB's founder institutions also available for our researchers to use, namely the Animal House (UB), Biobank (HC – IDIBAPS), Bioinformatics Unit (IDIBAPS), Cell Culture Unit (HC), Cytomics Unit (IDIBAPS), DNA Unit (HC), Electron Microscopy Unit, Evaluation, Support and Prevention Unit UASP (HC), Genomics Unit (IDIBAPS), Medical Imaging Platform, Medical Library (UB), Microscopy Section (SCT-UB), Nanobiotechnology Unit (IDIBAPS), Neurological Tissue Banc (HC – UB), Proteomics Unit (IDIBAPS – UB – PCB), Tumor Bank (HC) and the Unit for Optical Recording of Cell Signals.

But the most widely-used services by CRESIB researchers are its own Platforms, both the Biostatistics and Clinical Trial Unit and International Research collaborations.

Biostatistics/Clinical Trial Unit

Platform Leader: John J. Aponte (until September 2010) / Sergi Sanz (from September 2010)

Personnel working at the platform:

Edgar Ayala
Susana Méndez
Santiago Pérez-Hoyos
Llorenç Quintó
Sergi Sanz

Introduction

The Biostatistics Unit is a research support platform that helps CRESIB researchers with statistics questions. The Biostatistics Unit is widely established and has existed for over ten years. One of its main objectives is to provide support for every area of statistical research studies. This unit supports the drafting of the statistics section of protocols and requests for scientific studies. It also participate in drafting plans for data cleansing and analysis, data management, statistical analysis and writing of articles.

Objectives

The Biostatistics Unit's main objective is to participate in the statistical resolution of all the studies carried out by CRESIB. This support may be given either directly, by statistical work, or through collaboration, helping researchers to solve any statistics-related queries they may have. In addition to this objective, the Unit aims to keep up-to-date with the latest statistical techniques currently in use.

The Biostatistics Unit has specialized in STATA and aims to become a reference in this widely-used statistical software. However, other platforms and statistical analysis software are also known, used or evaluated. In this respect, and as another of the Unit's objectives, it offers training to CRESIB's researchers in basic statistics using STATA statistical software. As future objectives, the unit wants to offer more courses on statistical methods that it believes may be useful to CRESIB's researchers.

Summary of main results in 2010

Last year the members of the Unit participated in sixteen papers for scientific journals. It attended the STATA national meeting and contributed with a presentation that had a big impact.

International Research Collaborations

Platform Leader: Marga Sala

Personnel working at the platform:

Pascal Andignac
Pau Balcells
Pau Carreras
Marina Espriu
Elena Esteban
Carla Garrido
Enric Grau
Meritxell Graupera
Francesc Guil
Mireia Hernández
Alicia Llamas
Eva López
Sam Mardell
Esperanza Marín
Anna Massaneda
M.ª José Merino
Julia Riambau
Esther Roset
Noelia Sánchez
Mónica Solanes

Introduction

The International Cooperation Office (OCI, Spanish acronym) provides support for the administrative and financial management of International Health grants, projects and international collaborations of the organizations associated with the Hospital Clinic and the University of Barcelona (FCRB, IDIBAPS, CRESIB, ISGLOBAL).

The OCI comprises two main departments: Administration & Finance and Projects. Administration & Finance covers accounting, human resources and procurement activities. The Projects department includes fundraising and pre-award activities (calls, contracts, budgeting) as well as grants and project management (follow-up, reporting, auditing).

Objectives

The OCI's main objective is to guarantee transparency, responsibility, compliance and efficiency in the management of resources for all International Health grants and projects

Other objectives include:

- Support for the management and administrative and financial performance of the Research Platforms in Mozambique (CISM - Centro de Investigaçao en Saude de Manhiça), Morocco and Bolivia.
- Capacity building on project management for international partners in third countries.
- Contributing to international health human resources management (headquarters and expatriates), particularly during the processes of job profile definition, selection, recruitment and administrative follow-up.

Summary of main results in 2010

Besides the daily management of 145 grants, amounting to a multi-year budget of 61 M €, with partners in forty countries, the OCI contributed in 2010 to the following achievements:

- Global health projects received twenty-seven new grants, amounting to 5.5 M €, mainly coming from research donors and official development aid.
- The creation and organization of the new Institute for Global Health of Barcelona (ISGLOBAL).
- The consolidation of the Chagas disease platform in Bolivia, a joint initiative between CRESIB and the University Mayor de San Simón, Viedma Hospital and the Chagas Disease National Program (Ministry of Health), financed by the Spanish Agency for International Cooperation and Development.
- The implementation of the joint research lab in Rabat, in coordination with the University Hospital of Rabat (Morocco) and the Ministry of Health.

