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ISGlobal

Scientific Area

ANNUAL REPORT ISGLOBAL 2013

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UN 1170

Research

Antoni Plasència

Technical Director, CRESIB, ISGlobal Research Centre

In 2013, we have seen a substantial consolidation of ISGlobal research capabilities and outputs, which constitute the core of its mission. The total annual output has stabilized in recent years at around 160 papers, with malaria and viral and bacterial infections as the leading topics. Overall, one out of every three new projects submitted was approved and financed. At present, we have 177 active projects, amounting to a total budget of 17 million euro.

Competitive funding has increased overall and we have been successful in obtaining competitive research funds from a broader range of new public and private sources (accounting for 40% and 60%, respectively). According to a recent report,[1] for every euro provided by the Generalitat de Catalunya—CRESIB's main contributing Trustee—more than eight euros were obtained from external research funding sources, making CRESIB the most effective health research centre in Catalonia.

In 2013, CRESIB's first strategic cycle (2010-2013) was successfully completed and positively evaluated by its external Scientific Advisory Committee. Our translational activities have been strengthened with the creation of Innovex Therapeutics, a spin-off company oriented towards the creation of an exosome-based vaccine platform. At the same time, ISGlobal's position as a leading research centre in Global Health has been reinforced by its designation as a WHO Collaborating Centre for Malaria Control, Elimination and Eradication.

[1] Observatori del Sistema de Salut de Catalunya. Central de Resultats. Recerca en Ciències de la Salut. Dades 2012. Barcelona: Agència de Qualitat i Avaluació Sanitàries de Catalunya. Departament de Salut. Generalitat de Catalunya, 2014.

ISGlobal's research programme is carried out by CRESIB, an international health research centre that was founded some years before ISGlobal and that in 2013 was an independent entity. The scientific knowledge generated by CRESIB's research activity is enhanced through the work of ISGlobal's departments, creating a virtuous circle involving knowledge, action, and impact on health.

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Facts and Figures

WHO Collaborating Centre for Malaria Control, Elimination and Eradication

Articles & Reviews

157

% in First Quartile

67%

% in First Decile

33%

Normalized Impact 2007-11*

2.09

* Scimago Institutions Ranking 2013

Researchers

Innovation

Heparin-lipidic nanoparticle conjugates.

- Inventors: Fernàndez-Busquets, X., Marques, J., Moles, E.
- Institutions: IBEC, CRESIB
- Ref. number: EP13152187.4
- Priority countries: Europe
- Filing date: January 22, 2013

Main Active Research Projects

"A phase III study to evaluate, in infants and children, the efficacy of the RTS,S/AS01E candidate vaccine against malaria disease caused by *P. falciparum* infection, across malaria transmission settings in Africa"

PI: Pedro L. Alonso
Funding Institution: PATH/MVI
Funding: 9.6 M$
Calendar: 2009-2013

SYSMALVAC - "Identifying correlates of protection to accelerate vaccine trials: systems evaluation of two models of experimentally-induced immunity to malaria"

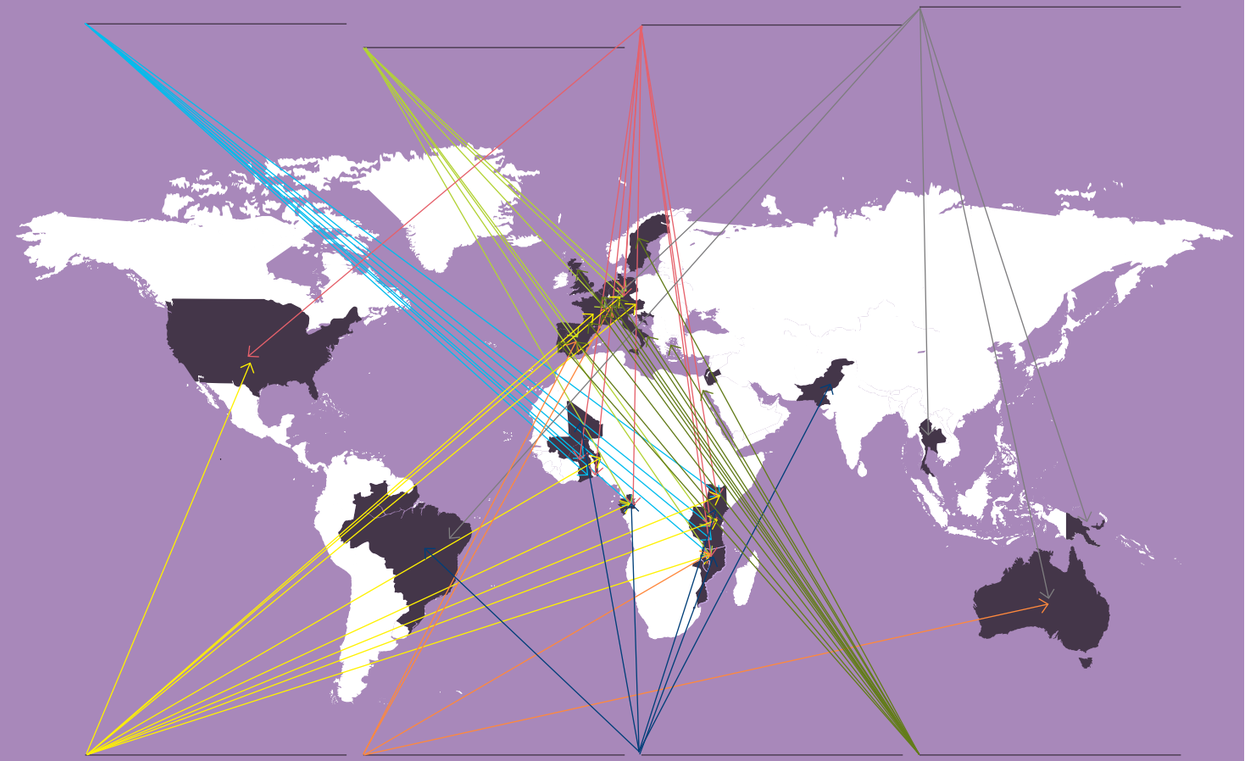
PI & Coordinator: Carlota Dobaño
Funding Institution: FP7 European Union
Funding: 2.8 M€
Calendar: 2013-2015

