

BARCELONA CENTRE FOR
INTERNATIONAL HEALTH
RESEARCH (CRESIB)

ANNUAL REPORT 2011



Hospital Clínic - Universitat de Barcelona

© **Barcelona Centre for International Health Research (CRESIB)**

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Table of contents

Foreword - Pedro L. Alonso	2
Introduction - Antoni Plasència	4
CRESIB Leading Research at ISGlobal	6
Organizational Chart	8
Governing Bodies and Directorate Staff	10
Facts and Figures	14
Research Areas	
· Public Health	18
· Medical Anthropology	20
· Maternal, Child and Reproductive Health	22
· Host-Pathogen Interactions	24
Research Programmes	
· Malaria	26
· Imported Diseases	30
· HIV/AIDS and Sexually Transmitted Infections (STI's)	32
· Viral and Bacterial Infections	34
Research Support Platforms	
· Biostatistics Unit	36
· International Research Collaborations	37
· Strategic Partnerships	38
Education and Training	42
CRESIB in the News	48
Publications	52
Personnel	65
Funding Organizations	68

CRESIB, a biomedical research centre with a strong commitment to development and building research capacity



Pedro L. Alonso
Director

July 2011 marked the 5th anniversary of the creation of the Barcelona Centre for International Health Research (CRESIB). As a result of the Catalan science and health systems commitment to global health, CRESIB has become a centre of excellence and a key international institution. In the midst of a complex financial context, especially in Spain, CRESIB has been capable of growth, not only maintaining its financial base, but actually increasing its competitive funding from diverse sources.

CRESIB's research staff has been strengthening since the establishment of the centre. At the same time, its scientific production increased steadily, not only in volume, but also in the impact of its publications, a trend that reflects a healthy and competitive scientific environment.

Since its inception, CRESIB has combined the willingness to become an outstanding biomedical research centre with a strong commitment to



development and building research capacity in low-income countries. In this sense the collaborative platforms in Mozambique through the Manhiça Health Research Centre (CISM); in Morocco with the Ministry of Health and the University of Rabat; and in Bolivia with our collaborators in Chochabamba, have become three strategic components of our centre.

The malaria programme continues to be the backbone of our research, but CRESIB has gone farther to create a strong and growing agenda in imported diseases, especially Chagas; viral and bacterial infections; and maternal, infant and reproductive health, among others. In addition, CRESIB has been the driving force behind the creation of the Barcelona Institute for Global Health (ISGlobal), a venture that came to fruition in 2011. As the principal research institution for ISGlobal, we hope that the scientific research conducted by CRESIB will help break the vicious cycle of illness and poverty that entraps the most vulnerable populations.

Finally, I would like to take advantage of this foreword to thank Dr. Núria Casamitjana for her excellent stewardship and management as CRESIB's Deputy Director during this initial phase, a position that she has left to take on a new challenge as the Director of Training at ISGlobal. I would also like to welcome Antoni Plasència, who came aboard in November as the centre's new Deputy Director after leaving his post as the Director of Public Health for the Generalitat of Catalonia. With his leadership, we face the future with optimism and energy to continue consolidating our research. ◆

2011. A year marked by CRESIB's prolific scientific production



Antoni Plasència

Deputy Director

2011 has been a year marked by CRESIB's prolific scientific production. In comparison to the previous year, CRESIB has doubled its number of scientific article publications (166), representing a four-fold increase from when the centre was created in 2006. The increase is even more significant in the total Impact Factor of the centre (834), which rose 157% in 2011, and consolidates a growth trend that firmly situates CRESIB among the major centres of scientific excellence in health research and hospitals in Catalonia.

CRESIB's scientific activity involves more than 100 institutions in 40 countries, across five continents. Its most notable achievements have been not only in the more established areas such as malaria, but also in new areas such as the effective treatment of yaws. The inclusion of the progress of the RTS,S vaccine against malaria as one of the top 10 most relevant scientific advances of 2011, according to *Science Magazine*, is evidence of CRESIB's significant scientific, social and media achievements.

In spite of the restrictive economic context, the efforts made in scientific investments have allowed the addition of Drs. Ivo Mueller and Alfred Cortés as Research Professor and Assistant Research Professor, respectively, to the staff, as well as the appointment of Dr. Alfredo Mayor and Dr. Carlota Dobaño as Associate Research Professors.

The number of doctoral theses defended rose to 11, and participation in training activities linked to



CRESIB, such as Masters in International Health (UB-UAB), in Public Health (UPF-UAB) and in Internationalization (UB), as well as various high-level workshops and seminars has also increased.

The year 2011 has also been marked by increased competitive fundraising, and achieving more than double the amount obtained in 2006. Competitive contributions account for 91.4% of total funds, putting the institutional contribution below 9%, and demonstrating our commitment to attract new competitive resources from diversified sources. Of note, despite the efforts of its founding institutions, the current economic environment is severely limiting their contributions, which when adjusted for inflation are now less than the original contributions.

Overall, in spite of the difficult economic and financial context, CRESIB has moved forward in its successes in:

- its development as a unique research centre in the field of International Health;
- its raising of a significant amount of funds for research and scientists;
- an important growth in its scientific production and impact factor;
- its progression as a key international player in certain strategic knowledge areas;
- its involvement in a network of highly relevant collaborators and strategic partners in epidemiology and social demographics.

I would like to convey my appreciation for the opportunity to take on the position of Deputy Director

of CRESIB, which until now has been very successfully developed by Núria Casamitjana. I hope that with the scientific coordination of Eva Casamitjana, the economic and finance direction of Marga Sala, and the collaboration of all the researchers and professionals at CRESIB, I will be able to rise to the level of confidence entrusted in me by Professor Pedro Alonso and the members of the Board. ♦

CRESIB
leading research
at ISGlobal



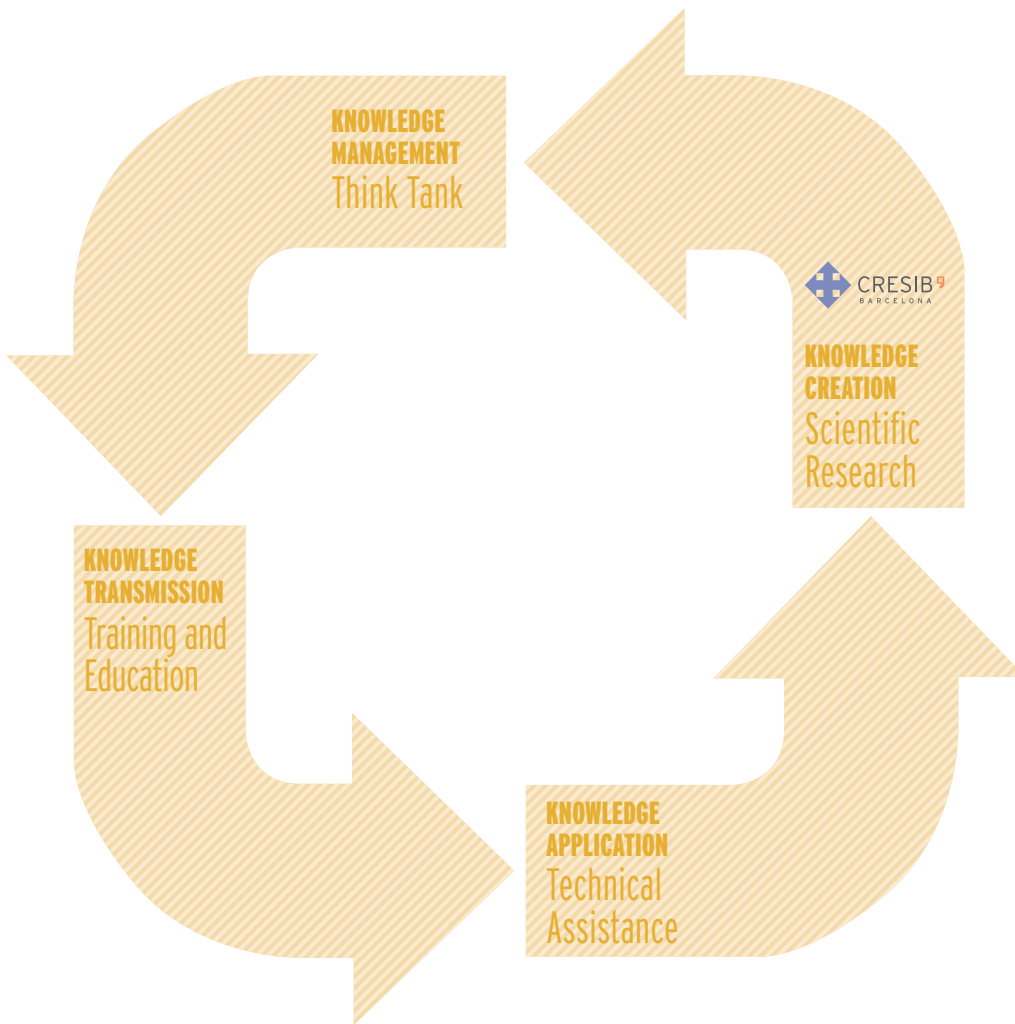
ISGlobal **Barcelona**
Institute for
Global Health

The Barcelona Centre for International Health Research (CRESIB) is a Centre of Excellence, whose mission is to improve global health through research and training.

CRESIB was founded in 2006 with the objective to expand the research and training activities being carried out by the Hospital Clinic and the University of Barcelona through the Tropical Medicine Department. Four years later, in 2010, the desire to extend the value chain from research to knowledge creation, management, transmission and application in the field, led to the creation of a new organization, the Barcelona Institute for Global Health (ISGlobal). Thereby, CRESIB is now the research arm of ISGlobal, and the *expertise* provided by its scientific staff will allow both centres to promote excellence in global health research and contribute to its social impact.

ISGlobal is the result of a collaboration between public and private institutions, and is supported by: the "la Caixa" Foundation, the Generalitat of Catalonia, the Ministry of Foreign Affairs/ Spanish Agency for International Cooperation, Hospital Clínic and the University of Barcelona. It aims to improve global health of vulnerable populations through four action areas:

- Scientific Research
- Think Tank
- Training and Education
- Technical Assistance