Education and training

Part of CRESIB's mission and one of its key priorities is to be a reference and a facilitator in the field of education and training in International Health, developing a training program aimed at training researchers as well as professionals working in the health sciences and other related disciplines.

To consolidate itself as a benchmark centre in this field, CRESIB carries out its own training programs as well as others in collaboration with various institutions, with three clearly differentiated goals:

- To train highly qualified researchers in specific areas related to international health, mainly through Masters, doctoral and ongoing education programs.
- To promote awareness and knowledge of global health problems and improve the training of healthcare professionals to deal with imported and tropical diseases.
- To train technical, medical and scientific personnel in low- and middle-income countries with the ultimate goal of strengthening local institutions and contributing to their development.

The centre is currently carrying out the following training programs on international health:

Postgraduate education

In 2010, CRESIB has been involved in teaching various subjects in the following Masters courses:

- New official Master in International Health at the University of Barcelona and the Autonomous University of Barcelona (2010-2011 academic year)
- Master in Tropical Medicine and International Health at the University of Barcelona (2009-2010 academic year)
- Master in International Health and Tropical Medicine at the Autonomous University of Barcelona (2009-2010 academic year)
- Official Master in Public Health at the University of Pompeu Fabra and at the Autonomous University of Barcelona (2009-2010 academic year)
- Official Master in Internationalization at the University of Barcelona (2009-2010 academic year)
- Official Master in Advanced Microbiology at the University of Barcelona

With regard to doctoral programs, CRESIB is involved in the Doctoral Program of Medicine of the Faculty of Medicine at the University of Barcelona, which has a quality award.

Doctoral theses read in 2010

- **Elisa Serra Casas.** Malaria during pregnancy in a rural area of Mozambique: parasitological and immunological study in the context of recommended control strategies. 22 June 2010. Directors: Dr. Alfredo Mayor and Dr. Clara Menéndez.

- **José Muñoz Gutiérrez.** Clinical-epidemiological evaluation of infection by *Trypanosoma cruzi* in Barcelona. 2 July 2010. Directors: Dr. Joaquim Gascón and Dr. Montserrat Portús.

- **Anna Fàbrega Santamaria.** Mechanisms of fluoroquinolone resistance in *Escherichia coli, Salmonella typhimurium* and *Yersinia enterocolitica*. Influence on expression of virulence factors. 24 November 2010. Director: Dr. Jordi Vila.

Programs for training researchers in Mozambique and Morocco

- "Training Fellows" training program in collaboration with the Health Research Centre of Manhiça (Mozambique). This program is aimed at Mozambique graduates and is intended to train researchers to enable them to follow Masters and doctorate courses, mainly at universities in Catalonia. Some thirty people have already passed through the program and all of them have rejoined African health centres.
- "Training Fellows" training program in Morocco; at present, two Moroccan graduates have completed their Masters (at the University of Barcelona and the University Pompeu Fabra) and started their doctorate course at the University of Barcelona.

Funded training projects

Title: "Support for creating a specialization in epidemiology and biostatistics at the National Health Administration Institute (INAS) in Rabat, Morocco"
Coordinating organization:
Clinic Foundation for Biomedical Research
Organizations involved: Clinic Foundation for Biomedical Research, CRESIB, University of Barcelona, Hospital Clínic de Barcelona, Pompeu Fabra University, Barcelona Public Health Agency
Project coordinator:
Dr. Núria Casamitjana and Mr. Enric Grau
Financial institution: La Caixa Foundation Social Projects
Amount: 180,000 €
Period: 2008 – 2011

Title: "Training program in health sciences in Mozambique: developing skills and boosting academic capacity at the Faculty of Medicine of the Eduardo Mondlane University"
Coordinating Organization:
Clinic Foundation for Biomedical Research
Organizations involved: Clinic Foundation for Biomedical Research, Faculty of Medicine of the Eduardo Mondlane University in Maputo (Mozambique), CRESIB, University of Barcelona, Hospital Clínic de Barcelona, Manhiça Health Research Centre (CISM, Mozambique)
Project coordinator:
Dr. Núria Casamitjana
Financial institution:
La Caixa Foundation Social Projects
Amount: 272,000 €
Period: 2008 – 2011

Title: "University Scholarship Program for Mozambique Women"
Coordinating Organization: CRESIB
Organizations involved: CRESIB, Foundation for Community Development of Mozambique (FDC)
Project coordinator:
Dr. Núria Casamitjana
Financial institution:
La Caixa Foundation Social Projects
Amount: 300,000 €
Period: January 2008 – June 2013

Ongoing training for researchers and health professionals

Seminars, workshops, working sessions and conferences

CRESIB seminars:

- 13/01/2010. **Dr. Ariel Achtman**. Walter and Eliza Hall Institute, Melbourne (Australia). **"Erythropoietic activity in bone marrow from children with severe malarial anemia"**.