"Understanding RTS,S malaria vaccine-induced protection through integrated analysis of antibody, B Cell and T Cell immune responses"

PI & Coordinator: Carlota Dobaño
Funding Institution: NIH
Funding: 3 M$
Calendar: 2012–2017

TRANSEPI - "The Comparative Epidemiology of *P. falciparum* and *P. vivax* transmission in Brazil, Thailand and Papua New Guinea"

PI & coordinator: Ivo Mueller
Funding Institution: Bill & Melinda Gates Foundation
Funding: 3.5 M$
Calendar: 2012–2015



MiPPAD - "Evaluation of alternative antimalarial drugs to sulphadoxine-pyremethamine for intermittent preventive treatment in pregnancy (IPTp) in the context of insecticide treated nets"

PI & coordinator: Clara Menéndez
Funding Institutions: EDCTP, Malaria in Pregnancy Consortium (MiPc) and Fondo de Investigaciones Sanitarias (FIS)
Funding: 6.6 M€
Calendar: 2008-2013

GAMA - "Development of novel gastrointestinal biomarkers for use in HIV incidence determination in a sub-Saharan African setting "

PI and Coordinator: Denise Naniche
Funding Institution: Bill & Melinda Gates Foundation
Funding: 1 M$
Calendar: 2012–2016

CaDMIA – "Validation of the Minimally Invasive Autopsy (MIA) tool for cause of death investigation in developing countries"

PI and Coordinators: Quique Bassat, Clara Menéndez and Jaume Ordi
Funding Institution: Bill & Melinda Gates Foundation
Funding: 1.4 M$
Calendar: 2013-2015

COMBACTE - "Combatting Bacterial Resistance in Europe"

PI: Jordi Vila
Funding Institution: Innovative Medicines Initiative (IMI), European Union
Funding: 2.5 M€
Calendar: 2013–2020

Malaria

Despite being an entirely preventable and treatable disease, malaria is still a serious health burden in large areas of the world—particularly sub-Saharan Africa—and in two of the most vulnerable population groups: children and pregnant women. Thanks to new tools and an increase in the available resources, we have witnessed spectacular progress over the last decade. However, the evidence shows that as soon as efforts relax the situation once again deteriorates. This is why the only long-term, sustainable solution is the complete elimination of the parasite in a given territory. In ISGlobal, the Malaria Elimination Initiative is the lynchpin for efforts focused on the elimination of this parasitic disease.

Main Lines of Research

- Enabling technologies for malaria research
- Parasite biology
- Physiopathology
- Malaria immunology
- Diagnostics
- Evaluation of preventive and therapeutic tools
- Epidemiology and clinical presentation of *Plasmodium falciparum* and *Plasmodium vivax*
- Vector biology and control
- Novel approaches and strategies for malaria elimination

Main Results 2013

● We assessed the performance of six multiplex commercial kits in the quantification of cytokine and chemokine responses in culture supernatants from *P. falciparum* stimulations. Luminex-based kits with magnetic beads were found to have the best performance (Moncunill *et al*, PLoS One, 2013a).

● Heparin was found to bind with high specificity to *P. falciparum*-infected red blood cells versus non-infected red blood cells. This finding opens the way for the design of heparin-based nanotherapies for the targeted delivery of antimalarial drugs (Valle-Delgado *et al*, Nanoscale, 2013).

● We reported the first evidence of the presence of sugar nucleotides in the blood stages of *P. falciparum* and described the active metabolic routes involved in their biosynthesis. In addition, the de *novo* route of GDP-Fuc, a metabolite probably involved in the biosynthesis of novel fucosylated glycans not yet described in the malaria parasite, was characterised (Sanz *et al*, J Biol Chem, 2013).

● It was demonstrated that malaria parasites can become resistant to toxic compounds such as drugs as a result of epigenetic switches in the expression of genes necessary for the formation of solute channels (Mira-Martinez *et al*, Cell Microbiol, 2013).

● Antibody responses to *P. falciparum* in pregnant women were shown to be affected by variables that influence the risk of exposure to the parasite, such as parity, season and neighbourhood. HIV infection modifies these associations between exposure and antibody responses, probably through its impact on the maintenance of IgG responses (Mayor *et al*, JID, 2013).

● We found evidence of *P. falciparum* parasites expressing specific VAR2CSA variants that have the potential to reach a high parasitaemia in the placenta and eventually increase the risk of poor pregnancy outcomes. The motifs in VAR2CSA associated with high placental parasitaemia in the study may be of relevance to our understanding of the molecular mechanisms that mediate parasite sequestration to host tissues and to the development of new preventive tools against placental malaria (Rovira-Vallbona *et al*, PLoS One, 2013).