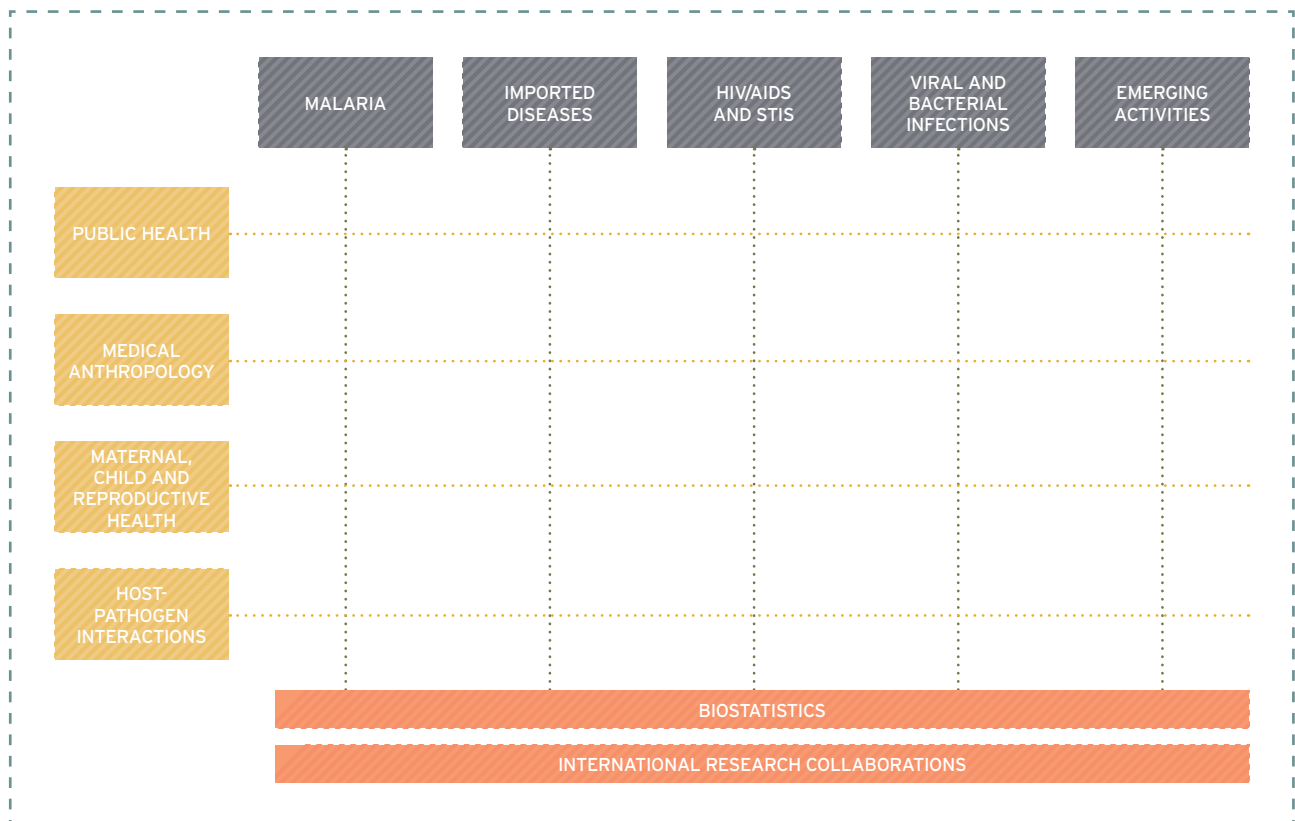


Organizational Chart

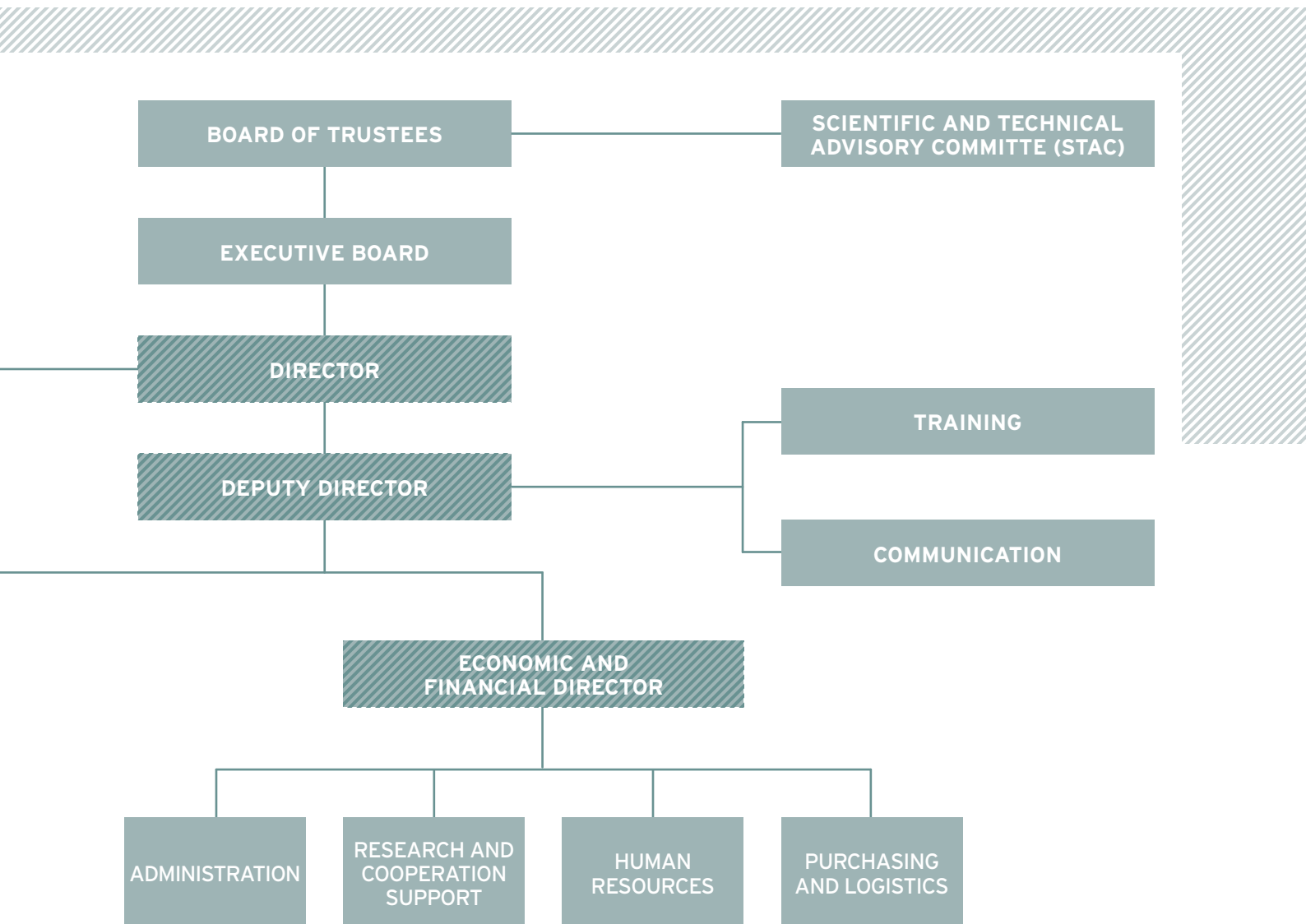
INTERNAL SCIENTIFIC COMMITTEE

SCIENTIFIC COORDINATION

CRESIB is a research institute created by some of the leading academic and biomedical research institutions in Barcelona -Hospital Clinic of Barcelona, the University of Barcelona (UB) and the August Pi i Sunyer Institute of Biomedical Research (IDIBAPS)- and the Catalan Government. Its mission is to improve global health through research and training and its director is Prof. Pedro L. Alonso, a world expert on malaria.



ORGANIZATIONAL CHART



- Directorate
- Research programmes
- Research areas
- Research support platforms

Governing Board, Directorate and Advisory Committees



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Hospital Clínic of Barcelona

RAMON GOMIS DE BARBARÀ

Director of Research
IDIBAPS Consortium

JORDI SEGARRA PIJUÁN

Fundació CELLEX

SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC)

Appointed by CRESIB's Board of Trustees and constituted by 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 programmes undertaken by CRESIB, including uptake of strategies, selection of research staff and evaluation of the Strategic Plan.

DR. JOSÉ ALCAMÍ

*Head, AIDS Immunopathology Unit
National Microbiology Centre
Instituto de Salud Carlos III
Madrid (Spain)*

DR. MARIANO ESTEBAN

*Director
National Biotechnology Centre
Consejo Superior de Investigaciones Científicas (CSIC)
Madrid (Spain)*

DR. MARIA C. FREIRE

*President
Lasker Foundation
New York (U.S.A.)*

DR. FEDERICO GÓMEZ DE LAS HERAS

*Retired. Formerly VP Director
Diseases of the Developing World Drug Discovery
GlaxoSmithKline
Tres Cantos, Madrid (Spain)*

DR. VICENTE LARRAGA

*Director
Biological Research Centre
Consejo Superior de Investigaciones Científicas (CSIC)
Madrid (Spain)*



PROF. MYRON M. LEVINE

*Grollman Distinguished Professor and Director
Center for Vaccine Development
School of Medicine, University of Maryland
Baltimore (U.S.A.)*

PROF. DAVID MABEY

*Professor of Transmittable Diseases
Clinical Research Unit
London School of Hygiene & Tropical Medicine
London (United Kingdom)*

DR. REGINA RABINOVICH

*Director of Infectious Diseases
Global Health Program
Bill & Melinda Gates Foundation
Seattle (U.S.A.)*

PROF. MARCEL TANNER (CHAIR)

*Professor and Director
Swiss Tropical and Public Health Institute
Basel (Switzerland)*



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DIRECTORATE

DIRECTOR:

PROF. PEDRO L. ALONSO

DEPUTY DIRECTOR

DR. NÚRIA CASAMITJANA (until October 2011),

DR. ANTONI PLASÈNCIA (since November 2011)

ECONOMIC AND FINANCIAL DIRECTOR

MS. MARGARITA SALA

INTERNAL SCIENTIFIC COMMITTEE (ISC)

The Internal Scientific Committee (ISC) is an internal body that advises the CRESIB directorate on scientific matters. It is constituted by the Director, the Deputy 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 compatible with its Scientific Programme.
- 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 2011 the committee was made up of the following members: Dr. P. L. Alonso, Dr. N. Casamitjana (until October 2011), Dr. A. Plasència (since November 2011), Dr. E. B. Hayes (chair), Dr. H. del Portillo, Dr. J. Gascon, Dr. C. Menéndez, Dr. I. Mueller, Dr. J. Ordi, Dr. R. Pool, Dr. T. Pumarola, Dr. A. Trilla, Dr. J. Vila, Dr. J. J. Aponte, Dr. C. Dobaño, Dr. A. Mayor and Dr. E. Casamitjana (secretary). ♦

Facts and Figures

CRESIB publications 2011

NUMBER OF
ARTICLES

166

TOTAL
IMPACT
FACTOR

834

WITHIN
THE 1ST
QUARTILE

106

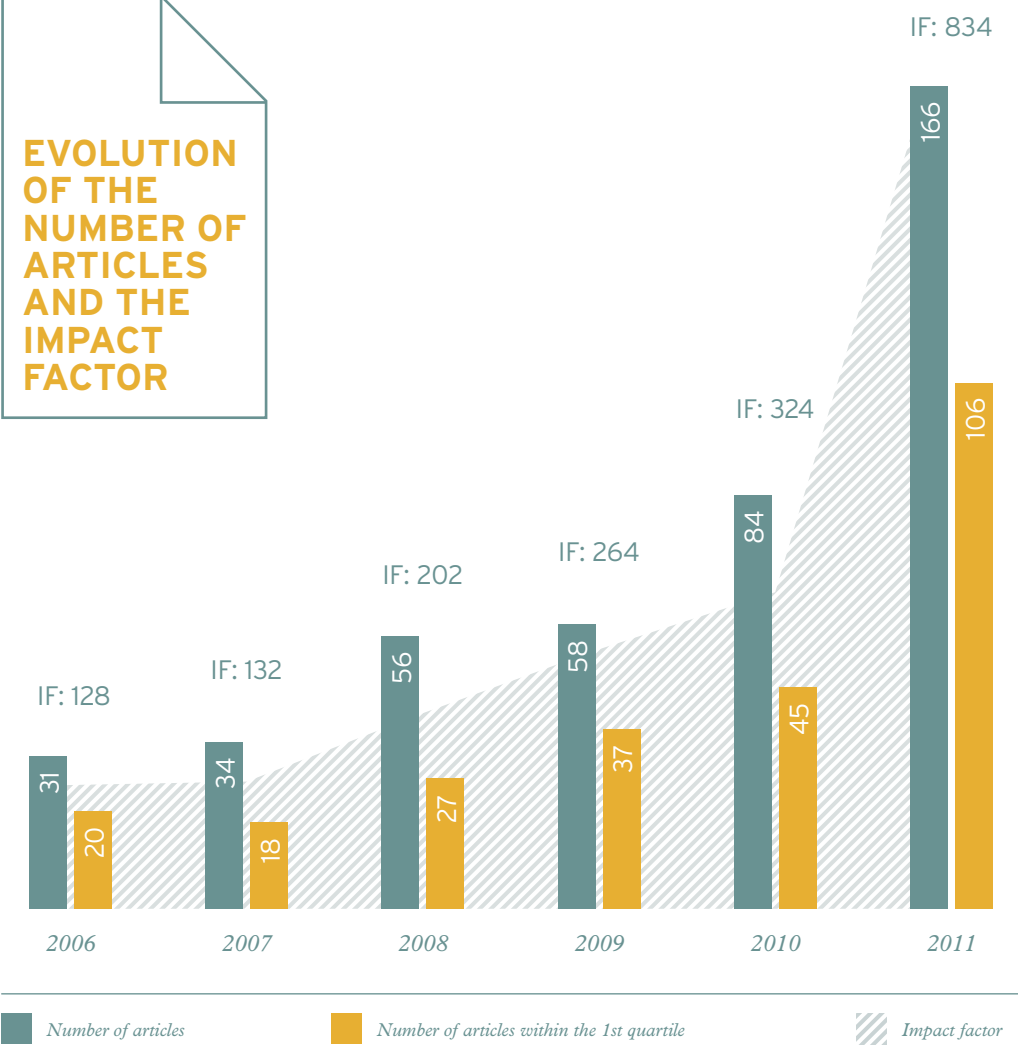
AVERAGE
IMPACT
FACTOR

5,02



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EVOLUTION OF THE NUMBER OF ARTICLES AND THE IMPACT FACTOR



NOTE

Number of articles, impact factor and articles in the first quartile of their speciality published by CRESIB researchers since its foundation.

This includes papers from researchers who are affiliated with CRESIB since January 2010 and who belong to CRESIB's trustee institutions, regardless of the affiliation indicated by the authors of the paper.

Annual Budget

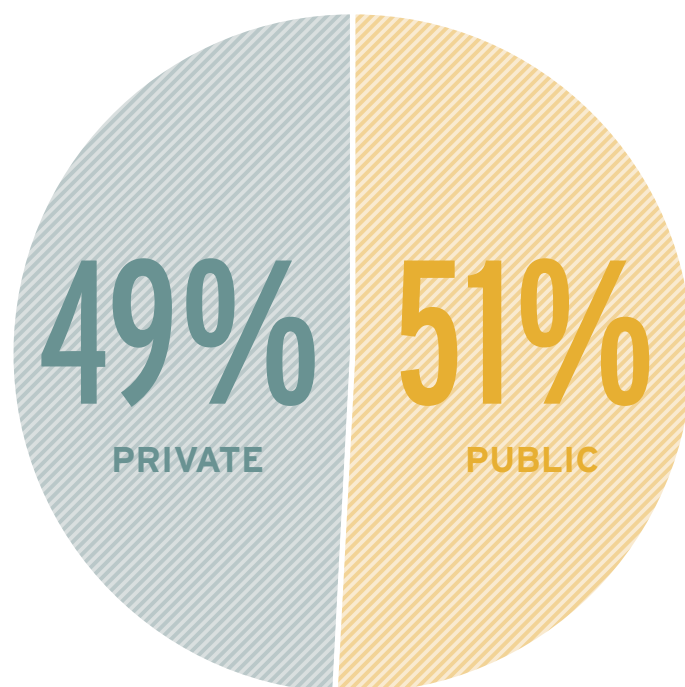


NOTE

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 Clinic of Barcelona, IDIBAPS, University of Barcelona) and the Clinic Foundation for Biomedical Research (FCRB), acting as the organization responsible for managing these funds.

(*) Provisional data.

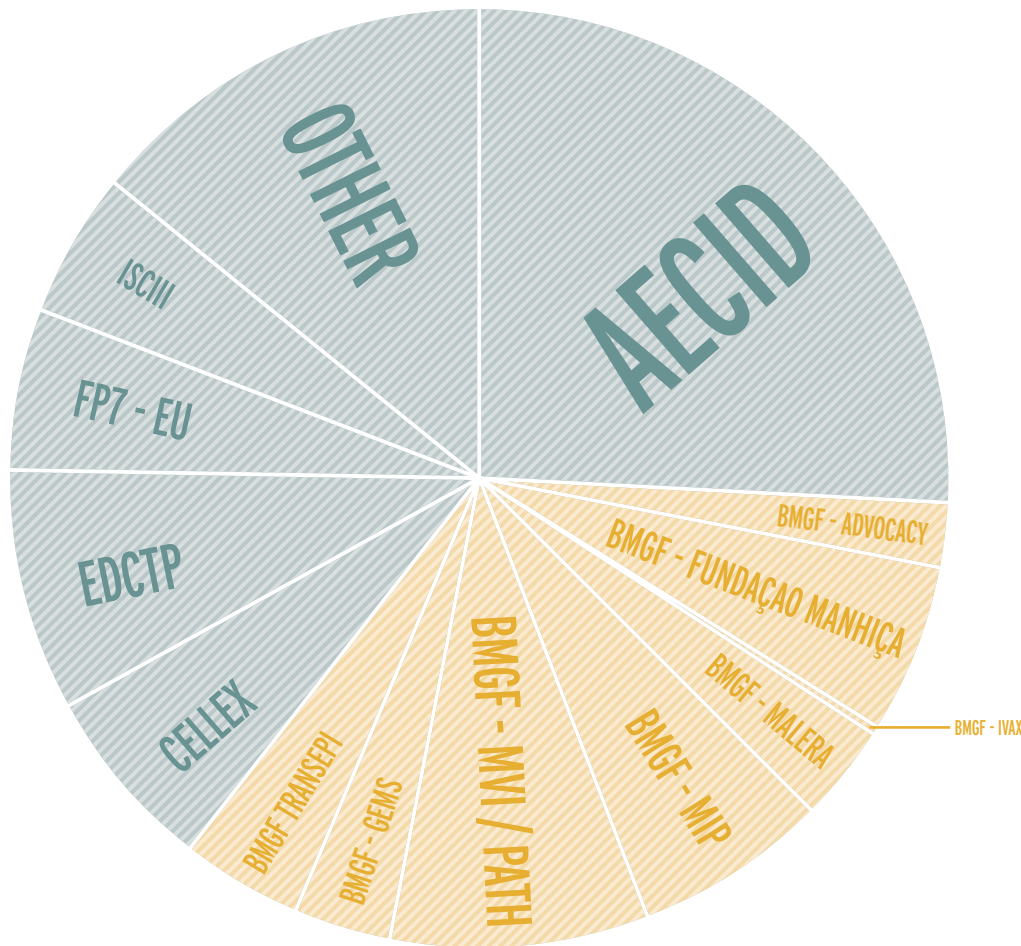
Funding sources



NOTE

Sources of funding (public or private) for project funds and grants active in 2011.

Main funders



NOTE

CRESIB's main funders, taking into account project funds and grants active in 2011. As in the Annual Budget graph, these include international health research funds awarded to CRESIB, to its founding institutions (Hospital Clinic, IDIBAPS, University of Barcelona) and to the Clinic Foundation for Biomedical Research (FCRB).