- 20/01/2010. **Dr. Lorena Martin**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"The role of the spleen and immunogenicity in exosomes in the Balb/c-*Plasmodium yoelii* malaria model".**

- 29/01/2010. **Dr. Laura Moya**. Consultant Dermatologist, Príncipe de Asturias Hospital, Alcalá de Henares, Madrid (Spain). **"Cutaneous leishmaniasis in Latin America: challenges for control"**.

- 29/01/2010. **Dr. Michel Duffy**. Senior Research Officer, Department of Medicine RMH/WH, University of Melbourne, Melbourne (Australia). **"Factors regulating *var* gene expression in *Plasmodium falciparum*"**.

- 03/02/2010. **Dr. María Aparecida Shikanai Yasuda**. Infectious and Parasitic Diseases Department, Faculty of Medicine, University of São Paulo, São Paulo (Brazil). **"Chagas disease and HIV infection"**.

- 24/02/2010. **Cristina O'Callaghan**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Etiology and epidemiology of viral pneumonia among hospitalized children in rural Mozambique, a malaria endemic area with high HIV prevalence"**.

- 03/03/2010. **Mireia Angulo**. Department of Strategic Marketing and Business Development, Clinic Foundation for Biomedical Research, Barcelona (Spain). **"Innovation and transfer of technology in the Hospital Clínic and associated organizations"**.

- 10/03/2010. **Dr. Rodrigo Louro**. EMBL Grenoble Outstation, Grenoble (France). **"Noncoding RNAs and complexity"**.

- 12/03/2010. **Dr. Theo Sowa**. Independent Consultant, Ghana. **"Development Policies: from planning to practice"**.

- 19/03/2010. **Prof. Xavier Pons**. Professor of International Public Law, University of Barcelona, Barcelona (Spain). **"Global public health and international law: a general overview"**.

- 24/03/2010. **Dr. Roger Paredes**. IRSI Caixa, Badalona (Spain). **"Ultrasensitive genotyping in HIV: clinical and pathogenic implications"**.
- 07/04/2010. **Prof. Graham Brown**. University of Melbourne and Director of the Nossal Institute of Global Health, Melbourne (Australia). **"The Nossal Institute of Global Health"**.

- 08/04/2010. **Dr. Francisco Javier López Domingo.** University of Granada, Granada (Spain). **"Computational techniques for analysing biomedical data"**.

- 16/04/2010. **Dr. Luís Carlos Ferreira**. Microbiology Department, University of São Paulo, São Paulo, (Brazil). **"Bacterial flagellins and vaccine development"**.

- 21/04/2010. **Dr. Alfredo Mayor**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"HIV and placenta modulate the appearance of *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine in the context of Intermittent Preventive Treatment"**.

- 28/04/2010. **Dr. Tomàs Pumarola**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Virological surveillance of flu in Catalonia"**.

- 05/05/2010. **Dr. Jordi Casabona**. CEEISCAT and AIDS and Society Foundation, Barcelona (Spain). **"The UALE Project: a comprehensive intervention on HIV/STI in Guatemala"**.

- 12/05/2010. **Joseph Joe Campo**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Flow cytometry for measurement of parasite burden in *Plasmodium falciparum* malaria studies"**.

- 26/05/2010. **Dr. Edward B. Hayes**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Epidemiology of dengue and chikungunya fevers"**.

- 02/06/2010. **Dr. Ivo Müller**. PNG Institute of Medical Research (Papua Nova Guinea). **"The effect of common red blood cell polymorphism on risk of *Plasmodium vivax* infection and disease in Papua Nova Guinea children"**.

- 09/06/2010. **Dr. Robert Pool**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Syndemics"**.

- 16/06/2010. **Dr. Laura Vinué**. University of La Rioja, Logroño (Spain). **"Genetic elements of acquisition and dissemination of antibiotic-resistant genes in *Escherichia coli*. Plasmids and Integrons"**.