● Different antimalarial compounds were assessed in two studies. Artemether/lumefantrine (AL) was found to be an acceptable, interim option for young children in co-endemic areas where *P. vivax* is resistant to chloroquine. AL produces a rapid clinical response against both *P. falciparum* and *P. vivax* malaria. However, it is associated with a high rate of *P. vivax* recurrent clinical episodes, and should therefore ideally be complemented with a course of primaquine (Senn *et al*, CID, 2013). Furthermore, analyses of different dihydroartemisinin-piperaquine dosing schedules demonstrated the excellent efficacy of the formulation in a wide range of transmission settings. Treatment failure was associated with a lower dose of piperaquine, particularly in young children, suggesting that there is potential for further dose optimisation (WorldWide Antimalarial Resistance Network DP Study Group, PLoS Med, 2013).

Malaria Elimination Initiative

● Advances in the development of an *in vitro* culture system for *P. vivax* were reported (Fernandez-Becerra *et al*, Mem Inst Oswaldo Cruz, 2013; Martín-Jaular *et al*, Malar J, 2013).

● A novel computational approach was used to redefine the subtelomeric *vir* superfamily of *P. vivax*. This methodology, resource and new classification of *vir* genes will contribute to a new structural framing of this multigene family and other multigene families in malaria parasites (Lopez *et al*, BMC Genomics, 2013).

● In a study undertaken to describe clinically relevant cytoadhesive phenotypes of *P. vivax*, rosetting was shown to be a frequent cytoadhesive phenotype in *P. vivax* infections associated with an increased risk of anaemia. No specific cytoadhesion phenotypes associated with pregnancy were observed, although a *P. vivax* haplotype was more frequent among pregnant women than non-pregnant hosts, suggesting that other, as yet unknown, parasite phenotypes may increase the propagation of certain *P. vivax* clones observed in pregnant hosts (Marín-Menéndez *et al*, PLoS Negl Trop Dis, 2013).

● In areas where *P. vivax* and *P. falciparum* are co-endemic, immunity to *P. vivax* seems to be acquired more rapidly. The high number of *P. vivax* clones that infect children in early childhood was shown to be likely to contribute substantially to the rapid acquisition of immunity against clinical *P. vivax* malaria (Koepfli *et al*, PLoS Negl Trop Dis, 2013). In addition, in a cohort of Papua New Guinea children aged 1 to 3 years, the presence of antibodies to Merozoite Surface Protein 3α (PvMSP3α) Block II and Merozoite Surface Protein 9 (PvMSP9) N-terminus was shown to be associated with protection against clinical *P. vivax* malaria. This suggests that (PvMSP3α) Block II and

(PvMSP9) N-terminus should be further investigated for their potential as *P. vivax* vaccine antigens (Stanisic *et al*, PLoS Negl Trop Dis, 2013).

● Age- and exposure-dependent immune responses to *Plasmodium* infections may be the key to understanding the role that age and exposure play in the acquisition and maintenance of naturally acquired immunity to malaria. We evaluated immune responses (cytokines, chemokines and IgG levels against blood stage proteins) using flow cytometry and Luminex in plasma from Mozambican adults and children and European adults living in Spain who had visited Africa (travellers) or lived there for at least one year (migrants). Our findings indicate that age does not play an important role in the immune response to a first malaria episode. Migrants had a different cytokine/chemokine and antibody profile compared to immune adults, but also to naive adults. Upon cessation of malaria exposure, IgG responses to malaria-specific antigens were maintained to a large extent, although the conservation and magnitude of the recall response depended on the nature of the antigen. However, control of pro-inflammatory responses and tolerance to *P. falciparum* appeared to be reduced (Moncunill *et al*, PLoS One, 2013 b,c,d).

● The influence of temperature on the effectiveness and toxicity of chemical insecticides was established, providing information pertinent to the impact of vector control tools. In particular, data on the impact of temperature variations throughout the day led the authors to suggest that testing recommendations for new tools should include a broader range of temperatures so as to allow their deployment in different environments. (Glunt *et al*, PLoS Pathog, 2013). Daily fluctuations in habitat temperature were also studied in relation to vector fitness. It was shown that a cool mean temperature significantly increased larval development and survival, whereas warm temperatures reduced these processes. These findings are essential to understanding the distribution limits of vectors and their response to climate change (Paaijmans, Global Change Biology, 2013).

● Malaria epidemiology on Lihir Island, Papua New Guinea, was investigated. A substantial reduction in the prevalence and incidence of *P. falciparum* and *P. vivax* was found in villages adjacent to a mining area where an integrated malaria control intervention had been implemented. In other areas of the island, parasitaemia levels remained high. The observed reduction confirmed the positive impact of malaria interventions on transmission patterns (Mitjà *et al*, Malaria Journal, 2013).

● The economic burden of malaria in children under five years of age was estimated in three sub-Saharan African countries. Both direct and indirect costs were calculated. The findings may assist policy makers in the design and introduction of future malaria control interventions, help to guide the introduction of new prophylactic measures and improve the current strategies for malaria control (Sicuri *et al*, Malaria Journal, 2013).

