

ACTIVITY REPORT 2011-2013



cism
centro de
investigação
em saúde de
manhiça

Letter from the President of the Manhica Foundation: Dr. Pascoal Mocumbi



On behalf of the Manhica Foundation Board of Trustees, I would like to congratulate the Manhica Health Research Centre (CISM) on the results it has achieved between 2011 and 2013. This success is the result of an effort on the part of the institution to establish and strengthen responsible and long-lasting national and international partnerships aimed at promoting better health care and biomedical training and research. With the help of these partnerships, the Foundation and its research centre can pursue the ambitious goal of finding solutions for the main communicable diseases that affect Mozambique and other developing countries. Collaboration with the government through the presentation of scientific evidence that can inform public health policies has resulted in the implementation of innovative measures that will combat the diseases that affect developing countries. These include the introduction of the pneumococcus vaccine and a study to investigate the feasibility and acceptability of implementing a programme to vaccinate pre-adolescents in rural and urban areas against the human papilloma virus (HPV).

Over the last three years, CISM has contributed to the development of Mozambique's human resources, collaborating with several national and international teaching and research institutions, including Eduardo Mondlane University, in particular the Medical and Veterinary faculties, the University of Barcelona, and the Barcelona Centre for International Health Research (CRESIB), research centre of the Barcelona Institute for Global Health (ISGlobal).

Through the quality of its scientific output, CISM has gained prestige and recognition from international partners, placing it squarely in the forefront of several initiatives that have had an impact on the region, including the

Phase II clinical trial of the AERAS-402 tuberculosis vaccine candidate in children, and the Elimination of Malaria project (zero local transmission and infection within a specific geographical area). As a result of its reputation, CISM is now a partner in research networks of excellence, such as TESA (Trials of Excellence in Southern Africa), promoted by the European & Developing Countries Clinical Trials Partnership (EDCTP), and the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH).

The alliance that has been consolidated over almost 20 years of shared history with the Spanish Government, CISM's main donor since the institute's inception, and the partnership between CISM/Manhica Foundation and CRESIB/ISGlobal are the result of the implementation over 17 years of a research and development model through which the centre has established itself as a key actor in the field of health research inside and outside of Mozambique. Nevertheless, the pursuit of sustainability continues to present new challenges, including a determination to establish a more stable partnership with the Mozambican State. It is through these and other strategic partnerships that CISM hopes to continue its journey of excellence and to achieve results that will have a direct impact on the health of the population of Mozambique and particularly on the problems that have limited the country's development potential.

Letter from the President of the Board of Governors of the Manhica Foundation: **Prof. Pedro L. Alonso**



During the last ten years, Africa has seen stronger economic growth than many other parts of the world. According to the World Bank, the annual growth rate in Mozambique between 2011 and 2013 was over 7%. However, despite the robust economic growth in the continent overall and Mozambique in particular, the impact of this improvement on poverty reduction is fairly small and the health situation of African countries is still a cause for concern.

Economic growth is an important factor in a country's development; however, sustained and robust development requires other elements. Knowledge generated by science and technology are two powerful tools that improve a country's health and promote economic and social development. It is precisely in this area that African countries need to make a greater effort because the continent's infrastructure for science and knowledge is still inadequate.

Since its creation in 1996, CISM has become the main instrument for the transfer of knowledge between Spain and Africa, with collaboration ties with the Hospital Clínic, the University of Barcelona and ISGlobal's research centre, CRESIB. Over the years CISM has become an internationally recognised scientific centre with a high level of credibility and visibility. CISM's development strategy based on biomedical research, evidence-based contributions to health policies and interventions, and support for the training of young professionals is proving to be decisive in the development of Mozambique's capacities in these areas.

At this time, as we celebrate the 20th anniversary of CISM's foundation, we should feel proud of this institution that was created as a programme of collaboration between countries and academic institutions and has now become a truly Mozambican knowledge centre, a vibrant, cutting edge institution open to the world. CISM is a centre searching for real solutions to the health problems of the most vulnerable population groups, not only in Mozambique or sub-Saharan Africa, but also in the world in general.

Letter from the Director of CISM: Dr. Eusébio Macete



The mission of Manhica Health Research Centre (CISM) is to use biomedical research to produce scientific evidence that will inform the creation and updating of health policies in Mozambique and other parts of the world.

Much of the work carried out over the last three years (2010–2013) has generated data that have played a crucial role in supporting the introduction of new prevention tools, such as a pneumococcal conjugate vaccine that protects children against infection by one of the main pneumonia pathogens. On the other hand, with the establishment of a surveillance and evaluation unit, we have launched the first studies to monitor the effectiveness of the antimalarial drugs currently in use and the accessibility and use of mosquito nets throughout the country. We have also started to evaluate the use of malaria rapid diagnostic tests and the impact of the introduction of a pneumococcal vaccine. In relation to the development of new vaccines, in 2014 we will complete a series of trials started in 2002 of RTS,S—a candidate that may become the world's first malaria vaccine. The results obtained have been very encouraging and will contribute to the development of the first generation of this vaccine.