AECID (Spanish International Development Cooperation Agency)	26,0%
BMGF (Bill & Melinda Gates Foundation)	34,7%
BMGF - ADVOCACY -	2,1%
BMGF - FUNDAÇÃO MANHIÇA -	5,8%
BMGF - IVAX -	0,4%
BMGF - malERA (Malaria Eradication Research Agenda) -	3,4%
BMGF - MIP (Malaria in Pregnancy Consortium) -	6,7%
BMGF - MVI / PATH (Malaria Vaccine Initiative/ Program for Appropriate Technology in Health) -	8,7%
BMGF - GEMS (Global Enteric Multi-Centre Study) -	3,4%
BMGF TRANSEPI (The comparative epidemiology of <i>P. falciparum</i> and <i>P. vivax</i> transmission in Brazil, Thailand and Papua New Guinea) -	4,2%
Fundació CELLEX	6,5%
EDCTP (European and Developing Countries Clinical Trials Partnership)	8,1%
FP7 - EU (Framework Programme 7 European Union)	5,7%
ISCIII (Carlos III Health Institute)	5,0%
OTHER	14,0%

Public Health



Area Leader

Edward B. Hayes

Researchers working in the area

Pedro L. Alonso, Joaquim Gascón, Clara Menéndez, Tomas Pumarola, Antoni Trilla, Quirque Bassat, Jose Muñoz, Denise Naniche, Anna Vilella, Jose M^a Bayas, Andreu Prat, Manuel Santiñà, Mikel Martínez, Elisa Sicuri, Jaume Grau, Imane Jroundi, Oriol Mitjà, Cinta Moraleda, Núria Díez, Cristina O'Callaghan, Alberto García-Basteiro

MAIN RESULTS OF 2011

CRESIB's work in the Public Health research area focused on gathering information to improve the effectiveness of disease prevention strategies. In 2011, our research ranged from determining the predominant circulating strains of influenza virus, to assessing the role of vaccine-preventable infections on the health of children in Morocco, to evaluating the effectiveness of a strategy to prevent yaws. The results of CRESIB's public health research are expected to guide development of new prevention strategies and to strengthen the application of strategies shown to be effective.

In 2011, CRESIB researchers documented the circulation of influenza C virus along with pandemic H1N1 virus during the 2009 influenza season in Spain. These findings are an exercise relevant to global efforts to track influenza virus activity and variation. A case-control study of adults with HIV infection in Barcelona found no impact of HIV status on the severity of influenza. Another study evaluated the effects of seasonal influenza on children's health and highlighted the importance of assuring adequate childhood influenza vaccine coverage.

CRESIB has a well-established record in researching the aetiology of respiratory and gastrointestinal infections in African children, with a focus on evaluating the potential impact of available vaccines on improving child health. CRESIB researchers published studies indicating that approximately half of

MAIN LINES OF RESEARCH IN 2011

- Assessment of the economic impact and effectiveness of disease prevention and control strategies
- Evaluation of impact and burden of diseases in resource-limited areas
- Assessments of the effectiveness and impact of vaccines and other prevention strategies
- Evaluation of impact and management of neonatal infections



PHOTO

Left: Girl being vaccinated at the Manhiça Health Centre, Mozambique.

Right: Medical staff at the Spanish Hospital of Tetuan, Morocco.

children with respiratory illness attended at a hospital in Mozambique had viral infections, and that the incidence of severe respiratory viral infections was higher among children with underlying HIV infection. Another study evaluated the proportion of childhood hospitalizations in Catalonia caused by rotavirus, and concluded that at current costs, universal rotavirus vaccination would not yield net financial savings in this setting.

Economic evaluations focussed on the cost-effectiveness of screening for Chagas disease in pregnant women and of intermittent preventive treatment of malaria in pregnancy. The first study indicated that from the healthcare system perspective, screening all Latin American women giving birth in Spain and their infants for Chagas disease was more cost-effective than not screening. The malaria study described several factors that influenced the cost-effectiveness of intermittent preventive treatment including malaria transmission rates, timing of treatment delivery in relation to seasonal transmission patterns, and level of drug resistance.

Researchers collaborated with partners in Papua New Guinea to evaluate the public health challenges of yaws and filariasis. A serologic survey of 233 children with clinically suspected yaws found that 59% could be serologically confirmed and highlighted the need for reliable diagnostic criteria for this disease. A non-inferiority RCT confirmed that a single dose of oral azithromycin is as effective as injectable penicillin, paving the way to a simplified

HIGHLIGHTED PUBLICATIONS



Antón A, Marcos MA, Codoner FM, de Molina P, Martínez A, Cardenosa N, Godoy P, Torner N, Martínez MJ, Ramón S, Tudó G, Isanta R, Gonzalo V, Jimenez de Anta MT, Pumarola T. 2011.

Influenza C virus surveillance during the first influenza A (H1N1) 2009 pandemic wave in Catalonia, Spain.

Diagnostic Microbiology and Infectious Disease 69 (4), 419-427.

O'callaghan-Gordo C, Bassat Q, Morais L, Díez-Padrís N, Machevo S, Nhampossa T, Nhalungo D, Sanz S, Quinto L, Alonso PL, Roca A. 2011.

Etiology and Epidemiology of Viral Pneumonia Among Hospitalized Children in Rural Mozambique: A Malaria Endemic Area With High Prevalence of Human Immunodeficiency Virus.

The Pediatric Infectious Disease Journal 30 (1), 39-44.

Mitjà O, Paru R, Hays R, Griffin L, Laban N, Samson M, Bassat Q. 2011.

The impact of a filariasis control program on Lihir island, Papua New Guinea.

PLoS Neglected Tropical Diseases 5 (8), e1286.

treatment that could facilitate mass drug administration campaigns. An ecological study of villages from areas with different filariasis infection rates found that the success of mass drug administration programmes seemed to depend on the baseline prevalence of infection.

Additional CRESIB research relevant to Public Health is covered more extensively in other sections of this report and includes studies to define the research agenda for malaria eradication, historical guidance for malaria eradication, evaluation of the potential health impacts of indoor spraying to control malaria, exploration of the determinants of bed net use to prevent malaria, assessment of the burden of measles and HIV in southern Mozambique, and evaluations of the seasonal dynamics of hospital admissions and of risk factors for infection in organ transplant recipients. ♦

Medical Anthropology



Area Leader
Robert Pool

Researchers working in the area

Robert Pool, Marjolein Gysels, Maria Roura, Arantza Meñaca, Erin W. Andrew, Natalie Evans, Christopher Pell

MAIN LINES OF RESEARCH IN 2011

- Migration and health, through the setting up of the Coordinating resources to assess and improve health status of migrants from Latin America project (COHEMI)

MAIN RESULTS OF 2011

In 2011, the anthropology team was primarily focused on the analysis and publication of study results from previous years. At the same time, a new line of research in migrant health (COHEMI) was awarded. The COHEMI project is a three-year initiative implemented by 10 partners and is supported by the European Commission 7th Framework Programme. This project aims at providing a clear understanding of the full migration cycle in relation to the health systems in Europe and Latin-America and to promote greater coordination in efforts to understand the social and cultural factors that influence the health-seeking behaviors of persons of Latin-American origin who have migrated to Europe.

A study of acute respiratory illness (ARI) in infants in Mozambique showed that health promotion should take into account the syncretism involved in local

explanations of ARIs in the context of care seeking for children. Further, it should draw upon lay interpretations and terminologies in order to stress the importance of seeking medical care for all locally defined illness categories related to ARI.

The Malaria in Pregnancy (MiP) study, in four African countries, showed that MiP is interpreted in locally defined categories rather than in biomedical terms. Local discourses and health workers' ideas influence concerns about MiP interventions. Understanding of antenatal care, health worker-client interactions, household decision-making, gender relations, cost and distance to health facilities affect pregnant women's access to interventions. Lack of healthcare infrastructure limits provision of interventions.

In the Microbicides Development Programme, integrated, qualitative social science highlighted the fallibility and fragility of quantitative trial data by demonstrating inconsistencies in key behavioral measurements. It also foregrounded the disjuncture between biomedical conceptions of microbicides and the meanings and uses of the study gel in the context of users' everyday lives. The research also showed that coital diaries (CDs) were capable of collecting more accurate data on numbers of sex acts and adherence than face-to-face interviews in the clinic setting, which has implications for measuring adherence during clinical trials.

A study of indoor residual spraying (IRS) for malaria prevention in Mozambique suggests that the



© Quirque Bassat

PHOTO

Left: Counseling session on Chagas disease at the Hospital Clinic of Barcelona.

Right: Briefing session on a clinical trial at Manhica, Mozambique.

contribution of IRS to malaria control is not entirely perceived by the beneficiaries, and that insecticide-treated nets are favoured. Adherence to IRS was influenced by socio-political factors. There is a need to redefine the community sensitization approaches in order to make IRS a genuinely participative, acceptable, and sustainable programme.

A study of youth sexuality in Uganda showed that adolescents are exposed to risk in both stable and casual sexual relationships. Relationships involve the exchange of gifts and money. Older partners are valued, despite the knowledge they are more likely to be HIV positive, because they offer greater financial rewards than age mates.

Four papers were published as part of the EC funded Reflecting the Positive Diversities of European Priorities for Research and Measurement in End of Life Care (PRISMA) project. Two systematic reviews of the research literature on this topic focused on minority ethnic groups in the UK context. One reviewed the evidence of 13 literature reviews and identified a range of social, institutional, epidemiological and cultural reasons for low service use and some distinct End of Life (EoL) preferences and needs. Key themes included: structural inequality; inequality by disease group; referrals; place of care and death; awareness and communication issues; and, cultural competency. The systematic review of the primary research synthesised forty-five studies which highlighted multiple and related factors that contribute to low service use and substand-

HIGHLIGHTED PUBLICATIONS



Gysels M, Pell C, Straus L, Pool R. 2011.

End of life care in sub-Saharan Africa: a systematic review of the qualitative literature.

BMC Palliative Care 10 (1), 6.

Pell C, Straus L, Andrew EVW, Meñaca A, Pool R. 2011.

Social and cultural factors affecting uptake of interventions for malaria in pregnancy in Africa: a systematic review of the qualitative research.

PLoS One 6 (7), e22452.

Montgomery CM, Pool R. 2011.

Critically engaging: integrating the social and the biomedical in international microbicides research.

J Int AIDS Soc 14 Suppl 2, S4.

ard quality of services experienced by minority ethnic groups. A systematic review of Italy, Spain and Portugal showed that the role of religion and the importance of family ties were the two main cultural factors to explain similarities in EoL preferences between these countries. The review pointed towards the important need for further research to investigate the differences identified. A scoping exercise of the socio-cultural factors in EoL care showed Belgium as providing a unique opportunity to witness how euthanasia is put into practice when legalized, and in synergy with palliative care.

A systematic review of the qualitative evidence on EoL care in sub-Saharan Africa was undertaken to contribute to the evidence-base which is needed for the development of effective and appropriate service provision. The data support or complement the findings from quantitative research. The review prompts a reconsideration of the assumption that in Africa the extended family care for the sick, and that people prefer home-based care. The review identifies areas relevant for a research agenda on socio-cultural issues at the EoL in sub-Saharan Africa. ♦

Maternal, Child and Reproductive Health



© Raquel González



Area Leader

Clara Menéndez

Researchers working in the area

Jaume Ordi, John Aponte, Carlota Dobaño, Alfredo Mayor, Azucena Bardají, Quique Bassat, Denise Naniche, Ruth Aguilar, Pilar Requena, Elisa Sicuri, Raquel González, Cinta Moraleda, María Rupérez, Ariel Magallón, María Nélia Manaca, Laura Moro, Eduard Rovira, Laura Puyol, Diana Barrios, Mercè Bosch, Pau Cisteró, Alfons Jiménez

MAIN LINES OF RESEARCH IN 2011

- Evaluation of alternative drugs for intermittent preventive treatment of malaria in pregnancy (MiPPAD project)
- Description of the epidemiology and clinical impact of *Plasmodium vivax* infection in pregnant women in three endemic regions (PregVax project)
- Description of the aetiology and risk factors of anemia among children in Mozambique
- Study of immunity and physiopathology of malaria in pregnancy
- Study of maternal mortality causes
- Study of HIV mother-to-child transmission factors

MAIN RESULTS OF 2011

CRESIB coordinates two major malaria in pregnancy consortiums, MiPPAD and PregVax. MiPPAD has completed its enrolment, and over 5,000 pregnant women have been recruited across five different African sites. Within the PregVax project, the enrolment and follow-up of 9,325 pregnant women across five *Plasmodium vivax* endemic areas has been completed. In addition to these projects, a number of studies were carried out.

One study assessed the impact of malaria at the end of pregnancy on infant mortality and morbidity. The detailed placental examination done in this study revealed that placental infections occurring at the end of pregnancy are those most likely to have an impact on infant survival. Clinical malaria episodes were more frequent and the incidence of first or only episodes higher among infants born to mothers with placental malaria.

Investigations on the role of intermittent preventative treatment in pregnancy (IPTp) with Sulphadoxine-Pyrimethamine (SP) on SP resistance showed that mutant infections wane rapidly after SP is eliminated from the bloodstream and are not translated into more severe infections or higher malaria-related morbidity in mothers and children. Thus, it is likely that IPTp with SP has only a subtle effect on SP resistance at the population level, especially in areas of endemicity, where competition from less-resistant parasites is intense and SP is not used as first-line therapy.

An immunological study has shown that parity and placental infection can modulate immune responses against malaria parasites during pregnancy. The study results confirm that immunity to parasites transcribing *var2csa* is pregnancy specific, but, importantly, also show that primigravidae have lower immune responses against parasites not specifically associated to pregnancy (i.e., those infecting children, men, and nonpregnant women) than women of higher parities.



© Azucena Bardají

PHOTO

Left: Pregnant woman undergoing HIV testing during the 1st antenatal care (ANC) visit at the Manhiça Health Centre, Mozambique.

Right: Pregnant woman being recruited for the PregVax study at the Bikaner Hospital, Rajasthan, India.

Another study has shown that although *var2csa* transcription predominates in placental and peripheral infections during pregnancy, pregnant women are also infected in their peripheral blood by parasites transcribing A, B, and/or C *var* genes at levels similar to those of isolates from nonpregnant adults. These findings are of interest for the design of malaria vaccines for pregnant women.

Recent published results demonstrate that HIV and placental infection modulate the appearance of drug-resistant *Plasmodium falciparum* in pregnant women who receive intermittent preventive treatment (IPT). These results support the concept that impaired adaptive immune responses in the placenta and in HIV-infected pregnant women contribute to increased *P. falciparum* parasitaemias.

Over the past years our team has conducted several studies of the burden and impact of HIV infection on maternal and infant health among pregnant women attending the Manhiça District Hospital in Mozambique. These studies have allowed us to determine HIV prevalence among the study participants and recently to estimate the HIV incidence in this population. In this region, HIV prevalence among women of reproductive age has increased significantly in the last 10 years. The results suggest that HIV incidence among pregnant women has recently reached a plateau, but the rate remains unacceptably high from a public health standpoint.

HIGHLIGHTED PUBLICATIONS



Bardají A, Sigauque B, Sanz S, Maixenchs M, Ordi J, Aponte JJ, Mabunda S, Alonso PL, Menéndez C. 2011.

Impact of malaria at the end of pregnancy on infant mortality and morbidity.

The Journal of Infectious Diseases 203 (5), 691-699.