- 17/06/2010. **Dr. Chetan Chitnis**. International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi (India). **"Red cell invasion by malaria parasites: from basic biology to vaccine development"**.

- 23/06/2010. **Antonio Delgado**. Legal Consultant, Hospital Clínic, Barcelona (Spain). **"How does the data protection law affect clinical research?"**.

- 30/06/2010. **Dr. Elisa Sicuri**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"The cost-effectiveness of averting anaemia: evidence from intermittent preventive treatment of malaria in infants in Gabon"**.

- 01/07/10 **Dr. Faustino Torrico**. Professor of Parasitic and Infectious Diseases, University of San Simón in Cochabamba, Cochabamba (Bolivia). **"Results of the Chagas platform in Cochabamba"**.

- 07/07/2010. **Dr. Victòria Fumadó**. Hospital Sant Joan de Déu, Barcelona (Spain). **"Prevalence of Malnutrition in children under five years of age at the Manhiça District Hospital, Mozambique"**.

- 08/07/2010. **Dr. Adrian Luty**. Malaria Immunologist, The Netherlands. **"Yes we can: inducing sustained sterile immunity to *Plasmodium falciparum* in humans"**.

- 14/07/2010. **Dr. Jaime Altcheh**. Ricardo Gutiérrez Children's Hospital, Buenos Aires (Argentina). **"Chagas disease in children"**.

- 21/07/2010. **Dr. Imane Jroundi**. National Health Administration Institute (INAS), Rabat (Morocco). **"The situation of the HIV pandemic in Morocco"**.

- 01/09/2010. **Dr. George Dimopoulos**. Bloomberg School of Public Health, Johns Hopkins University, Baltimore (USA). **"Targeting human pathogens in the belly of the beast"**.

- 06/10/2010. **Dr. Edward B. Hayes**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Emerging diseases in an interconnected world"**.

- 13/10/2010. **Emili Letang**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Predictors of paradoxical Immune Reconstitution Inflammatory Syndrome associated with Kaposi Sarcoma in sub-Saharan Africa and the UK. Developing a predictive score"**.

- 20/10/2010. **Eduard Rovira**. Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-University of Barcelona), Barcelona (Spain). **"Transcription of *var* genes other than *var2csa* in *Plasmodium falciparum* isolates infecting pregnant women in Mozambique"**.

- 27/10/2010. **Dr. Renia Coghland**. Associate Director - Global Access, Medicines for Malaria Venture (MMV), Geneva (Switzerland). **"Bridging the malaria medicines gap: from public health to measurable market change"**.

- 08/11/2010. **Dr. Kitsos Louis**. Insect Molecular Genetics Group, Institute of Molecular Biology and Biotechnology, University of Crete, Crete (Greece). **"From Aristotle to malaria control: a bioinformatic approach"**.

- 10/11/2010. **Dr. Philip L. Felgner.** Director, Protein Microarray Laboratory, Infectious Disease, School of Medicine, University of California, Irvine (USA). **"Predicting naturally acquired humoral immunity against malaria on a genome-wide scale"**.

- 17/11/2010. **Dr. Joan Grimalt**. Department of Environmental Chemistry Institute of Environmental Assessment and Water Research (IDÆA-CSIC), Barcelona (Spain). **"What's the problem with organohalogenate compounds, the environment and human health?"**.

- 24/11/2010. **Dr. João Rodrigues**. Institute of Hygiene and Tropical Medicine, Universidade Nova de Lisboa, Lisbon (Portugal). **"Hosts, parasites and their interactions in the proteomic era"**.

- 01/12/2010. **Albert Picado**. Research Associate, Institute of Tropical Medicine, Antwerp (Belgium). **"Long lasting insecticidal nets for the prevention of *Leishmania donovani* infection in India and Nepal: paired cluster randomised trial"**.

- 15/12/2010. **Dr. Charlotte Pierrat**. University of Paris I Pantheon – Sorbonne, Development Research Institute (IRD), Paris (France). **"Environmental determinants of malaria for a cohort of new-borns in Southern Benin"**.

- 20/12/2010. **Dr. Juan M. Bustamante**. Center for Tropical and Emerging Global Diseases, University of Georgia, Athens (USA). **"Treatment efficacy and immune resistance in *Trypanosoma cruzi* infection"**.