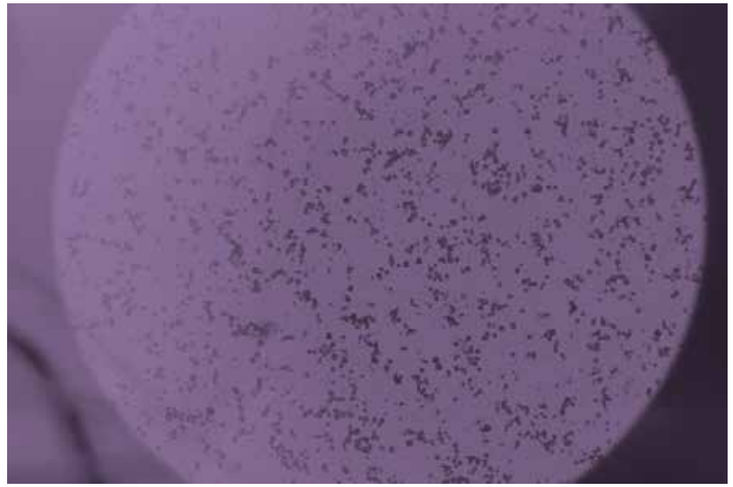
● Strategic thinking on the key challenges and prospects for malaria control and elimination highlighted the risks posed by insecticide and drug resistance, weak health systems and declining funding, while stressing the importance of further R&D to improve malaria control and progress towards elimination. The authors also emphasized the need to address both *P. falciparum* and *P. vivax* in any elimination campaign (Alonso and Tanner, Nat Med, 2013).

Chagas Disease

Because of the potential for transmission and chronic health complications, Chagas disease clearly affects the health of Latin American immigrants living in Spain, where the disease is not endemic, and the Spanish health system. Since 2002, we have been involved in research on this imported disease in Spain. In 2008, we launched an intervention strategy in Bolivia, the endemic country most affected by this neglected disease.

Main Lines of Research

- Epidemiology of Chagas disease in non-endemic areas
-Biomarkers for therapeutic efficacy in treated patients and early diagnosis of cardiac damage in patients with Chagas disease
-Clinical trials for new drugs to treat Chagas disease parasitologically
-Studies on the pharmacokinetics of benznidazole



Main Results 2013

● Migratory flows have facilitated the spread of Chagas disease into areas where it was previously unknown. Economic, social and cultural factors play a significant role in the presence and perpetuation of the disease. We undertook a systematic review to provide a comprehensive overview of the qualitative research on Chagas disease in both endemic and non-endemic countries. Most interventions do not address clinical, environmental, social and cultural aspects together. Therefore, an explicitly multidimensional approach, incorporating the experiences of people affected by Chagas disease, is a potential tool for the development of successful long-term programmes (Ventura-García *et al*, PLoS Negl Trop Dis, 2013).

● Following our work on biomarkers, we evaluated an ELISA test based on a mucin glycoprotein antigen from *Trypanosoma cruzi*. This technique, which allows the serological detection of lytic antibodies against the parasite, proved to be highly sensitive and specific. This assay can therefore be used to detect active *T. cruzi* infection and to monitor trypanosomicidal treatment (Izquierdo *et al*, Mem Inst Oswaldo Cruz, 2013).

● Immunosuppression, which has become an increasingly common clinical condition in recent years, modifies the natural history of *T. cruzi* infection in most patients with Chagas disease. Parasitaemia is the most important defining feature of reactivation. We analysed the relationship between Chagas disease and immunosuppressive conditions and provided recommendations for the management of these patients based on our experience and on the data in the literature (Pinazo *et al*, PloS Negl Trop Dis, 2013).

● Cure biomarkers are crucial in assessing the efficacy of antiparasitic drugs in clinical trials. The lack of a reliable method to for assessing whether Chagas disease has been

cured is a major concern. Several potential biomarkers have been proposed for the detection of early cardiac or gastrointestinal disease. The validation of these clinical tools is essential to identify high-risk patients who require intensive monitoring and early therapy. We conducted a systematic review of biomarkers that are potentially useful in Chagas disease to provide an overview of the subject and help researchers choose future lines of research (Requena-Mendez *et al*, Expert Rev Anti Infect Ther, 2013).

● Information on the pharmacokinetics of benznidazole is limited. The data from our study show that benznidazole at a dosage of 5 mg/kg/day results in mean serum concentrations at the top of the trypanocidal range (3 to 6 µg/mL), indicating that this regimen is appropriate for obtaining therapeutic drug concentrations. Moreover, mean serum concentrations were below toxic levels. Adverse events were not related to serum concentrations in this cohort of patients (Pinazo *et al*, Antimicrob Agents Chemother, 2013).

● Together with the Platform for the Integral Care of Patients With Chagas Disease and the Drugs for Neglected Diseases Initiative (DNDi), we carried out a Phase II clinical trial of the experimental drug candidate E1224 as a treatment for Chagas disease. The new drug showed good safety and was effective in clearing the parasite that causes Chagas disease but its sustained efficacy over time was low (30%) compared to that of the current treatment, benznidazole (80%).

Maternal, Infant and Reproductive Health

Global health indicators show that maternal health is still the area in which the greatest inequities persist. Every year, around 287,000 women die as a result of complications related to pregnancy, childbirth or the postpartum period, and more than eight million children under five years of age die. Almost all of these deaths are from preventable causes and many could be avoided with the adequate use of evidence-based technology, preventive and therapeutic tools, and cost-effective measures. In the last decade, we have contributed to achievements in women's and children's health through field research undertaken to create tools that will lead to better and more effective application of knowledge generated in low and middle income countries.