Menéndez C, Serra-Casas E, Scahill MD, Sanz S, Nhabomba A, Bardají A, Sigauque B, Cisteró P, Mandomando I, Dobaño C, Alonso PL, Mayor A. 2011.

HIV and Placental Infection Modulate the Appearance of Drug-Resistant *Plasmodium falciparum* in Pregnant Women who Receive Intermittent Preventive Treatment.

Clinical Infectious Diseases 52 (1), 41-48.

Sicuri E, Bardají A, Sigauque B, Maixenchs M, Nhacolo A, Nhalungo D, Macete E, Alonso PL, Menéndez C. 2011.

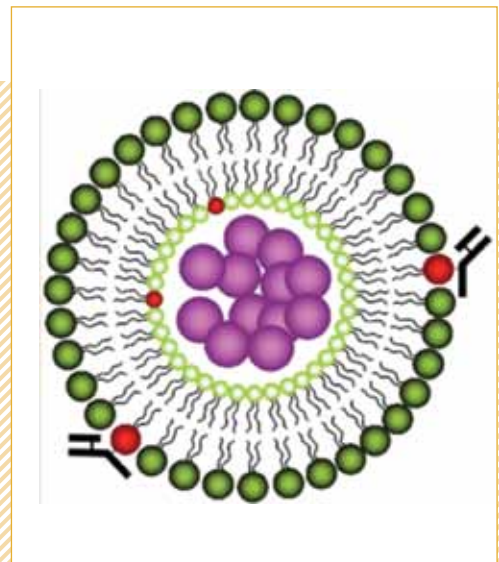
Costs associated with low birth weight in a rural area of southern Mozambique.

PLoS One 6 (12), e28744.

Our group has also conducted the first cost evaluation of Low Birth Weight (LBW) in a low-income country, showing that reducing the prevalence of LBW would translate into important cost savings to health systems and households.

In addition, for the first time DDT concentrations of breast milk samples in a rural population from Mozambique where DDT was reintroduced by Indoor Residual Spraying have been described. Breast milk concentrations of most DDT compounds were significantly higher in primiparae than multiparae women. These results, and previous studies on deleterious health effects of in-utero low doses of DDT in infants, recommend the implementation of monitoring surveys to assess the health effects of the DDT from its initial period of use. ♦

Host-Pathogen Interactions



Area Leader

Hernando del Portillo

Researchers working in the area

Hernando del Portillo, Joaquim Gascón, Edward.B. Hayes, Jaume Ordí, Tomàs Pumarola, Jordi Vila, Carlota Dobaño, Alfredo Mayor, Miriam Álvarez, Alfred Cortés, Carmen Fernández-Becerra, Xavier Fernández-Busquets, Luis Izquierdo, Denise Naniche, Joaquim Ruiz, Sara Soto, Ruth Aguilar, Núria Anton, Anna Fàbrega, Francisco Javier López, Lorena Martín, Mikel Martínez, Gemma Moncunill, Cristina Pitart, Pilar Requena, Edmilson Rui, Juan José Valle, Joseph Joe Campo, Andrés Anton, Maria Joana A. Marques, Clara Ballesté, Maria Bernabeu, Patricia de Molina, Núria Díez, Paula Andrea Espinal, Mireia Ferrer, Elisabet Guiral, Yuly López, Ariel Magallón, Ernest Moles, Laura Moro, Noraida Mosqueda, Cristina O'Callaghan, Maria Jesús Pons, Emma Rey, Eduard Rovira, Cèlia Serna, Mar Solé, Patricia Urbán, Xavier Vila, Laura Puyol, Josep Astola, Diana Barrios, Pau Cisteró, Alfons Jiménez, Laura Muñoz, Miriam Ramirez, Núria Rovira

MAIN LINES OF RESEARCH IN 2011

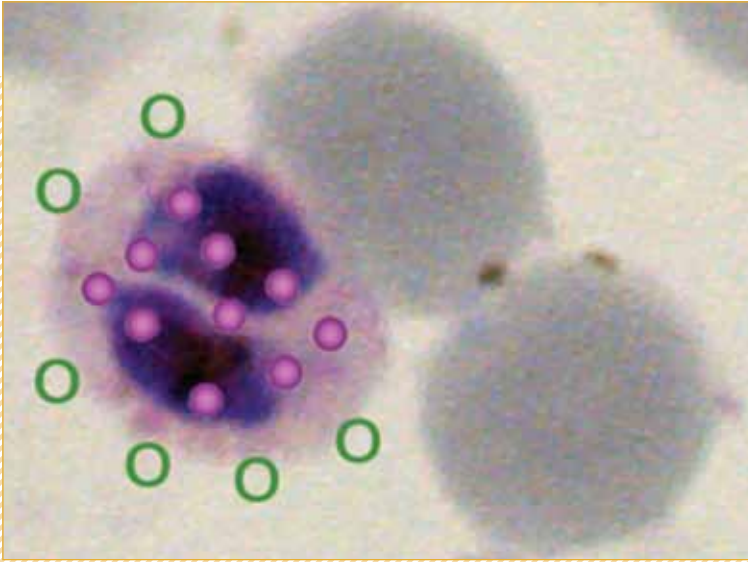
- Naturally-acquired and vaccine-induced protection
- Antigen discovery and vaccine development
- Drug discovery and targeted drug delivery
- Molecular mechanisms of drug resistance
- Molecular and serological markers of disease
- Immune responses and markers in co-infections
- Molecular basis of pathology
- Vertical transmission of infectious diseases

MAIN RESULTS OF 2011

The host-pathogen interactions area has increased with the incorporation of Dr. Alfred Cortes as an Assistant Research Professor. He and his group bring more expertise on invasion mechanisms and control of gene expression in malaria.

Several significant advances have been achieved in the different programmes pertaining to this area. In malaria: better understanding of the RTS,S vaccine-induced immune responses, including longevity of antibody responses against asexual blood stage antigens of the parasite after four years; the discovery for the first time that exosomes from malaria infections are capable of antigen presentation suggesting their use as a new vaccine and platform against malaria; proof of concept that 100% *in vitro* targeted-drug delivery to infected red blood cells using nanovesicles is feasible; the discovery that *P. vivax* adheres to endothelial receptors and identification of a new mechanism for evasion of spleen clearance; findings that not only *var2csa* genes are expressed during pregnancy and that parity and placental infection affect antibody responses against the parasite; identification of a new receptor likely involved in malaria pathology; and the use of molecular markers to understand the dynamics of parasite populations in natural infections as well as treatment failures.

In Chagas disease new serological markers to monitor active infection and treatment efficacy are



PHOTO

Left: Cartoon of a quantum dot-containing liposome functionalized with half-antibodies against *Plasmodium falciparum*-infected red blood cells.

Right: Graphical scheme of the performance of such immunoliposomal nanovector when added to a *P. falciparum* culture containing both infected and non-infected cells.

(Urban P. et al., *Control Release*. 2011 Apr 30;151(2):202-11).

being evaluated, as well as new biochemical markers such as HPLC to monitor the pharmacokinetics of benznidazole in treated patients. Evaluation of myocardial deformation, particularly of radial strain, also appears to be a potentially sensitive technique for early detection of myocardial involvement.

Studies of Enteropathogens have identified several different mechanisms of drug resistance, these include: integrons in strains responsible for traveler's diarrhoea, the demonstration of expression of new genes associated with resistance in different species, the acquisition of pathogenic islands through horizontal gene transfer increasing the possibilities of spreading drug resistance, the use of qPCR to detect asymptomatic vs. symptomatic infections, identification of efflux pumps in species not previously known to have this mechanism of drug resistance.

In the area of viral diseases, studies of T Cell Subsets in HIV-infected adults with co-infections revealed the intriguing observation that yellow fever viral RNA persists for up to six months after vaccination. Another study found that suppression of HIV-RNA is associated with improved control of immune activation in adults.

Work in co-infections showed that HIV and placental infection modulate the appearance of drug-resistant *Plasmodium falciparum* in pregnant women who received intermittent preventive treatment. Also the possibilities of developing molecular tests

HIGHLIGHTED PUBLICATIONS



Urban P, Estelrich J, Cortés A, Fernández-Busquets X. 2011.

A nanovector with complete discrimination for targeted delivery to *Plasmodium falciparum*-infected versus non-infected red blood cells in vitro.

Journal of Controlled Release 151 (2), 202-211.

Martin-Jaular L, Ferrer M, Calvo M, Rosanas-Urgell A, Kalko S, Graewe S, Soria G, Cortadellas N, Ordi J, Planas A, Burns J, Heussler V, Del Portillo HA. 2011.

Strain-specific spleen remodelling in *Plasmodium yoelii* infections in *Balb/c* mice facilitates adherence and spleen macrophage-clearance escape.

Cellular Microbiology 13 (1), 109-22.

Miguel J. Martínez, Anna Vilella, Tomás Pumarola, Montserrat Roldan, Víctor G. Sequera, Isabel Vera, Edward B. Hayes. 2011.

Persistence of yellow fever vaccine RNA in urine.

Vaccine. 2011; 29: 3374-3376.

distinguishing malaria from severe pneumonia and other diseases among hospitalized children were explored.

Studies in enabling technologies produced robust and reproducible expression on a small-scale of soluble malaria proteins in the wheat germ system for coupling to luminex beads that facilitates studies of naturally acquired immune responses using suspension array assays; intravital and magnetic resonance imaging of rodent malaria models allowing studies of the dynamic passage of parasites through different organs *in vivo*. In addition, flow cytometry for measurements of *P. falciparum* parasite burden in endemic malaria development was developed. ♦

Malaria



Researchers working in the programme

Pedro L. Alonso, Hernando A. del Portillo, Clara Menéndez, Ivo Mueller, Jaume Ordi, Robert Pool, John J. Aponte, Carlota Dobaño, Alfredo Mayor, Azucena Bardají, Quique Bassat, Alfred Cortés, Carmen Fernández-Becerra, Xavier Fernández-Busquets, Caterina Guinovart, Luis Izquierdo, Ruth Aguilar, Núria Anton, Francisco Javier López, Lorena Martín, Arantza Meñaca, Gemma Moncunill, Charlotte Pierrat, Pilar Requena, Edmilson Rui, Elisa Sicuri, Juan José Valle, Raquel González, Miguel Lanaspa, María Ruperez, Joseph Joe Campo, María Joana A. Marques, María Bernabeu, Mireia Ferrer, Ariel Magallón, Ernest Moles, Laura Moro, Eduard Rovira, Patricia Urbán, Pedro Aide, Inoni Betuela, María Nelia Manaca, Diana Quelhas, Laura Puyol, Josep Astola, Diana Barrios, Pau Cisteró, Alfons Jiménez, Miriam Ramírez, Núria Rovira



Programme Leaders

Pedro L. Alonso and Hernando del Portillo

MAIN LINES OF RESEARCH IN 2011

- Antigen discovery and vaccine development
- Drug discovery and targeted-delivery
- Glycobiology, molecular basis of pathology and pathophysiology
- Epigenetic regulation of gene expression
- Malaria immunology
- Burden and clinical impact
- Intervention studies: vaccines and drugs
- Monitoring and evaluation
- Economic burden and cost-effectiveness of malaria interventions
- Socio-cultural aspects of malaria

MAIN RESULTS OF 2011

Malaria is one of the strongest programmes at CRESIB, including a comprehensive research portfolio with a translational view (from discovery through development to delivery) on the two most common *Plasmodium* species: *falciparum* and *vivax*.

Several enabling technologies have been published during 2011 to improve malaria research. A comparison of proteins produced on a small scale using cell-free systems has demonstrated that proteins produced in wheat germ are soluble and mostly intact, allowing coupling to luminex beads for suspension array assays. This technology and proteins are now widely used by several different research projects in malaria to understand naturally-acquired humoral immune responses from patients in different epidemiological contexts.

The feasibility of a flow cytometry-based method based on bidimensional assessment of YOYO-1 and autofluorescence for measurements of *P. falciparum* parasite burden in malaria endemic areas was demonstrated. In addition, four microsphere suspension array technologies were compared in terms of reproducibility and the absolute quantity of cytokine detected. These data provided an accurate assessment of the four techniques with regards to sample volume, the number of cytokines measured and the time and cost of the assays, which permits selecting the tool best suited for subsequent immunological studies.



PHOTO

The new clinical trials unit, where antimalarial drug trials can be performed in Manhica's District Hospital.

In the area of antigen discovery, vaccine development and molecular basis of pathology, significant results have been published this year. *P. vivax* has a unique tropism for reticulocytes, immature red blood cells that in their maturation process release 50-100 nm nanovesicles termed exosomes (rex). Exosomes are now the subject of intense research activities as intercellular messengers and conveyors of immune responses and vaccines. Notably, using a reticulocyte-prone non-lethal rodent malaria model that replicates these biological aspects in *P. vivax*, it has been shown that *P. yoelii*-infected reticulocytes release exosomes containing parasite proteins involved in antigen presentation and modulation of immune responses. This is the first report of immune responses elicited by rex and opens promising new avenues for vaccine development against *P. vivax*.

In addition, using this rodent malaria model, it has also been shown that infected reticulocytes cytoadhere to a parasite-induced spleen-blood barrier of fibroblastic origin, thereby avoiding complete macrophage clearance. This is a new model of immune evasion in malaria, and challenges the current view that malaria parasites are physically (not actively) retained in the spleen, and suggests that the spleen might actually have a role in chronic infections.

Targeted-drug delivery is presently one of the most important research areas in human diseases, including malaria. Current administration methods of anti-malarial drugs, however, deliver the free compound in the bloodstream, where it can be unspecifically

HIGHLIGHTED PUBLICATIONS



The RTS,S Clinical Trials Partnership. 2011.
First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children.
 The New England Journal of Medicine 365 (20), 1863-1875.

Alonso PL, Brown G, Arévalo-Herrera M, Binka F, Chitnis C, Collins F, Doumbo OK, Greenwood B, Hall BF, Levine MM, Mendis K, Newman RD, Plowe CV, Rodríguez MH, Sinden R, Slutsker L, Tanner M. 2011.

A research agenda to underpin malaria eradication.
 PLoS Medicine 8(1), e1000406.

The Four Artemisinin-Based Combinations (4ABC) Study Group. 2011.

A Head-to-Head Comparison of Four Artemisinin-Based Combinations for Treating Uncomplicated Malaria in African Children: A Randomized Trial.
 PLoS Medicine 8 (11), e1001119.

Rovira-Vallbona E, Dobaño C, Bardají A, Cisteró P, Romagosa C, Serra-Casas E, Quinto L, Bassat Q, Sigauque B, Alonso PL, Ordi J, Menéndez C, Mayor A. 2011.

Transcription of var Genes Other Than var2csa in Plasmodium falciparum Parasites Infecting Mozambican Pregnant Women.
 The Journal of Infectious Diseases 204 (1), 27-35.

Martin-Jaular L, Nakayasu ES, Ferrer M, Almeida IC, Del Portillo HA. 2011.

Exosomes from Plasmodium yoelii-Infected Reticulocytes Protect Mice from Lethal Infections.
 PLoS One 6 (10), e26588.

taken up by all cells, and not only by *Plasmodium*-infected red blood cells (pRBCs). Using a liposome engineered to have an antibody that recognizes an asexual blood stage antigen of *P. falciparum*, it has been shown that 100% *in vitro* targeted-drug delivered to pRBCs using nanovesicles is feasible.