CISM is still focussed on the specialist training of young Mozambicans in different areas of biomedical research and related fields. We believe that this is the best contribution we can make to building a sustainable country and to reaching a critical mass of qualified personnel in spheres, such as public health, that are crucial to the country's development.

Over the next few years, we expect to continue expanding our activities in order to reach out to other areas of Mozambique to monitor the epidemiological trends of

current and emerging diseases, and to strengthen partnerships and collaboration with national academic and research institutions. In addition, we expect to strengthen our international strategic collaboration ties, which have been providing us with a global perspective.

In recognition of our contribution to the improvement of the health of the population through research, CISM was recently awarded the Bagamoyo Medal, an award that recognises the essential role of education in building and developing our country. This and other achievements would not be possible without the assistance of our collaborators, including the people of Manhica, all those who have participated in CISM's studies, the local, provincial and national authorities, as well as our international partners and donors, including the Spanish Agency for International Development (AECID), among others.

To all of you, our deepest gratitude.

Management of the Manhiça Health Research Centre (CISM)

CISM was set up in 1996 to promote and carry out biomedical research in priority health areas. Since then the development of the centre has been guided by a bilateral programme of cooperation between the governments of Mozambique and Spain.

CISM is managed by Manhiça Foundation, a non-profit institution created in 2008 by the governments of Mozambique and Spain, the Mozambican National Institute of Health and the Fundació Clínic per la Recerca Biomèdica (Hospital Clínic-Universitat de Barcelona), with Dr. Pascoal Mocumbi as the honorary founding member. In 2010, the Fundação para o Desenvolvimento da Comunidade (FDC - Foundation for Community Development) and Eduardo Mondlane University joined Manhiça Foundation as members of the Board of Trustees. The Foundation was set up because of the founders' conviction that biomedical research plays a central role in improving the health of the population and in a country's economic and social development.

The creation of the Manhiça Foundation was one of the most important landmarks in the development of CISM, because it provided the research centre with a Mozambican legal structure and represented an important step away from being a bilateral collaboration project towards becoming a Mozambican institution.

Manhiça Foundation is governed by a **Board of Trustees** and a **Board of Governors**. Technical support is provided by an **External Scientific Committee**.

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ORGANIC STRUCTURE OF CISM

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Eusébio Macete

**DEPUTY DIRECTOR – FINANCIAL
ADMINISTRATION**
Delino Nhalungo (since July 2013)

DEPUTY SCIENTIFIC DIRECTOR
Inácio Mandomando
(since November 2013)

The three pillars of CISM's work are research, training and technical assistance, with the last two complementing and supporting the research. The centre's research activities are carried out by four departments (Clinical Services, Demography, Laboratory, and Data Management/Information Technology), and three platforms relating to geographical and demographic research and morbidity surveillance.