Main Lines of Research

- Malaria in pregnancy
- Operational research on the acceptability and feasibility of the implementation of a human papillomavirus (HPV) vaccination programme for preadolescent girls in Africa.
- Pharmacovigilance studies of antiretroviral and antimalarial drugs in pregnant women
- Aetiology and risk factors for anaemia in children
- Causes of death in low-income countries

Main Results 2013

● In a study undertaken to describe clinically relevant cytoadhesive phenotypes of *P. vivax*, rosetting was shown to be a frequent cytoadhesive phenotype in *P. vivax* infections associated with an increased risk of anaemia. No specific cytoadhesion phenotypes associated with pregnancy were observed, although a *P. vivax* haplotype was more frequent among pregnant women than non-pregnant hosts, suggesting that other, as yet unknown, parasite phenotypes may increase the propagation of certain *P. vivax* clones observed in pregnant hosts (Marín-Menéndez *et al*, PLoS Negl Trop Dis, 2013).

● Antibody responses to *P. falciparum* in pregnant women were shown to be affected by variables that influence the risk of exposure to the parasite, such as parity, season and neighbourhood. HIV infection modifies these associations between exposure and antibody responses, probably through its impact on the maintenance of IgG responses (Mayor *et al*, JID, 2013).

● We found evidence of *P. falciparum* parasites expressing specific VAR2CSA variants that have the potential to reach a high parasitaemia in the placenta and eventually increase the risk of poor pregnancy outcomes. The motifs inVAR2CSA associated with high placentalparasitaemia in the study may be of relevance to our understanding of the molecular mechanisms that mediate parasite sequestration to host tissues and to the development of new preventive tools against placental malaria (Rovira-Vallbona *et al*, PLoS One, 2013).

● The concentrations of dichlorodiphenyltrichloroethane (DDT) compounds in the cord blood of 214 children born between 2003 and 2006 in Manhiça (Mozambique) were determined. The strongest factor affecting DDT concentration was parity. A well-defined decreasing concentration trend was observed for the cord blood concentrations in the period of study. Children from multiparous women showed much lower concentrations than primiparous women (Manaca *et al*, Envion Sci Pollut Res Int, 2013).

● Women with HIV RNA in breast milk showed a different pattern of microbiological composition, suggesting specific immunopathological phenomena in HIV-infected women. Both breast milk and faecal microbiota composition varied with lactation period. These findings provide insight into interactions between commensal bacteria and HIV infection in human milk and the role of these bacteria in mucosal protection against infections in breastfed infants (Gonzalez *et al*, PLoS One, 2013).

● Severe malnutrition among hospitalised children in Mozambique was found to be common but frequently undetected despite the association with a high risk of death. Measures to improve the recognition of severe malnutrition by clinicians responsible for the first evaluation of patients at the out-patient level are urgently needed in order to improve the likelihood of survival (Nhampossa *et al*, Public Health Nutr, 2013).

● In a prospective autopsy study that included all consecutive pregnancy-related deaths in a tertiary referral hospital in Maputo, Mozambique, between October 2002 and December 2006, extensive sampling of all major viscera was performed. Massive visceral sequestration of *P. falciparum*-infected erythrocytes with significant involvement of the central nervous system was found to be an infrequent but definite direct cause of maternal death in endemic areas of Africa (Castillo *et al*, Clin Microbiol Infect, 2013).

Viral and Bacterial Infections

Viral and bacterial infections account for a substantial proportion of the burden of disease, especially in under five years of age children in low-income countries. In particular, resistance to antimicrobial drugs is a serious global problem for many reasons: it threatens our ability to treat infectious diseases, it increases healthcare costs, and it poses a serious threat to the progress made in global health by individuals and communities over the past few decades. We have deployed our expertise in research in this area to contribute to the effort to fight the various causes of antimicrobial resistance.

Main Lines of Research

- Design of new tools for the rapid diagnosis of infectious diseases
- Molecular bases of antimicrobial resistance
- Relationship between virulence and antimicrobial resistance
- Discovery and assessment of new antibiotics
- Surveillance, phylogeny and clinical impact of the influenza virus and emergent viruses
- Search for biomarkers for the diagnosis and prognosis of bacterial and viral infections
- Pathogenesis and antimicrobial resistance of microorganisms that cause neonatal sepsis
- Treatment of yaws in Papua New Guinea

Main Results 2013

● In a multicentre study, 9,439 children with moderate-to-severe diarrhoea seeking care at health centres together with one to three randomly selected matched community control children without diarrhoea (13,129) were recruited in four sites in Africa and three in Asia. By analysing adjusted population attributable fractions, we found that most attributable cases of moderate-to-severe diarrhoea were due to four pathogens: rotavirus, *Cryptosporidium*, enterotoxigenic *Escherichia coli* producing heat-stable toxin (ST-ETEC, with or without co-expression of heat-labile enterotoxin), and *Shigella* (Kotloff *et al*, Lancet, 2013).

● In the predominantly rural Manhiça district in southern Mozambique, diarrhoea is one of the leading causes of death among children under five years of age. A survey on the use of healthcare services for gastroenteritis found that independent risk factors for seeking healthcare included the presence of diarrhoea with fever and ignorance of the signs of dehydration. Having a television at home was related with an independent decreased use of medical facilities. In another survey, the use of health services was significantly associated with diarrhoea accompanied by fever and vomiting. Establishment of continuous prospective monitoring would make it possible to account for changes in healthcare use that may be a result of seasonality or secular events (Nhampossa, Am J Trop Med Hy, 2013).