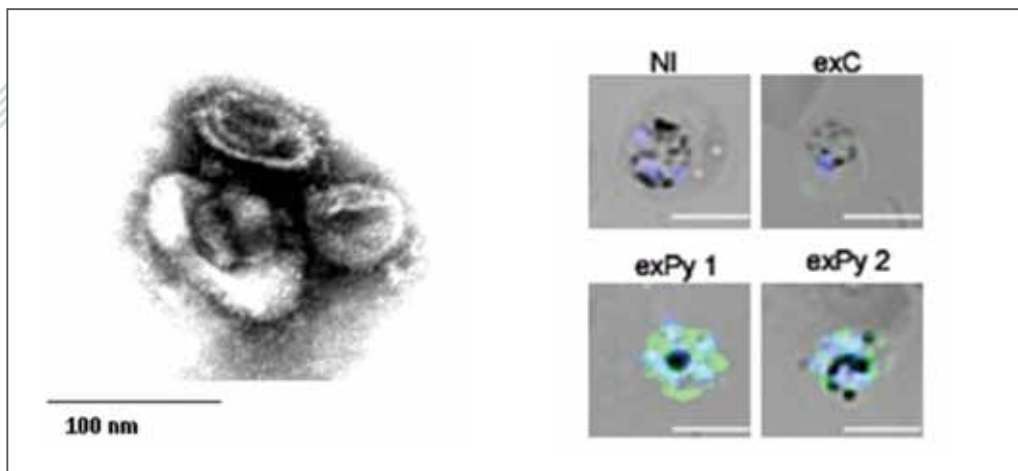
Proper diagnosis is a key challenge for common paediatric diseases such as malaria or acute respiratory infections. A hospital-based study in Manhica, Mozambique explored the diagnostic and manage-

PHOTO

Left: Reticulocyte-derived exosomes from malaria infections elicit protective immune responses upon immunizations. Left panel: electron-micrograph of reticulocyte-derived exosomes; scale bar 100nm. Right Panel: immunofluorescence of infected red blood cells using the sera of a normal mouse (NI), a mouse immunized with rex from a normal animal (exC) and two different mice immunized with rex from infections (exPy).

(Martin-Jaular L. Et al., PLoS One. 2011; 6(10):e26588)

Right: Mother and her children wait for a follow-up control as part of the RTS,S/AS01 malaria vaccine trial.



ment challenges represented by the large subgroup of children fulfilling simultaneous clinical criteria for severe pneumonia and malaria. Although symptom overlap between malaria and severe pneumonia was frequent, true disease overlap was uncommon. Clinical presentation and laboratory determinations were ineffective in reliably distinguishing between the two diseases. In addition, infections with HIV differentially influenced the epidemiology and clinical presentation of both infectious diseases, making even more difficult their discrimination on clinical grounds.

In a different study, the relation between erythropoietin (EPO) and malaria-attributable severe disease in Manhiça, an area with moderate malaria transmission, was assessed, but the results showed that EPO cannot be used to improve clinical diagnosis of severe malaria. The study did, however, contribute to understanding the pathophysiological processes underlying the expression of EPO.

Severe malaria has been attributed partly to the sequestration of *P. falciparum*-infected erythrocytes in the microvasculature of vital host organs. We reported a role for platelet-mediated clumping, rosetting and adhesion to gC1qR (a novel host receptor) in the pathogenesis of severe malaria, suggesting that inhibition of these cytoadherence phenotypes may reduce the occurrence or improve the prognosis of severe malaria outcomes.

Malaria during pregnancy is a major global health concern, resulting in poor maternal health and adverse birth outcomes. There is also some consensus that it may negatively affect infant mortality and malaria morbidity, but there is less evidence concerning the factors involved. In a study conducted in Man-

hiça, malaria infection at the end of pregnancy and maternal clinical malaria were shown to negatively impact survival and malaria morbidity in infancy. In addition, it was shown that parasites infecting pregnant women persist after delivery and increase the risk of malaria during the postpartum period. Altogether, these results suggest that effective clinical management and interventions to prevent malaria in pregnancy may improve the risk of postpartum infection and infant health and survival.

The pathophysiology of placental malaria was further studied by investigating the contribution of parasites transcribing *var* genes other than *var2csa* to maternal infections. The results showed that, although *var2csa* transcription predominates in placental and peripherals infections during pregnancy, pregnant women are also infected in their peripheral blood by parasites transcribing A, B, and/or C *var* genes at levels similar to those of isolates from nonpregnant adults. These findings are interesting for the design of malaria vaccines for pregnant women.

In 2011, CRESIB's malaria programme continued to make important contributions on the development and delivery of malaria control tools. Significant advances have been achieved in the clinical development of the GlaxoSmithKline RTS,S malaria vaccine candidate (currently the most clinically advanced). The first results of the ongoing Phase III trial of the RTS,S/AS01 malaria vaccine showed that the vaccine provided protection against both clinical and severe malaria in African children. The statistical methodology for the evaluation of vaccine efficacy in this Phase III multi-centre trial has also been reported. In addition, two studies have contributed to

a better understanding of the antibody responses induced by RTS,S to the circumsporozoite protein of *P. falciparum*, to the hepatitis B surface antigen and to blood stages of *P. falciparum* parasites.

The use of Intermittent Preventive Treatment [delivering treatment doses of an antimalarial drug at specified times during pregnancy (IPTp) or during routine Expanded Program on Immunization (EPI) visits (IPTi)], has been further studied as an effective prevention tool. The determinants of the cost-effectiveness of IPTi have been reported. In addition, the impact of IPTi on immune responses to malaria has been studied, showing that IPTi with sulfadoxine-pyremethamine (SP) did not negatively affect the development of IgG against *P. falciparum* variant surface antigens and growth-inhibitory antibodies thought to be major contributors to the acquisition of immunity to malaria in infancy. Regarding IPTp, it has been shown that IPTp with SP increases the prevalence of resistance markers in the placenta and in HIV-infected women at delivery, suggesting that host immunity is key for the clearance of drug-resistant infections. However, this effect of IPTp is limited to the period when blood levels of SP are likely to be significant and does not translate into more-severe infections or adverse clinical outcomes.

Another malaria control tool, indoor residual spraying (IRS) with dichlorodiphenyltrichloroethane (DDT), to reduce malaria transmission had a reinforced recommendation by the World Health Organization (WHO) in 2006. To understand the implementation process, reception and acceptability of the IRS programme in Manhica district, a qualitative study was developed. The results showed that the contribution of IRS to malaria and mosquito control is not entirely perceived by the beneficiaries, and that other as cost effective interventions such as insecticide-treated nets are favoured over IRS.

Furthermore, the impact of IRS with DDT on the levels of insecticides in human samples has been assessed. Specifically, breast milk concentrations of 4,4'-DDT and its related compounds were studied in samples collected in 2002 and 2006 from two



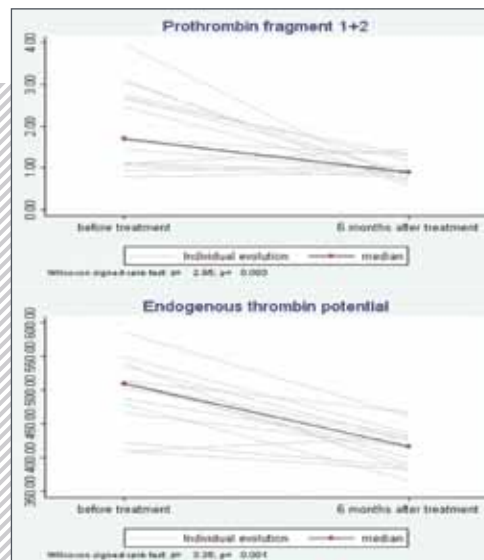
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populations of mothers in Manhica. Significant differences were found between the concentrations of DDT and related compounds in breast milk according to parity, with higher concentrations in primiparae than multiparae women. These differences overcome the age effect in DDT accumulation between the two groups, and provide evidence that women transfer a significant proportion of their body burden of DDT and its metabolites to their infants.

With regards to treatment, during 2011, different publications reported results of safety and efficacy trials of antimalarial drugs conducted in Manhica as part of individual or multicentre trials. The Four Artemisinin-Based Combinations (4ABC) Study confirmed that in Africa, the antimalarial combinations DHA-PQP, AL, and AQ-AS were similarly efficacious to treat malaria, but that the first one was better at preventing new infections. The evaluation of the fourth combination (CDA-AS), also part of the trial, was abandoned due to lower cure rates and safety concerns due to its potential to induce haemolysis. In Manhica, the *in-vivo* efficacy of the non-ACT combination of fosmidomycin and clindamycin was also assessed in a small trial, yielding unacceptably low cure rates (<50%) that caused the interruption of the clinical development of this combination.

Finally, in 2011 the conclusions of the Malaria Eradication Research Agenda (maERA) exercise were published (as a PLoS Medicine collection). This initiative, coordinated by CRESIB, brought together over 200 malaria experts from around the world during a two-year period, to discuss and propose the necessary research agenda and development priorities for definitively interrupting transmission of the parasite that causes malaria. ♦

Imported Diseases



Researchers working in the programme

Joaquim Gascon, Magdalena Alcover, Edelweiss Aldasoro, Cristina Ballart, Soledad Castillejo, Montserrat Gállego, Jose Muñoz, Inés Oliveira, Maria Jesús Pinazo, Montserrat Portús, Elizabeth Posada, Ana Requena, Maria Roura, Sílvia Tebar

Programme Leader

Joaquim Gascon

MAIN LINES OF RESEARCH IN 2011

- Epidemiology of Chagas disease in non-endemic areas
- Biomarkers for therapeutic efficacy of treated patients and early diagnosis of cardiac damage in patients with Chagas disease
- Clinical trials for the new drugs for Chagas parasitological treatment
- Studies on the pharmacokinetics of benznidazole
- Clinical research on imported dengue fever
- Epidemiology and vectoral control of leishmaniasis
- Clinical research on imported malaria
- Migrant health

MAIN RESULTS OF 2011

During the year 2011, two epidemiological studies on Chagas disease have been published: A seroprevalence study based in a Primary Health Center and a cost-benefit study related to a control programme for vertical transmission of Chagas disease. The seroprevalence study revealed that among Latin American patients who use primary care services, 15% of Bolivian patients are seroposi-

tive. Primary care should play a role in Chagas control. The results of the latter study showed that it is more cost effective to have a control programme to detect and treat children before they turn one year of age, than to wait to provide treatment when they are older and cardiac and digestive complications have developed. These results reinforce the need to implement such programmes in Latin-American pregnant women in Catalonia.

A study conducted in collaboration with the Hemotherapy & Hemostasis Department of the Hospital Clinic of Barcelona (HCB) addressed the current controversy over the hypothesis that a number of thromboembolic events could be related to hypercoagulable state in patients with chronic Chagas disease. Despite statistically significant differences in several markers, only ETP and F1+2 showed values outside normal levels in patients compared with controls. The levels of these markers drop after six months of benznidazole treatment. These results may be relevant in clinical practice, because if Chagas is considered as a thromboembolic risk factor, the antiparasitic treatment strategy could be reinforced. The results also support further research on haemostasis parameters as candidates for early surrogate biomarkers of therapeutic efficacy of Chagas disease.

Similar results have been obtained in a collaborative study with the Department of Molecular Biology, Instituto de Parasitología y Biomedicina López Neyra, Granada, Spain. The recombinant antigens KMP11, PFR2, Tgp63 and HSP70 are recognized by



PHOTO

Left: Descriptive and univariate analysis between averages of the haemostasis parameters pre-cure and six months post-treatment with benznidazole (N=15) (absolute values).

Grey lines: individual evolution; black lines with diamonds: median.

Right: Counseling session on Chagas disease at the Hospital Clínic of Barcelona.

Chagas disease patients' sera at any clinical stage of the disease. Shortly after benznidazole treatment, a drop in reactivity against three of these antigens is produced in an antigen-specific manner. Analysis of the reactivity against these recombinant antigens may be useful for monitoring the effectiveness of benznidazole treatment.

Work in collaboration with the Cardiology Department of HCB showed that reduced nitroglycerin-mediated vasodilatation suggesting dysfunction of vascular smooth muscle cells was found in patients with chronic Chagas cardiomyopathy. In addition, higher C-reactive protein levels were observed in the indeterminate form and early stages of chronic Chagas cardiomyopathy, which could be related to the inflammatory response to the infection or early cardiovascular involvement. On the other hand, evaluation of myocardial deformation, particularly of radial strain, appears to be a potentially sensitive technique for early detection of myocardial involvement in patients in the indeterminate form and may provide insights into the still unrevealed pathophysiology of Chagas heart involvement.

Epidemiological studies of leishmaniosis have been conducted in collaboration with the University of Granada, Spain. These studies focus on the emergence of leishmaniosis in the Pyrenean areas of Spain. Two proven sandfly vectors of *Leishmania infantum* have been captured (*Phlebotomus ariasi* and *P. perniciosus*) in Barcelona and Girona Pyrenees. The possible emergence of *Leishmania tropica* in

HIGHLIGHTED PUBLICATIONS



Pinazo MJ, Tassies D, Muñoz J, Fisa R, de Jesus Posada E, Monteagudo J, Ayala E, Gallego M, Reverter JC, Gascon J. 2011.

Hypercoagulability biomarkers in *Trypanosoma cruzi*-infected patients.

Thrombosis and Haemostasis 106 (4), 617-23.

Roca C, Pinazo MJ, Lopez-Chejade P, Bayo J, Posada E, Lopez-Solana J, Gallego M, Portus M, Gascon J. 2011.

Chagas Disease among the Latin American Adult Population Attending in a Primary Care Center in Barcelona, Spain.

PLoS Neglected Tropical Diseases 5 (4), e1135.

Sicuri E, Muñoz J, Pinazo MJ, Posada E, Sanchez J, Alonso PL, Gascon J. 2011.

Economic evaluation of Chagas disease screening of pregnant Latin American women and of their infants in a non endemic area.

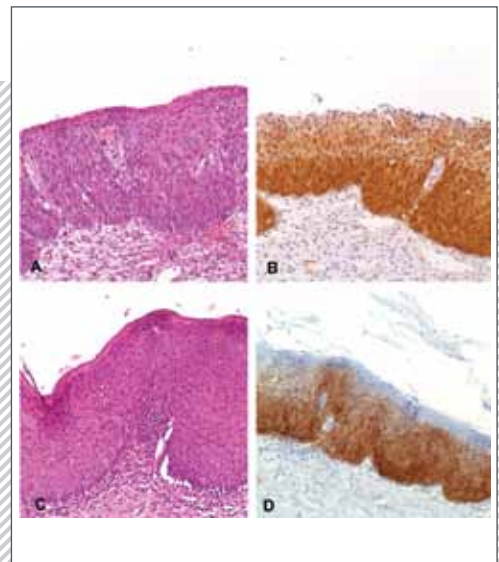
Acta Tropica 118 (2), 110-117.

Spain is being investigated through the capture and molecular study of its vector, *P. sergenti*.