Workshops, working sessions and conferences organized by CRESIB

1 February 2010

VI Workshop on Imported Chagas Disease: Immunosupression and Transplants
Coordinator: Joaquim Gascón (CRESIB)
Place: Barcelona

15 March 2010

Sustaining the Momentum: The role of partnerships in the fight against malaria
Joint organizer: Medicines for Malaria Venture (MMV)
Place: CosmoCaixa, Barcelona

8 and 9 April 2010

Seminars on "Culture and End-of-life"
Coordinator: Marjolein Gysels
Place: Vic

Publications

This list of publications includes papers from researchers of CRESIB founder institutions attached to CRESIB since January 2010, regardless of the affiliation of the paper.

1. Aide P, Aponte JJ, Renom M, Nhampossa T, Sacarlal J, Mandomando I, Bassat Q, Manaca MN, Leach A, Lievens M, Vekemans J, Dubois MC, Loucq C, Ballou WR, Cohen J, Alonso PL. Safety, immunogenicity and duration of protection of the RTS,S/AS02(D) malaria vaccine: one year follow-up of a randomized controlled phase I/IIb trial. **PLoS ONE.** 2010;5(11):e13838.

2. Antón A, López-Iglesias AA, Tórtola T, Ruiz-Camps I, Abrisqueta P, Llopart L, Marcos MÁ, Martínez MJ, Tudó G, Bosch F, Pahissa A, de Anta MT, Pumarola T. Selection and viral load kinetics of an oseltamivir-resistant pandemic influenza A (H1N1) virus in an immunocompromised patient during treatment with neuraminidase inhibitors. **Diagn Microbiol Infect Dis.** 2010 Nov;68(3):214-219.

3. Antón A, Marcos MA, Martínez MJ, Ramón S, Isanta R, de Molina P, de Anta MT, Pumarola T. Double (V27A/S31N) mutant 2009 pandemic influenza A (H1N1) virus isolated from adamantane non-treated immunocompetent child. **Diagn Microbiol Infect Dis.** 2010 May;67(1):114-115.

4. Antón A, Marcos MA, Martínez MJ, Ramón S, Martínez A, Cardeñosa N, Godoy P, Torner N, De Molina P, Isanta R, Jiménez de Anta MT, Pumarola T. D225G mutation in the hemagglutinin protein found in three severe cases of 2009 pandemic influenza A (H1N1) in Spain. **Diagn Microbiol Infect Dis.** 2010 Jun;67(2):207-208.

5. Armstrong Schellenberg JRM, Shirima K, Maokola W, Manzi F, Mrisho M, Mushi A, Mshinda H, Alonso P, Tanner M, Schellenberg DM. Community effectiveness of intermittent preventive treatment for infants (IPTi) in rural southern Tanzania. **Am J Trop Med Hyg.** 2010 May;82(5):772-781.

6. Ballesta S, García I, Sánchez-Céspedez J, Vila J, Pascual A. Intracellular penetration and activity of UB-8902 in human polymorphonuclear leukocytes. **Enferm Infecc Microbiol Clin.** 2010 Nov;28(9):612-614.

7. Bausewein C, Booth S, Gysels M, Kühnbach R, Haberland B, Higginson IJ. Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study. **Palliat Med.** 2010 Dec;24(8):777-786.

8. Bausewein C, Booth S, Gysels M, Kühnbach R, Haberland B, Higginson IJ. Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. **J Palliat Med.** 2010 Sep;13(9):1109-1118.

9. Bausewein C, Booth S, Gysels M, Kuhnbach R, Higginson IJ. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. **BMC Palliat Care.** 2010 Oct 19;9(1):22.

10. Behrens RH, Carroll B, Hellgren U, Visser LG, Siikamaki H, Vestergaard LS, Calleri G, Jänisch T, Myrvang B, Gascon J, Hatz C. The incidence of malaria in travellers to South-East Asia: is local malaria transmission a useful risk indicator? **Malar J.** 2010 Oct 4;9(1):266.

11. Bergeron C, Ordi J, Schmidt D, Trunk MJ, Keller T, Ridder R. Conjunctive p16INK4a testing significantly increases accuracy in diagnosing high-grade cervical intraepithelial neoplasia. **Am J Clin Pathol.** 2010 Mar;133(3):395-406.

12. Bermejo-Martin JF, Martin-Loeches I, Rello J, Anton A, Almansa R, Xu L, Lopez-Campos G, Pumarola T, Ran L, Ramirez P, Banner D, Ng DC, Socias L, Loza A, Andaluz D, Maravi E, Gómez-Sánchez MJ, Gordón M, Gallegos MC, Fernandez V, Aldunate S, León C, Merino P, Blanco J, Martin-Sanchez F, Rico L, Varillas D, Iglesias V, Marcos MÁ, Gandía F, Bobillo F, Nogueira B, Rojo S, Resino S, Castro C, Ortiz de Lejarazu R, Kelvin D. Host adaptive immunity deficiency in severe pandemic influenza. **Crit Care.** 2010 Sep 14;14(5):R167.