● Among enterotoxigenic *E. coli*, the most frequent toxin was STh, and the most frequent colonisation factors (CFs) were CS21, CS6, and CS3 (Rivera *et al*, J Clin Microbiol, 2013).

● We investigated whether hospitalisation for lower respiratory tract infections (LRTI) associated with rhinovirus during infancy was associated with an increased risk of wheezing. The findings suggest

that there is a short-term increased risk of wheezing after an initial episode of LRTI with rhinovirus (O'Callaghan-Gordo *et al*, PLoS one, 2013).

● We analysed the viral load (VL) of human metapneumovirus and human bocavirus in infants aged under 12 months admitted for bronchiolitis. VL correlated with length of hospital stay in both viruses: human metapneumovirus VL correlated with the duration of oxygen therapy and human bocavirus VL correlated inversely with days of respiratory effort before admission (Ricart *et al*, Pediatr Infect Dis, 2013).

● The *Haemophilus influenzae* type b (Hib) conjugate vaccine has dramatically reduced invasive Hib disease worldwide. However, data on the vaccine's efficacy in protecting against pneumonia in children with HIV are limited. The impact of the introduction of Hib conjugate vaccine in 2009 in a rural, high-HIV-prevalence area in Mozambique was evaluated. A considerable reduction in invasive disease and pneumonia following the introduction of the Hib conjugate vaccine in a high-HIV area was observed. Continued surveillance is needed to monitor the long-term effects of Hib conjugate vaccine, particularly among children with HIV (Sigauque *et al*, J Pediat, 2013).

● In 2012, one oral dose of azithromycin was shown to be as effective as intramuscular penicillin in the treatment of yaws, and the WHO launched a new initiative to eradicate the disease by 2020 (Mitjà *et al*, Lancet, 2013).

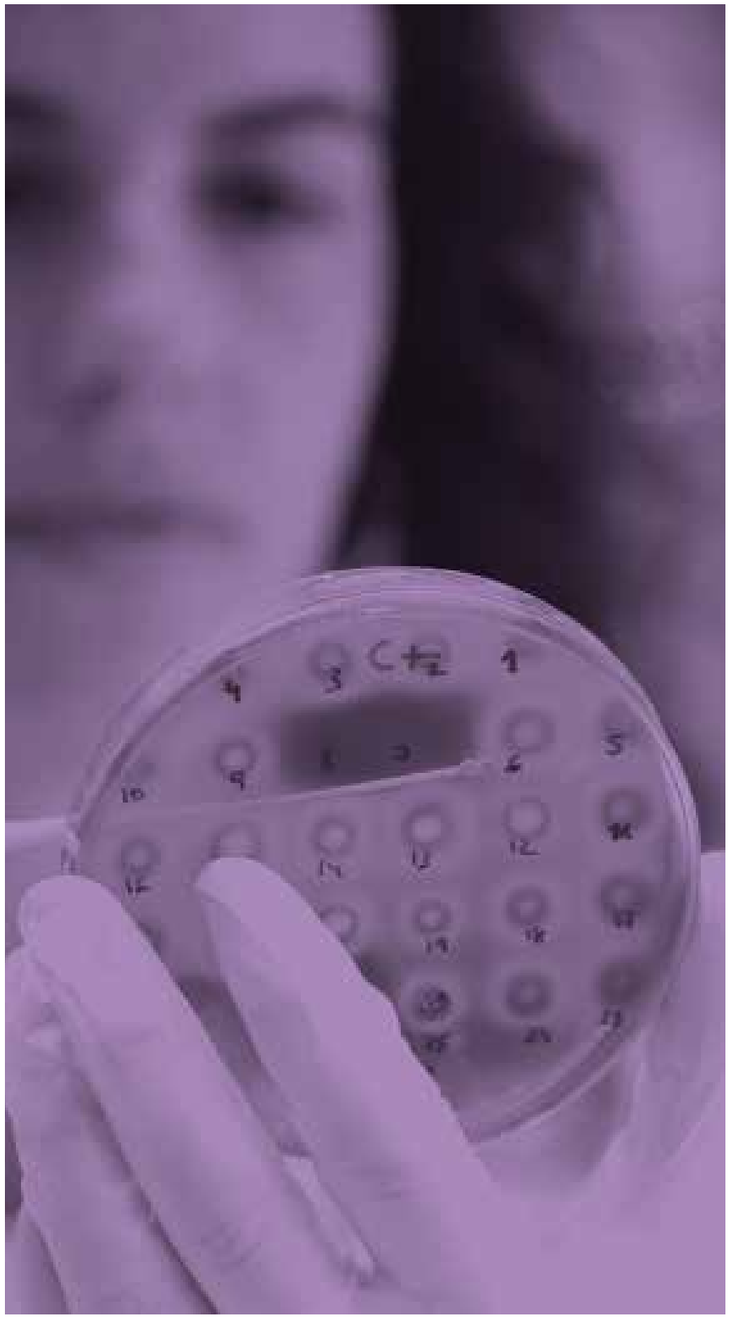
Antibiotic Resistance Initiative

● Multidrug resistance is a problem in the management of tuberculosis (TB), and new regimens that include currently available drugs are urgently needed. Of the various combinations of antimicrobials tested, the levofloxacin/amikacin/ethambutol combination was the most potent against *Mycobacterium tuberculosis* multiplying inside macrophages (Rey Jurado *et al*, Int J Antimicrob Agents, 2013).