In a collaborative study with the Public Health Agency of Barcelona, the epidemiology and trends of imported malaria in patients <20 years old in Barcelona are described. The majority of malaria cases in this population occurred in immigrants travelling to Africa for visiting family and relatives (VFR). *Plasmodium falciparum* was the most frequently detected malaria parasite. Awareness of malaria, especially among children of immigrants who travel to their parent's home country for VFR is recommended. Better access to pre-travel advice should be provided.

Epidemiological studies have shown that some strains of dengue might be associated with increased severity and higher transmission rates than others. In this context, surveillance and identification of the appearance or introduction of more virulent strains, along with fluctuation of DENV among endemic areas, are now considered essential public health activities. The European collaborative study demonstrates the importance of routine application of molecular epidemiology analyses in dengue diagnosis laboratories. African strains characterized in this study have provided valuable data on dengue virus circulation worldwide. ♦

HIV/AIDS and Sexually Transmitted Infections (STI's)



Programme Leader

Denise Naniche

Researchers working in the programme

Clara Menendez, Jaume Ordi, Robert Pool, Tomas Pumarola, Raquel Gonzalez, Emili Letang, Cinta Moraleda, Celia Serna, Ágata Sánchez, Mercè Bosch

MAIN LINES OF RESEARCH IN 2011

- Strategies to prevent mother-to-child transmission of HIV and to assess the impact of maternal HIV infection on infant health
- Evaluation of the impact of highly active antiretroviral therapy (HAART) on morbidity, mortality and interactions with co-infections
- Pathogenesis of acute and early HIV infection
- Community epidemiology and feasibility studies in Mozambique to inform future HIV vaccine and microbicide trials and studies on the safety and effectiveness of HPV vaccines
- Pathology of human papilloma virus and cervical cancer

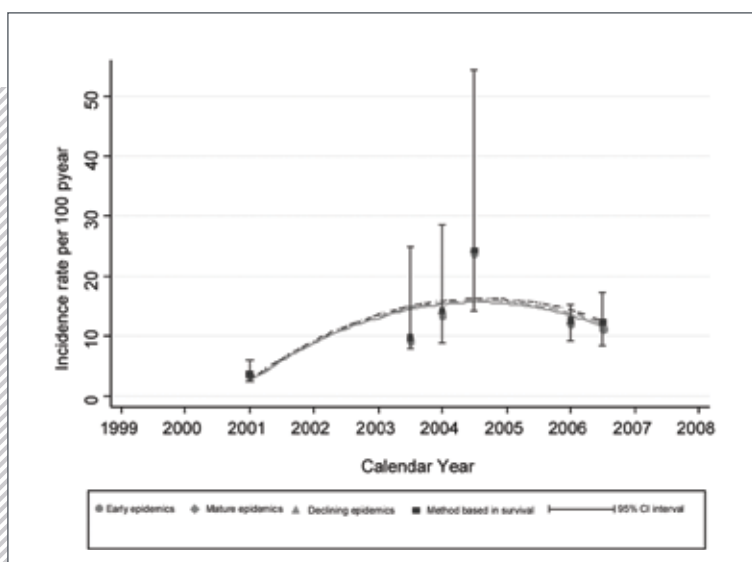
MAIN RESULTS OF 2011

The results of the HIV/AIDS and Sexually Transmitted Infections research programme exemplify the transversal nature of CRESIB's research, especially in terms of epidemiology, the impact of maternal HIV infection on infant health, immunology, clinical science, molecular biology and anthropology.

A study conducted in an antenatal clinic in Manhica, Mozambique assessed the temporal trend in HIV incidence in women of reproductive age using prevalence data collected between 1999 and 2008. The findings indicate that the prevalence of HIV infection among women of reproductive age in Manhica has increased significantly in less than 10 years. HIV prevalence in this population rose from 12% in 1999 to 36% in 2005. This was accompanied by a significant increase in HIV incidence from 1999 to 2005, and then a plateau from 2005 onwards, despite a steadily increasing prevalence. These trends reflect the critical situation of the HIV epidemic in southern Africa and the need for increased and innovative HIV prevention strategies.

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 to HIV-positive women and those born to HIV-negative women.

In order to inform HIV prevention trials, in the context of the African European HIV Vaccine Development Network (Afrevacc) and the Microbicide Development Programme (MDP), feasibility studies for HIV vaccine trials and microbicide trials have been completed. The fieldwork to assess the feasibility of an HIV vaccine trial in the Manhica community was completed and results will give insight into strategies to ensure good participant practice in future HIV vaccine clinical trials. In addition, the CRESIB Medical Anthropology group



PHOTO

Left: A and B: Human papillomavirus 16-positive high-grade cervical intraepithelial lesion (CIN3). A) Hematoxylin and eosin staining, B) p16 immunostaining; C and D: HPV-negative high-grade cervical intraepithelial lesion (CIN2). C) Hematoxylin and eosin staining, D) p16 immunostaining.

Right: Trend in HIV estimated incidence rates in women of reproductive age in Manhica, Mozambique. Incidence is estimated from point prevalence estimates and calculations under three scenarios of AIDS mortality (early, mature or declining epidemic). A second method estimates incidence from prevalence using a Weibull distribution of survival from seroconversion (From Perez-Hoyos et al, 2011).

has completed an analysis of the acceptability of microbicides as an HIV prevention tool. Integrating social science into clinical trials can be productive in spite of epistemological and methodological tensions between the social and biomedical sciences. Well-funded, integrated social science may provide more meaningful results to Randomized Clinical Trials (particularly where the result is flat or “negative”) since social science can illuminate the interplay of continuous, uncontrolled and otherwise unmeasured variables potentially determining biological and behavioural endpoints.

The pathogenesis of acute and recent HIV infection is being investigated at CRESIB. In 2011, fieldwork was completed for studies assessing early infection and viral load setpoint within the first year of infection. These data are currently under analysis.

With regard to the implementation of clinical management strategies for decreasing early morbidity and mortality associated with antiretroviral therapy, 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 Manhica, Mozambique revealed a prevalence of 26.5% in patients initiating HAART at the Manhica district hospital. Median time to IRIS onset was two months from ART initiation, and almost half of the IRIS patients developed systemic opportunistic infections (predominantly tuberculosis and Kaposi sarcoma). The remaining IRIS patients presented with mucocutaneous forms of IRIS.

HIGHLIGHTED PUBLICATIONS



Letang E, Miro JM, Nhampossa T, Ayala E, Gascon J, Menendez C, Alonso PL, Naniche D. 2011.

Incidence and predictors of immune reconstitution inflammatory syndrome in a rural area of Mozambique.

PLoS One 6 (2), e16946.

Perez-Hoyos S, Naniche D, Macete E, Aponte J, Sacarlal J, Sigauque B, Bardaji A, Moraleda C, de Deus N, Alonso P, Menendez C. 2011.

Stabilization of HIV incidence in women of reproductive age in southern Mozambique.

HIV Medicine 12, 500-505.

Del Pino M, Rodriguez-Carunchio L, Alonso I, Torne A, Rodriguez A, Fuste P, Castillo P, Nonell R, Abu-Lhiga N, Ordi J. 2011.

Clinical, colposcopic and pathological characteristics of cervical and vaginal high-grade lesions negative for HPV by Hybrid Capture 2.

Gynecologic Oncology 122 (3), 515-20.

Risk factors for IRIS were a low baseline CD4 (<50 cells/mm³) count and low body mass index (<18.5).

CRESIB studies of human papilloma virus (HPV) investigated the relationship between HPV, cancer of the vulva and cervical lesions. HPV-positive and negative tumours of the vulva showed no differences in prognosis. However, we identified high grade cervical intraepithelial lesions which were negative for the current gold-standard technique for HPV detection (Hybrid Capture 2 -HC2). Our results confirmed that the proportion of HC2 false-negative high-grade cervical intraepithelial lesions is very small (approximately 3.1%). Older women and patients with small lesions had a higher rate of HC2 negative results. We also described that triaging Pap negative/HPV positive screening test results with p16/Ki-67 dual-stained cytology could identify women with a high probability of underlying CIN2+ and may efficiently complement HPV-based screening programmes to prevent cervical cancer. ♦

Viral and Bacterial Infections



Programme Leader
Jordi Vila

Researchers working in the programme

Pedro L. Alonso, Joaquim Gascón, Tomas Pumarola, Antoni Trilla, Miriam Álvarez, Quique Bassat, José Muñoz, Ignasi Roca, Joaquim Ruiz, Sara Soto, Anna Vilella, Julià González, Francesc Marco, M^a Ángeles Marco, Anna Fàbrega, Mikel Martínez, Cristina Pitart, Griselda Tudó, Oscar Fraile, Andrés Anton, Clara Ballesté, Patricia de Molina, Núria Diez, Paula Andrea Espinal, Elisabet Guiral, Yuly López, Cristina O'Callaghan, Maria Jesús Pons, Emma Rey, Mar Solé, Xavier Vila, Rachid Ben Messaoud, Tacilta Nhamposa, Laura Muñoz

MAIN LINES OF RESEARCH IN 2011

- Knowledge of the emergence and dissemination of 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
- Identification and characterization of new biomarkers to diagnose infectious diseases such as pneumonia
- Investigation of the aetiology and prevalence of gastroenteritis in children in developing countries
- Investigation of early and late neonatal sepsis and the pathogenesis of neonatal sepsis caused by *Escherichia coli*
- Improvement of clinical quality and safety in hospitals in developing countries
- Definition of clinical aspects of yaws

MAIN RESULTS OF 2011

The main findings of the research conducted over the last year pertain to antimicrobial resistance. Travellers' diarrhoea is a major public health problem. From patients in whom diarrhoea developed after travel to India, five enteroaggregative *Escherichia coli* strains carrying β -lactamase CTX-M-15 were identified; three belonged to clonal complex sequence type 38. This β -lactamase contributes to the multidrug resistance of enteroaggregative *E. coli*, thereby limiting therapeutic alternatives. This study showed: dissemination of an extended-spectrum β -lactamase (CTX-M-15) enteroaggregative *E. coli* (EAEC) clone in India; the spread of this clone to Catalonia transferred by a traveller to India, this clone shows multiresistance which limits the therapeutic options to treat infections caused by this microorganism; and in some CTX-M-15 producing EAEC strains the gene encoding the CTX-M-15 was located in a conjugative plasmid which can favor the dissemination of this gene. Another study characterized an *E. coli* strain carrying the carbapenemase NDM-1 isolated from a traveller to India. The strain showed multidrug resistance and was only susceptible to tigecycline and colistin. In addition, the first outbreak of a plasmid-mediated carbapenem hydrolyzing OXA-48 β -lactamase in *Klebsiella pneumoniae* in Spain has been studied, showing that the primary case was a patient coming from Morocco. These studies highlight the potential spread of multidrug resistant bacteria by travellers to developing countries.



PHOTO

Testing for serological markers of yaws infection at Lihir Island, Papua New Guinea.

A global resurgence of yaws in developing countries highlights the need for reliable diagnostic criteria for this neglected infection. A clinical and serologic survey of 233 children less than 15 years of age who had clinically suspected yaws was conducted. A total of 138 (59%) cases were confirmed serologically, and 10 of 12 primary stage cases showed positive results for *Treponema pallidum* using a polymerase chain reaction assay that has not yet been validated for identification of yaws. A high proportion of cases (46%) were in the secondary stage; 92% of them had osteoarticular involvement, and only 24% had a Venereal Disease Research Laboratory titer greater than 1:32. In addition, it was shown that osteoperiostitis occurred some weeks after the primary infection, and the most common finding was hypertrophic periostitis of long bones. All treated patients had excellent responses to benzyl-penicillin therapy. Moreover, to estimate failure rates after treatment with benzathine penicillin and to identify determinants of failure that affected outcomes for yaws, a cohort study of 138 patients was carried out; treatment failed in 24 (17.4%). Having low initial titers on Venereal Disease Research Laboratory test and living in a village where yaws baseline incidence was high were associated with increased likelihood of treatment failure.

Several studies related to gastroenteritis in Peruvian children have been performed, such as analysis of the phylogenetic relationships of Shiga toxin-producing *Escherichia coli* (STEC), and norovirus

HIGHLIGHTED PUBLICATIONS



Mitjà O, Hays R, Ipaí A, Wau B, Bassat Q. 2011. **Osteoperiostitis in early yaws: case series and literature review.**

Clinical Infectious Diseases 52 (6), 771-774.

Sole M, Pitart C, Roca I, Fàbrega A, Salvador P, Muñoz L, Oliveira I, Gascón J, Marco F, Vila J. 2011.

First description of an *Escherichia coli* strain producing NDM-1 carbapenemase in Spain.

Antimicrobial Agents and Chemotherapy 55 (9), 4402-2.

Guiral E, Méndez-Arancibia E, Soto SM, Salvador P, Fàbrega A, Gascón J, Vila J. 2011.

CTX-M-15-producing Enteroaggregative *Escherichia coli* as Cause of Travelers' Diarrhea.

Emerging Infectious Diseases 17 (10), 1950-1953

prevalence in "pathogen negative" gastroenteritis in children from periurban areas in Lima, Peru. A quantitative Real-Time polymerase chain reaction was established to detect for enteropathogenic *Escherichia coli*: as a tool for investigation of asymptomatic versus symptomatic infections. ◆

Biostatistics Unit



Platform Leader
Sergi Sanz

Personnel working at the platform

Llorenç Quinto, Elisa de Lazzari, Susana Méndez, Elena Rodríguez (Since June 2011)

PLATFORM ACTIVITIES AND OBJECTIVES

The Biostatistics Unit is a platform for scientific research that helps CRESIB in statistical questions and to maintain statistical rigor in its work. The Biostatistics Unit is well established, and has existed for over 10 years. Its main objectives are to support all statistical aspects of research studies and to provide training in statistical methods. This unit supports the drafting of the statistics portion of research protocols and requests for scientific studies. It also participates in drafting plans for data analysis and data cleansing, data management, statistical analysis and writing journal articles.

The Biostatistics Unit's principal function is to participate in the statistical analysis for all CRESIB studies. This participation may be given directly through data analysis or in collaboration time advising researchers on how to resolve their statistical questions. As part of this function, the Unit aims to provide the most novel resources and analyses, and keeps abreast of new statistical techniques that are being used worldwide.

The Biostatistics Unit has specialized in STATA statistical software and aims to become a reference point in this area, although other platforms for statistical analysis are evaluated and used accordingly. ♦

MAIN ACTIVITIES AND RESULTS OF 2011

- Participated in 24 drafts of scientific articles
- Formed part of the organizing committee of the National Stata Congress in Spain, a national meeting where high-impact work is presented
- Conduct a Stata course on-line and on-site in Manhiça, Mozambique
- Conduct a virtual edition of Stata courses for CRESIB's personnel

International Research Collaborations



Platform Leader
Marga Sala

Personnel working at the platform

Carles Alemany, Carole Amroune, Pascal Andignac, Fernando Andrés, Pau Balcells, Pau Carreras, Marina Espriu, Elena Esteban, Solenne Garnier, Carla Garrido, Meritxell Graupera, Francesc Guil, Alicia Llamas, Eva López, Sam Mardell, Esperanza Marín, Anna Massaneda, M^a José Merino, Sira Rodrigo, Esther Roset, Noelia Sánchez, Mónica Solanes, Jordi Vilalta

PLATFORM ACTIVITIES AND OBJECTIVES

The International Cooperation Office (OCI) provides support for the administrative and financial management of International Health grants, projects and international collaborations among the organizations associated with the Hospital Clínic 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 for proposals, contracts, budgeting) as well as grants and project management (follow-up, reporting, auditing, etc.).