13. Borrmann S, Sallas WM, Machevo S, González R, Björkman A, Mårtensson A, Hamel M, Juma E, Peshu J, Ogutu B, Djimdé A, D'Alessandro U, Marrast AC, Lefèvre G, Kern SE. The effect of food consumption on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablets (Coartem) for acute uncomplicated *Plasmodium falciparum* malaria. **Trop Med Int Health.** 2010 Apr;15(4):434-441.

14. Carod-Artal FJ, Gascon J. Chagas disease and stroke. **Lancet Neurol.** 2010 May;9(5):533-542.

15. Carvalho BO, Lopes SCP, Nogueira PA, Orlandi PP, Bargieri DY, Blanco YC, Mamoni R, Leite JA, Rodrigues MM, Soares IS, Oliveira TR, Wunderlich G, Lacerda MV, del Portillo HA, Araújo MO, Russell B, Suwanarusk R, Snounou G, Rénia L, Costa FT. On the cytoadhesion of *Plasmodium vivax*-infected erythrocytes. **J Infect Dis.** 2010 Aug 15;202(4):638-647.

16. Casals G, Ordi J, Creus M, Fábregues F, Carmona F, Casamitjana R, Balasch J. Osteopontin and alphavbeta3 integrin as markers of endometrial receptivity: the effect of different hormone therapies. **Reprod Biomed Online.** 2010 Sep;21(3):349-359.

17. Conteh L, Sicuri E, Manzi F, Hutton G, Obonyo B, Tediosi F, Biao P, Masika P, Matovu F, Otieno P, Gosling RD, Hamel M, Odhiambo FO, Grobusch MP, Kremsner PG, Chandramohan D, Aponte JJ, Egan A, Schellenberg D, Macete E, Slutsker L, Newman RD, Alonso P, Menéndez C, Tanner M. The cost-effectiveness of intermittent preventive treatment for malaria in infants in Sub-Saharan Africa. **PLoS ONE.** 2010;5(6):e10313.

18. Davy CP, Sicuri E, Ome M, Lawrence-Wood E, Siba P, Wavi G, Mueller I, Conteh L. Seeking treatment for symptomatic malaria in Papua New Guinea. **Malar J**. 2010 Oct 6;9(1):268.

19. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, Tous S, Felix A, Bravo LE, Shin HR, Vallejos CS, de Ruíz PA, Lima MA, Guimera N, Clavero O, Alejo M, Llombart-Bosch A, Cheng-Yang C, Tatti SA, Kasamatsu E, Iljazovic E, Odida M, Prado R, Seoud M, Grce M, Usubutun A, Jain A, Suarez GA, Lombardi LE, Banjo A, Menéndez C, Domingo EJ, Velasco J, Nessa A, Chichareon SC, Qiao YL, Lerma E, Garland SM, Sasagawa T, Ferrera A, Hammouda D, Mariani L, Pelayo A, Steiner I, Oliva E, Meijer CJ, Al-Jassar WF, Cruz E, Wright TC, Puras A, Llave CL, Tzardi M, Agorastos T, Garcia-Barriola V, Clavel C, Ordi J, Andújar M, Castellsagué X, Sánchez GI, Nowakowski AM, Bornstein J, Muñoz N, Bosch FX; Retrospective international survey and HPV time trends study group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. **Lancet Oncol.** 2010 Nov;11(11):1048-1056.

20. Del Pino M, Torne A, Alonso I, Mula R, Masoller N, Fuste V, Ordi J. Colposcopy prediction of progression in human papillomavirus infections with minor cervical lesions. **Obstet Gynecol.** 2010 Dec;116(6):1324-1331.

21. Del Valle LJ, Flores L, Vargas M, García-de-la-Guarda R, Quispe RL, Ibañez ZB, Alvarado D, Ramírez P, Ruíz J. *Bartonella bacilliformis*, endemic pathogen of the Andean region, is intrinsically resistant to quinolones. **Int J Infect Dis.** 2010 Jun;14(6):e506-e510.

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Book Chapters and Other Publications

- *Guía de terapéutica antimicrobiana 2010*. Editors: J. Mensa, J. M. Gatell, J. E. García Sánchez, E. Letang, E. López Suñé. Ed. Antares.

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