● We found high levels of resistance to ampicillin and cotrimoxazol in diarrhoeagenic *E. coli* in children under five years of age in Lima, Peru. We also found that there is tendency to overuse antibiotics for diagnosed pharyngitis, bronchospasm and the common cold (Ecker *et al*, Pediatric, 2013; Rev Peru Med Exp Salud Public, 2013).

● Among 362 *Salmonella enterica* isolates of non-Typhimurium serotypes isolated in Terres de l'Ebre (Catalonia, Spain), 16.5% showed multidrug resistance (MDR). Overall, 35 isolates (9.2% of all isolates and 54% of MDR isolates) belonging to 15 different serotypes carried class 1 integrons. On investigating the antimicrobial resistance of *Shigella* sp. causing traveller's diarrhoea, an increase in nalidixic acid and tetracycline resistance was observed (Pérez-Moreno *et al*, Int J Med Microbiol, 2013; Pons *et al*, Travel Med Infect Dis, 2013).

● It has been suggested that efflux pumps are the main mechanism of resistance to rifaximin in *E. coli* isolates and that efflux pumps play a role in the basal levels and development of azithromycin resistance in *S boydii*. The combination of antibiotics and efflux pump inhibitors appears to be a good solution for reducing the frequency of mutation in *E. coli* and *Shigella* sp. clinical isolates (Gomes *et al*, Trans R Soc Trop Med Hyg, 2013; Microb Drug Resist, 2013; Int J Antimicrob Agents, 2103).



● Carbapenem-resistant *Acinetobacter baumannii* clinical isolate belonging to European clone II is on the rise worldwide, mainly in association with the production of OXA-23. The first description of this clone in Spain and an outbreak caused by an OXA-23 carbapenemase-producing *A. baumannii* were reported (Mosqueda *et al*, Antimicrob Agents Chemother, 2013; Espinal *et al*, Antimicrob Agents Chemother, 2013).

● The *in vitro* activity of ozenoxacin, a novel nonfluorinated topical quinolone, was compared with the activity of other quinolones against well-characterised quinolone-susceptible and quinolone-resistant gram-positive bacteria. Ozenoxacin was 3-fold to 321-fold more active than other quinolones. Ozenoxacin could be a first-in-class nonfluorinated quinolone for the topical treatment of a broad range of dermatological infections (Lopez *et al*, Antimicrob Agents Chemother, 2013).

HIV/AIDS

Remarkable inroads have been made against the global HIV epidemic over the past few years. New HIV infections and HIV-related deaths are decreasing more rapidly than ever before, and treatment programmes have expanded rapidly. However, more than two million people are newly infected with HIV every year, antiretroviral coverage still lags in some regions, and important disparities persist, notably for men, pregnant women, adolescents and key populations. Our research in HIV/AIDS focuses on sub-Saharan Africa and predominantly women and children, the groups hardest hit by the epidemic.

Main Lines of Research

- HIV and maternal and child health
- Pathogenesis of acute and early HIV infection
- Community epidemiology studies to inform future HIV-prevention interventions
- Immune reconstitution inflammatory syndrome (IRIS)
- Vaccination response in HIV-infected patients
- HIV testing modalities

Main Results 2013

● The incidence and mortality of immune reconstitution inflammatory syndrome associated with Kaposi sarcoma (KS-IRIS) was found to be higher in sub-Saharan Africa than in the United Kingdom. This was largely explained by the more advanced Kaposi sarcoma disease and lower availability of chemotherapy in Africa. Our findings support the need to continue the progressive scale-up and earlier initiation of antiretroviral drugs, better clinician and patient education to encourage earlier presentation, referral and diagnosis of KS, and high-level advocacy on improving access to optimal chemotherapy in order to decrease the unacceptably high mortality of KS and KS-IRIS in Africa (Letang *et al*, AIDS, 2013).

● HIV seropositivity is considered a risk factor for complications in hepatitis A virus infection. Factors associated with the immune response to hepatitis A vaccination in HIV-infected patients were described. The findings underscore the importance of identifying strategies that optimise the timing and effectiveness of hepatitis A vaccination in HIV-infected patients and the need for further studies on individual factors, such as sex and hepatitis C co-infection, that may affect the response to vaccination (Mena *et al*, Vaccine, 2013).

● A systematic review of the operational implementation of provider-initiated testing and counselling (PITC) programmes in sub-Saharan Africa found that the widespread adoption of PITC provides an unprecedented opportunity to identify HIV-positive individuals who are already in contact with health services. PITC programmes should be accompanied by measures aimed at strengthening health systems and fostering the normalisation of HIV at the community level, but the resources and effort needed to do this successfully should not be underestimated (Roura *et al*, AIDS, 2013).