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, administrative and financial performance of the Research Platforms in Mozambique (Manhiça Health Research Centre, CISM), Morocco and Bolivia
- Capacity building on project management for international partners in developing 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. ♦

MAIN ACTIVITIES AND RESULTS OF 2011

In addition to the daily management of 162 grants, amounting to a multi-year budget of 66 million €, with partners in 40 countries, the OCI contributed in 2011 to the following achievements:

- Global health projects received 42 new grants, amounting to 6.327.186 €, mainly coming from research donors and official development aid
- Support to the ISGlobal administration, finance and grants management
- Successful change of management software (from A3 to SAP)
- Start of the implementation of standard operational procedures in order to improve the processes related to purchases, travel expenses, staff holidays and leaves

Strategic Partnerships



PHOTO

Antenatal session at the Manhica Health Centre, Mozambique.

MOZAMBIQUE

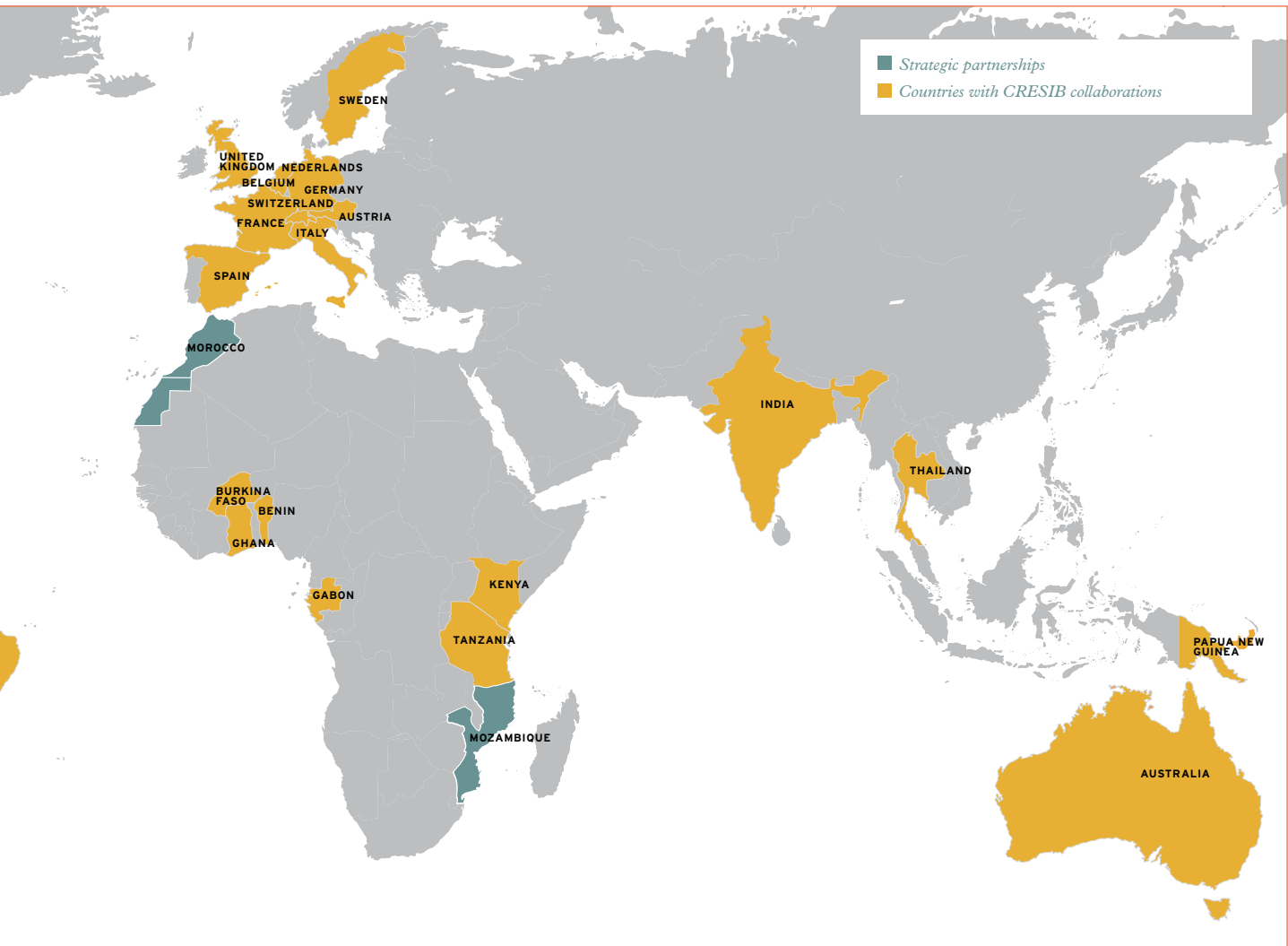
The Manhica Health Research Centre (CISM, www.manhica.org) is a non-profit Mozambican organization that fosters and conducts biomedical research in priority areas to promote and safeguard the health of the population. In recent years, the Centre has developed a comprehensive research agenda, trained researchers and technical personnel, and supported the provision of health care in Manhica District. Today, the CISM is one of the leading research centres in sub-Saharan Africa, contributing to better health at national, regional and global levels.

CRESIB has played a relevant role in the establishment, development and sustainability of CISM. In 1996, the Hospital Clínic of Barcelona established CISM under the leadership of Prof. Pedro L. Alonso. Since its creation, the Centre has developed with full support from Hospital Clínic and, since 2006,



from CRESIB, which has provided scientific leadership, administrative management and capacity building. CRESIB support to strengthen CISM’s institutional capacities resulted in the creation of the Manhica Foundation in 2008, which is currently responsible for the scientific and administrative management of CISM. CRESIB continues to have a long-term commitment to CISM’s development through research collaboration, capacity building and administrative support.

The main research activities of the CISM during 2011 included the publication of the results of the RTS,S malaria vaccine candidate Phase III trial, the start of the Phase II TB vaccine trial and the start of a study on the efficacy of anti-malarial drugs. The recruitment of pregnant women for the study on new drugs for malaria in pregnancy prevention has reached 95%, and the first protocols outside the Manhica district (Sofala, Dondo, Tete, Chowke,



Montepuez) have already begun. In addition, CISM has contributed to the follow-up of the introduction of the HiB vaccine over the past two years, and also has assisted the Ministry of Health to be eligible for GAVI support for the introduction of the *Pneumococcus* vaccine countrywide.

CISM hosted the XI INDEPTH Network conference, and promoted the creation of the first Health Bioethics Institutional Committee in Mozambique. Finally, the creation of the “Manhiça Senior Research Fellowship” aims to contribute to talent retention in Mozambique in the field of health and biomedical research.

With regards to training, the main courses carried out during 2011 were Lab Good Clinical Practices and Demography and Data Management. The training fellows programme continues to support several PhD students.

In terms of infrastructure and equipment, the laboratory BSL-III (TB Lab) was finished and is already operational. Electric infrastructure was completely renewed; WI-FI access is available throughout the Centre. Clinical trials (Open Clinica), lab management and human resources management software were implemented. PDAs for demographic data collection were made available, and the refurbishment of peripheral health posts (Ilha Josina, Palmeira, Malavel) and of the administration store (225 m²) and offices were completed.

The Manhiça Foundation has organized four Executive Board and Board of Trustees meetings this year, consolidating its role of governance and leadership for CISM. Remarkable progress has been achieved in positioning the Manhiça Foundation as the leading national health research organization, increasing its presence in international scientific events and its competitiveness in international grants and projects awarded.

PHOTO

*Newborn at the
Maternity Ward of the
Spanish Hospital of
Tetuan, Morocco.*



© Susana Oforio

MOROCCO

CRESIB's maternal health care programme in Morocco, which started in 1999 (by Hospital Clínic of Barcelona prior to CRESIB's creation), has evolved into a broad portfolio of activities in maternal and child health in partnership with the Moroccan Ministry of Health, the University Hospital of Rabat and two leading hospitals. Current activities strengthen the national response to maternal and perinatal morbidity and mortality reduction. Key elements of this partnership are a joint research platform in maternal and perinatal health and a training programme for health professionals and researchers in epidemiology and maternal health.

During 2011 research activities in maternal and child health continued to be implemented in the joint research lab at the Children's Hospital of the University Hospital of Rabat. More specifically, one protocol on aetiology of severe pneumonias and one on etiology of diarrheal diseases in children under five years of age finished their recruitment phases. In addition, new research protocols were designed for meningitis and *Streptococcus*. The collaboration with the Ministry of Health resulted in the publication of the first National Report on

Maternal Deaths, a key tool to guide the Safe Motherhood national programme.

In terms of research capacity building, new equipment (genetic analyser 3500, 7500 Fast real-time system) and techniques (screening of the viral and atypical bacteria in nasopharyngeal aspirate and implementation of a real time PCR) have been introduced.

A Lab Quality Assurance Unit was created to start the process of accreditation under the ISO 15189 norm. The first activities were the creation of Standard Operating Procedures (SOPs) necessary to correctly manage all documentation, stocks, equipment, human resources and the research studies in progress. Working groups were established to implement and coordinate circuits, and an internal continuous training programme has been developed for all lab staff.

In medical training, the new Masters in Health Administration in the National Institute of Health Administration integrated epidemiology and biostatistics, and the academic staff participated in the second edition of the modular course on Training for Trainers. A new initiative using e-learning

technologies and methodology has been piloted for the Diploma in Early Detection of Cervical Cancer, in collaboration with the Ministry of Health, the Association Lalla Salma de Lutte Contre le Cancer and the University of Fez.

In maternal and new-born care, a perinatology network has been created between the Children's Hospital and the Maternité des Orangers of Rabat to strengthen coordination between both hospitals and to improve new-born care. The high-risk pregnancy consultation is fully operational in the Maternité des Orangers. Finally, the Maternity Ward of the Spanish Hospital of Tetuan finished its health care activities in December 2011.

BOLIVIA

CRESIB's work on Chagas disease with the immigrant population in Spain evolved into a partnership with a number of institutions in Bolivia, including the Universidad Mayor de San Simón de Cochabamba, the Viedma Hospital, CEADES (a local NGO) and the Bolivian Ministry of Health. In addition to health care and training activities, CRESIB's work with the Bolivian partners also includes research undertaken to gain a better understanding of the epidemiology, clinical presentation and immunology of Chagas disease and to develop new diagnostic tools and treatments. In collaboration with the Drugs for Neglected Diseases initiative (DNDi), CRESIB is currently conducting a clinical trial of a drug to treat Chagas disease. The centre has also promoted the creation of the Latin-American network NEPACHA, an organization whose aim is to accelerate the development of new diagnostic tools and treatments for Chagas disease.

During 2011, health care activities for Chagas patients were expanded to rural areas of the Cochabamba (Sacaba) and Chuquisaca Regions. The strategy of developing a Chagas Disease Platform in Bolivia combining health care, research and training is progressively integrating other key actors in additional areas of the country with high prevalence

rates, and is consolidating its first progresses. Data bases, clinical practice guidelines and lab quality controls have been implemented in all structures and with teams participating in the Chagas Disease Platform.

Regarding research, several studies are in progress, such as the clinical trial of a drug candidate (E-1224) for the treatment of Chagas disease in collaboration with DNDi, entomological surveillance,



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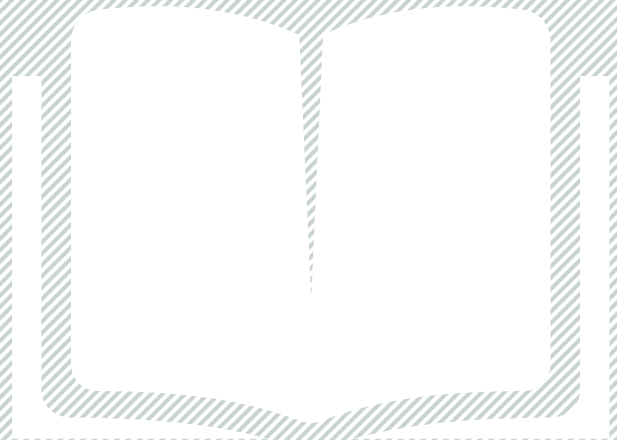
and in November 2011 a new study about biological markers (BNP) began the patient recruitment phase. Research capacity building has included the equipping of research labs, several exchange visits between Bolivia and Barcelona professionals, and the participation in scientific events in Barcelona, Buenos Aires, and Bogotá.

In training, a continued education programme for Chagas disease in Cochabamba and Barcelona has been implemented, including topics such as: echocardiography, electrocardiography, integral clinical care for Chagas patients, lab diagnostics for Chagas patients, clinical case discussions, among others. In addition, CRESIB supported CEADES in its community oriented activities that include Chagas prevention in schools and at social events. ♦

PHOTO

Chagas Disease Platform in Bolivia.

Education and Training



Part of CRESIB's mission and one of its key priorities is to be a reference and a facilitator in education and training in International Health. To this end, CRESIB is continuously developing a programme 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 programmes, as well as others in collaboration with several 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 programmes
- 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

CRESIB is a partner and executive board member of the European Academic Global Health Alliance (EAGHA, www.eagha.org), of the TropEd network of education and training in International Health (www.troped.org), and of the Eurolife International Health Alliance (EIHA).

CRESIB's current training programmes in International Health are listed below.

POSTGRADUATE EDUCATION

In 2011, CRESIB has been involved in teaching various subjects in the following Masters courses:

- **Official Master in International Health** - University of Barcelona and Autonomous University of Barcelona (2011-2012 academic year)
- **Official Master in Public Health** - Pompeu Fabra University and Autonomous University of Barcelona (2010-2011 academic year)
- **Official Master in Internationalization** - University of Barcelona (2010-2011 academic year)

With regards to doctoral programmes, CRESIB is involved in the Doctoral Programme of Medicine of the Faculty of Medicine at the University of Barcelona, which has a mark of excellence from the National Agency for Quality Assessment and Accreditation.

DOCTORAL THESES READ IN 2011

Role of VP30 phosphorylation in the Ebolavirus replication cycle

Mikel Martínez Yoldi

Faculty of Medicine, University of Barcelona
4th March 2011

Directors: Dr. Viktor Volkov and Dr. Jordi Vila Estapé



Effectiveness of long lasting insecticidal nets in the prevention of Kala-azar

Albert Picado

Faculty of Medicine, University of Barcelona
20th May 2011

Director: Dr. Pedro L. Alonso

Immune responses to *Plasmodium falciparum* in Mozambican infants receiving Intermittent Preventive Treatment with Sufadoxine-Pyrimethamine

Diana Iris Silveira Quelhas

Faculty of Medicine, University of Barcelona
29th June 2011

Directors: Dra. C. Dobaño and Dra. C. Menéndez

Characterization of immune reconstitution inflammatory syndrome (IRIS) and Kaposi's sarcoma-associated IRIS after initiation of antiretroviral treatment in sub-Saharan Africa

Emili Letang Jiménez-de- Anta

Faculty of Medicine, University of Barcelona
5th July 2011

Directors: Dra. Denise Naniche and Dr. Pedro L. Alonso

Evaluation of tools to prevent malaria during the first years of life

John Aponte Varón

Faculty of Medicine, University of Barcelona
6th September 2011

Director: Dr. Pedro L. Alonso

Malària durant l'embaràs: immunitat materna i expressió de gens implicats en la citoadhesió de *Plasmodium falciparum*

Eduard Rovira Vallbona

Faculty of Medicine, University of Barcelona
8th September 2011

Director: Dr. Alfredo Mayor

Exposure to organochlorine compounds at the early stages of DDT use for indoor residual spraying in domestic environments in Manhica, Mozambique

M. Nelia Manaca

University Pompeu Fabra
27th September 2011

Directors: Dra. C. Dobaño and Dr. Joan O. Grimalt

Safety, immunogenicity and duration of protection of a candidate malaria vaccine in Mozambique.