Main Lines of Research

- Migrants' health and travel medicine
- *Leishmania*
- Evaluation of vaccination campaigns
- Pathology of premalignant lesions and neoplasias related to human papillomavirus infection

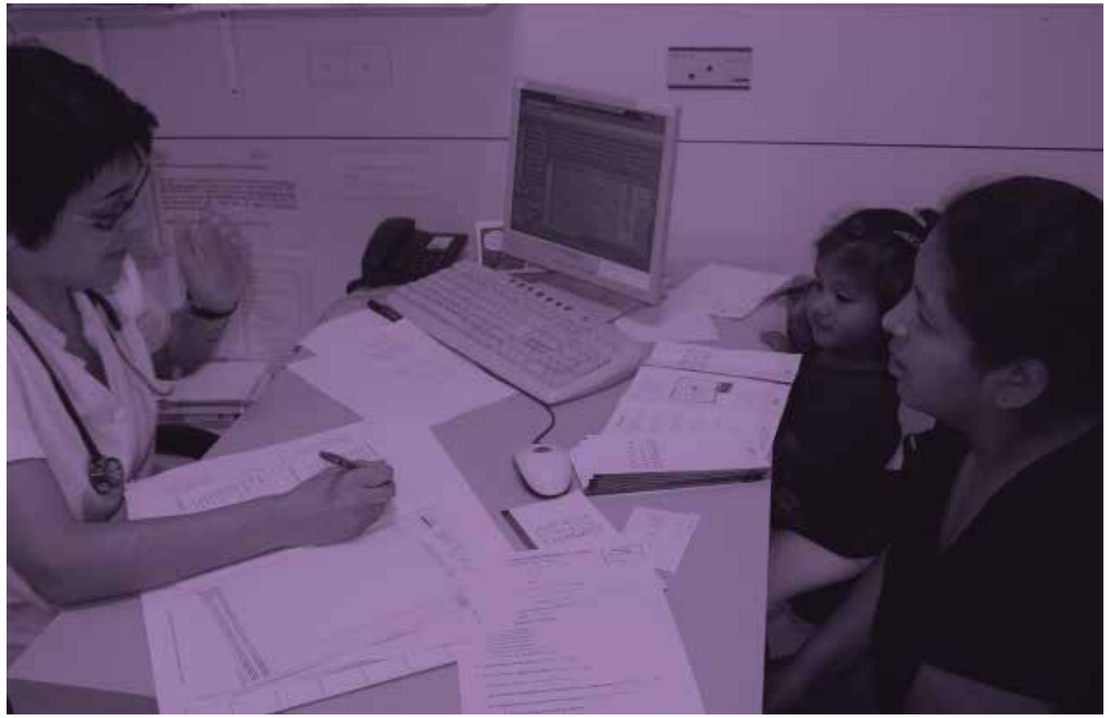
Main Results 2013

● A systematic review of the qualitative literature on TB in migrant populations indicated that immigrants' knowledge of and attitudes towards TB are largely a result of their previous experiences. The review concluded that in addition to escalating current interventions and increasing monitoring of the incidence and prevalence of TB in immigrant populations, it is crucial to understand immigrants' perceptions of TB and the specific obstacles they face in accessing the health system, seeking a diagnosis and adhering to a treatment programme (Abarca *et al*, PLoS One, 2013).

● Improved clinical management and diagnosis of infectious diseases that primarily affect travellers have been proposed for strongyloidiasis (Requena-Méndez *et al*, PLoS Negl Trop Dis, 2013), refractory giardiasis (Muñoz *et al*, Travel Med Infect Dis, 2013), schistosomiasis (Muñoz *et al*, PLoS Negl Trop Dis, 2013) and the neurological complications of dengue virus infection (Carod-Artal *et al*, Lancet Neurol, 2013).

● We described the case of Japanese encephalitis in Spain (Doti *et al*, Eurosurveillance, 2013).

● Epidemiological studies on canine *leishmaniasis* in the Balearic Islands (Alcover *et al*, Acta Tropica, 2013) and Lleida (Ballart *et al*, Prev Vet Med, 20113) found an apparent emergence of canine *leishmaniasis* in Menorca and the presence of an autochthonous focus of canine *leishmaniasis* in the Pallars Sobirà region of Lleida.



- An evaluation of an influenza vaccination campaign among health care workers at a university hospital in Barcelona found that increasing the information provided to health care workers and heightening their risk perception do not necessarily lead to greater acceptance of influenza vaccination (Llupià *et al*, Am J Infect Control, 2013). In addition, an evaluation of the effect of three vaccination promotion strategies on the intention of medical students to get vaccinated and an analysis of associated factors showed that having done clinical rotations and having received previous influenza vaccinations were independently associated with the intention to get vaccinated. Online promotional campaigns seemed to improve the intention to get vaccinated (Mena *et al*, BMC Med Educ, 2013).

- The pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma were reviewed (del Pino *et al*, Histopathology, 2013).

- It was shown that a negative result or low Viral Load (VL) in the preconisation hr-HPV test is associated with the absence of cervical intraepithelial neoplasia in the loop electrosurgical excision procedure. In addition, patients with a negative preconisation hr-HPV test or a low VL have a low risk of postconisation recurrence (Rodriguez-Manfredi *et al*, Gynecologic Oncology, 2013).

- In a pilot study, intraoperative postconisation (IOP) human papillomavirus (HPV) testing was assessed for early detection of treatment failure in patients with cervical intraepithelial neoplasia. IOP-HPV testing was shown to be feasible and to accurately predict treatment failure in patients with CIN2–3. This new approach may allow the early identification of patients with treatment failure, thereby facilitating the scheduling of less intense follow-up for negative patients who are at very low risk of persistent disease (Torné *et al*, Gynecologic Oncology, 2013a).

- We evaluated transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR) as a new method for sentinel lymph node (SLN) detection in endometrial cancer. TUMIR was shown to be a safe, feasible method for SLN detection in patients with endometrial cancer. It has a good detection rate and provides representative information on the lymphatic drainage of endometrial cancer (Torné *et al*, Gynecologic Oncology, 2013b).