Pedro Aide

Faculty of Medicine, University of Barcelona
30th September 2011

Director: Dr. Pedro L. Alonso

Epidemiologia de les infeccions respiratòries víriques en pacients pediàtrics a Manhica, una zona rural de Moçambic.

Cristina O'Callaghan Gordo

Faculty of Medicine, University of Barcelona
20th December 2011

Director: Dra. Anna Roca

Resistencia antibiótica asociada a integrones de clase I en aislados humanos de enterobacterias de dos contextos epidemiológicos: zoonosis por *Salmonella enterica* e infecciones por *Klebsiella pneumoniae* adquirida en un centro sociosanitario

Mar Olga Pérez Moreno

Faculty of Medicine, University of Barcelona
21th December 2011

Director: Dr. Joaquim Ruiz

The use of biomarkers for the diagnosis of severe infections in rural Africa

Núria Díez Padrís

Faculty of Medicine, University of Barcelona
22th December 2011

Director: Dra. Anna Roca



PHOTO

CRESIB course at the Faculty of Medicine of the University of Barcelona.

TRAINING FELLOWS PROGRAMME

Training Fellows programme in collaboration with the **Manhiça Health Research Centre (CISM Mozambique)**, is aimed at Mozambican graduates and is intended to train researchers to enable them to follow Masters and doctorate courses, mainly at universities in Catalonia. Over thirty people have already passed through the programme, and all of them have rejoined African health centres.

Training Fellows programme in **Morocco**; at present, two Moroccan graduates have completed their Masters (at the University of Barcelona and the Pompeu Fabra University) and have started the PhD programme at the University of Barcelona.

Training Fellows programme in **Papua New Guinea**; at present, one graduate student from this country started his PhD 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 programme 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 Programme 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

CRESIB seminars

19/01/2011

Raquel González. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).
High HIV prevalence in a semi-rural area of southern Mozambique: population-based data compared with antenatal clinic prevalence estimations

25/01/2011

Dr. María Paula Mourão. Fundação de Medicina Tropical Dr. Heitor Vieira Dourado - Manaus (Brasil).
Arbovirosis y Malaria vivax en la Amazonia Brasileña

16/02/2011

Dr. Sara Soto. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).
Virulencia y resistencia en aislamientos clínicos de *Escherichia coli* extraintestinal

02/03/2011

Prof. Sanjeev Krishna. St. George's Hospital Medical School, University of London, London (UK).
Monkeying around with malaria

16/03/2011

Dr. Ignasi Roca. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).
Resistencia asociada a bombas de expulsión activa en *Acinetobacter baumannii*

21/03/2011

Dr. Anja Scholzen. Radboud University Nijmegen Medical Center, Nijmegen (The Netherlands).
How Malaria Modulates Memory

23/03/2011

Dr. Agustí Pérez-Foguet. Grup de Recerca en Cooperació i Desenvolupament Humà (GRECDH), Universitat Politècnica de Catalunya (UPC), Barcelona (Spain).
Impacto de una adecuada provisión de los servicios de Agua y Saneamiento sobre la población beneficiaria. Experiencias en África y América Latina

30/03/2011

Prof. Didier Pittet. Infection Control Programme and World Health Organization (WHO) Collaborating Centre on Patient Safety, University of Geneva Hospitals and Faculty of Medicine, Geneva (Switzerland). First Global Patient Safety Challenge, WHO Patient Safety, WHO Headquarters, Geneva (Switzerland).
Engaging Nations in a Commitment to Patient Safety

06/04/2011

Dr. Maria Montoya. Centre de Recerca en Sanitat Animal (CRESA), Bellaterra, Barcelona (Spain).
Lecciones aprendidas del virus de la gripe porcina y del virus pandémico H1N1 (2009) en infecciones animales

11/05/2011

Dr. Michael Gaunt. London School of Hygiene and Tropical Medicine, London (UK).
The genetic diversity of *Trypanosoma cruzi*, TC1

16/05/2011

Dr. Núria Casamitjana. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).

Programa de doctorado en medicina: Salud Internacional. Nuevos procedimientos

08/06/2011

Dr. Maria Roura. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).

Scaling up stigma? The Effect of Antiretroviral provision on stigma and Voluntary Counseling and Testing uptake

15/06/2011

Sandra Bestraten. Profesora de la ET Superior de Arquitectura de Barcelona. Cátedra UNESCO de Sostenibilidad (Spain).

La prevención del mal de chagas, arquitectura y salud

22/06/2011

Dr. Harald Noedl. Medical University of Vienna, Vienna (Austria).

Malaria control in the time of artemisinin resistance

06/07/2011

Dr. Quim Ruiz. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).

Diarrea Infantil en zonas periurbanas de Lima: Etiología, Caracterización Microbiológica y Aspectos Sociales

19/07/2011

Dr. Carlos Castillo-Salgado. Special Adviser to the American Public Health Forum at the Panamerican Health Organization (PAHO/WHO), seconded to the Bloomberg School of Public Health (JHSPH). Associate Adjunct Professor in the Epidemiology Department and Associate in the Health Policy and Administration Department of the Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore (USA).

Cambios y Tendencias en la Vigilancia de la Salud Pública Global

07/09/2011

Prof. Steve Meshnick. Professor of Epidemiology at the University of North Carolina Gillings School of Global Public Health, North Carolina, (USA).

A longitudinal ultrasound study of malaria-exposed pregnant women in Kinshasa

09/09/2011

Dra. Mònica Arman. Centre for Cardiovascular Sciences, University of Birmingham (UK). Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin (Ireland).

Agregación entre plaquetas y eritrocitos infectados por *Plasmodium falciparum*: en busca de los mecanismos moleculares implicados

14/09/2011

Rony Brauman. Founder and President of Médicins Sans Frontières (1982-1994), Associate Professor at the Institut d'Études Politiques, Paris (France).

La Medicina Humanitaria

21/09/2011

Dr. Alfredo Mayor. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).

Reduction of Antimalarial Antibodies by HIV Infection is Associated with Increased Risk of *Plasmodium falciparum* Cord Blood Infection

19/10/2011

Dr. Lorena Martin. Centre de Recerca en Salut Internacional de Barcelona (CRESIB, Hospital Clínic - Universitat de Barcelona), Barcelona (Spain).

Exosomes from *Plasmodium yoelii*-infected reticulocytes protect mice from lethal infection

3/11/2011

Prof. Artur Scherf. Directeur de Recherche au CNRS Institut Pasteur, Paris (France).

A Critical Role of Perinuclear Filamentous Actin in Spatial Repositioning and Mutually Exclusive Expression of Virulence Genes in Malaria Parasites



9/11/2011

Dr. Laura Lechuga. Nanobiosensors and Bioanalytical Applications Group, Research Center on Nanoscience and Nanotechnology (CIN2) CSIC and CIBERDBBN, Barcelona (Spain).

Advanced Nanobiosensor platforms for point-of-care diagnostics

16/11/2011

Dr. Michel Garenne. Epidemiology of Emerging Diseases, Institut Pasteur, Paris (France).

Assessing Maternal Mortality in the context of severe HIV/AIDS epidemics: examples from South-Africa

23/11/2011

Dr. EJ Remarque. Department of Parasitology, Biomedical Primate Research centre, Rijswijk (The Netherlands).

Apical Membrane Antigen 1, A Polymorphic Vaccine Candidate: Can Antibody Responses to Common Epitopes Protect?

Workshops, working sessions and conferences organized by CRESIB

7th March 2011

VII Workshop on Imported Chagas Disease: New tools for the diagnostic and management of Chagas disease

Coordinator: Dr. Joaquim Gascón (CRESIB)

Venue: Residència d'Investigadors CSIC-Generalitat de Catalunya, Barcelona

9th and 10th March 2011

Migrant Health and Imported Diseases: meeting research challenges

Coorganizer: Centre Internacional per al Debat Científic (CIDC)

Venue: CosmoCaixa, Barcelona

7th June 2011

Workshop "Impact of the new geographic recommendations for yellow fever vaccination"

Coorganizer: Barcelona Institute for Global Health (ISGlobal)

Venue: ISGlobal, Barcelona

3rd to 6th October 2011 (see page 48 for further details)

7th European Congress on Tropical Medicine & International Health. Global change, migration and health

Coorganizer: Barcelona Institute for Global Health (ISGlobal), Federation of European Societies for Tropical Medicine and International Health (FESTMIH) and the Spanish Society of Tropical Medicine and International Health (SEMTSI).

Venue: Barcelona's International Convention Centre (CCIB), Barcelona

21st to 25th November 2011

Imported Diseases: from travel medicine to migrant's health

Coorganizer: Barcelona Institute for Global Health (ISGlobal), Hospital Clinic and University of Barcelona

Venue: Faculty of Medicine, University of Barcelona

PHOTO

Plenary Session 3 on The Science of Elimination at the 7th European Congress on Tropical Medicine & International Health at Barcelona.

CRESIB in the News



PLOS MEDICINE PUBLISHED A MONOGRAPHIC VOLUME HIGHLIGHTING THE OUTCOMES OF THE MALARIA ERADICATION RESEARCH AGENDA (malERA) INITIATIVE

In January 2011, the open access, general medical journal **PLoS Medicine** published a collection of 12 reviews comprised of three reflective pieces and nine research and development agendas, highlighting the outcomes of a series of consultations among more than 200 experts from 36 countries that were undertaken by the Malaria Eradication Research Agenda (malERA) initiative. The agenda identified research and development priorities for definitively interrupting transmission of the parasite that causes malaria.

The introductory article by Pedro L. Alonso and colleagues, “A Research Agenda to Underpin Malaria Eradication” set the malERA programme in context. The nine research and development agendas defined the priority research areas for eight different thematic areas including basic science and enabling technologies; drugs; vaccines; vector control; health systems and operational research; modeling; diagnoses and diagnostics; and monitoring, evaluation and surveillance. An additional paper identified research priorities that are common to several thematic areas. The collection included an analysis from Jose Najera (formerly of the WHO, Geneva) and colleagues from the last Global Malaria Eradication Program (1955-1969) and outlined lessons for future eradication programmes. A second analysis by Myron M. Levine (University of Maryland School of Medicine, Baltimore, USA) and colleagues examined the role research has played in eradication or elimination initiatives for smallpox, poliomyelitis, and measles and from this analysis derived nine cross-cutting lessons for malaria eradication.

Building on the publication of the malERA agenda in 2011, the Malaria Eradication Scientific Alliance (MESA) was launched in Barcelona in May 2012. The MESA Project aims to advance the science of malaria eradication, and is in its initial phase. The secretariat is based at ISGlobal Barcelona.



WORLD MALARIA DAY

For World Malaria Day, 25 April 2011, the director of CRESIB, Prof. Pedro L. Alonso, wrote an editorial for **El País**, Spain's most widely read newspaper.

Under the title "Advances towards Malaria Eradication," Prof. Alonso pointed out that the impetus for malaria control and the long-term goal of malaria eradication has been reestablished, and highlighted the Malaria Eradication Research Agenda (maERA) as an important step towards this goal. **El Mundo**, the second most popular newspaper in Spain, also referred to CRESIB and maERA in an article titled "Objective: eradicate malaria."

That same day, news radio programmes on **Cadena Ser** and **Com Ràdio** interviewed CRESIB speakers on different malaria issues, from general facts to the RTS,S vaccine.

7TH EUROPEAN CONGRESS OF TROPICAL MEDICINE AND INTERNATIONAL HEALTH

The 7th European Congress of Tropical Medicine and International Health (ECTMIH), which takes place every two years under the auspices of the Federation of European Societies for Tropical Medicine and International Health (FESTMIH), was organized by CRESIB and ISGlobal from October 3-6, 2011, in Barcelona.

The 7th edition of the congress was held at the International Convention Centre of Barcelona (CCIB) and brought together more than 1.600 specialists and 335 speakers from 80 different countries to discuss a wide range of topics related to tropical medicine and to analyse the challenges currently facing global health. The four-day event was highlighted by the main Spanish print and online media such as **La Vanguardia**, **Diario Médico**, **Diari Ara**, **La Región**, **Europapress**, among others.

FIRST RESULTS FROM THE ONGOING PHASE III TRIAL OF THE MALARIA VACCINE CANDIDATE RTS,S

The *New England Journal of Medicine* (NEJM) published the first results from the Phase III trial of RTS,S vaccine in October 2011. Results show that the malaria vaccine provides significant protection against clinical and severe malaria in African children.

The ongoing trial is being conducted at 11 trial sites in 7 countries across sub-Saharan Africa, and showed that 3 doses of RTS,S reduced the risk of children experiencing clinical malaria by 56% and severe malaria by 47%. These findings refer to the analysis of results from the first 6,000 children aged 5 to 17 months over a 12-month period following vaccination. The trial, which has enrolled over 15,000 African children, started in May 2009 and is expected to finish in 2014.

These Phase III results confirm the findings of research conducted over the last 10 years by a team led by Prof. Pedro L. Alonso, the Manhica Health Research Centre (CISM) in Mozambique, and the Barcelona Centre for International Health Research (CRESIB, Hospital Clínic and University of Barcelona).

The publication of the first results had a great media impact worldwide. Print media from the USA, France and Spain, such as *The Wall Street Journal*, *Les Echos*, *El País*, *El Mundo*, *La Vanguardia*, *Diario Médico*, *ABC*, *La Razón*, etc, highlighted the findings, and the news spread quickly over online media.





RTS,S MALARIA VACCINE SELECTED AS ONE OF THE TOP TEN MEDICAL BREAKTHROUGHS IN 2011

The choice of the RTS,S vaccine as one of the top scientific achievements of 2011 came after the October 2011 publication by **The New England Journal of Medicine** (NEJM) of the preliminary results of Phase III clinical trial with the vaccine candidate.

Time magazine was the first publication to announce its decision to include the malaria vaccine in its New Year list of medical breakthroughs. A few days later, the prestigious scientific journal **Science** also recognized the advance. The decision made by these two influential publications reflects the scientific community's recognition of a vaccine which, despite its moderate effectiveness, nonetheless represents an unprecedented breakthrough in the complex struggle against the parasite that causes over 650,000 deaths a year.



Publications



This list of publications includes papers from researchers who are affiliated with CRESIB since January 2010 and who belong to CRESIB's trustee institutions, regardless of the affiliation indicated by the authors of the paper.

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