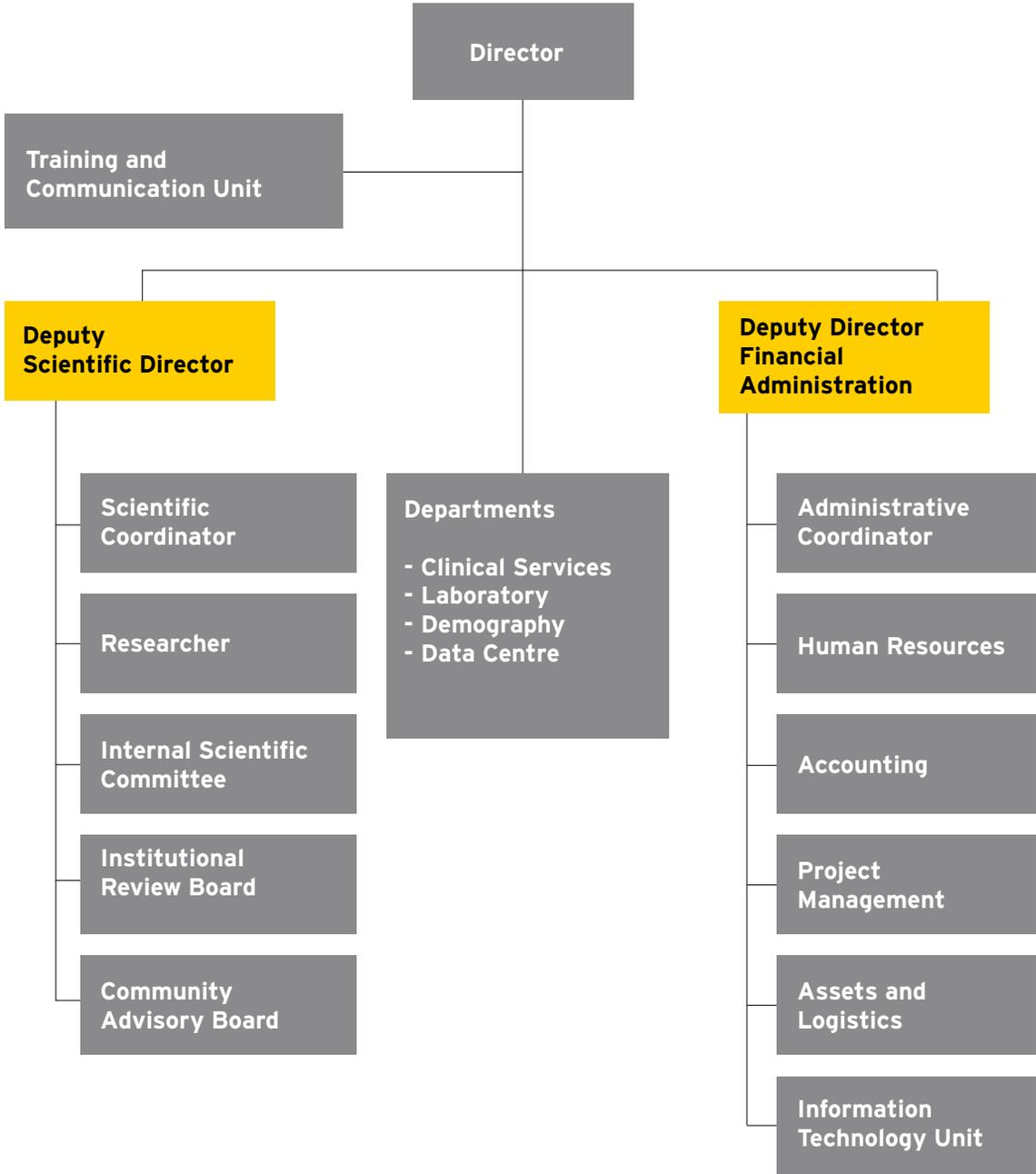
Three internal committees complete the structure. These serve to strengthen scientific management and community participation in research projects.

The **Internal Scientific Committee** is composed of the most senior researchers and chaired by the Scientific Director. Its responsibilities include advising the leadership and management team on scientific issues, analysing internal research proposals, and assessing new proposals for partnerships submitted by collaborators interested in conducting research in collaboration with CISM.

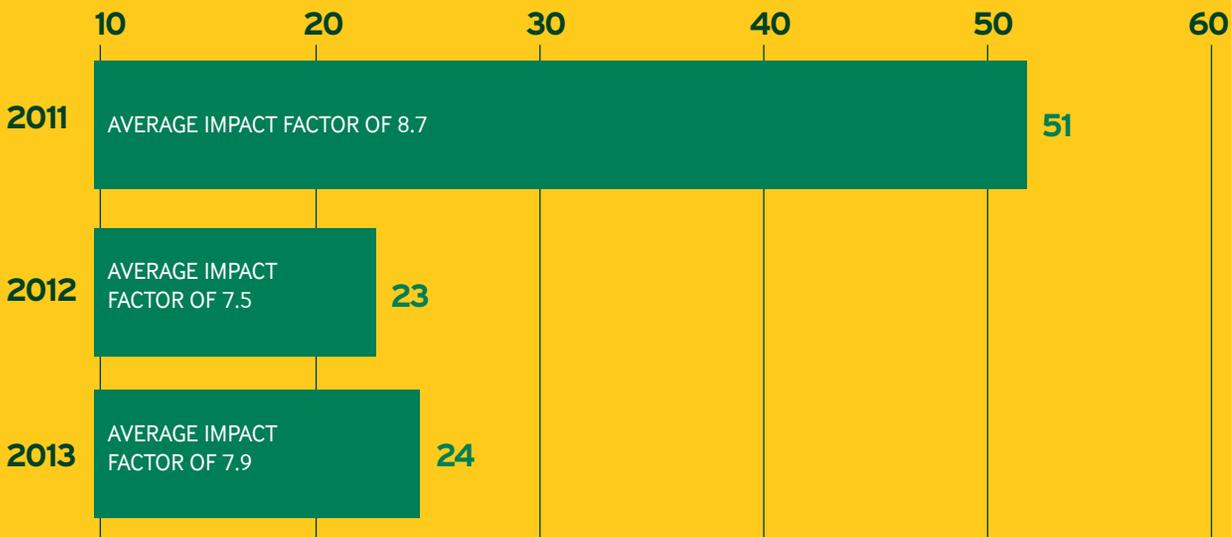
The **Institutional Review Board**, chaired by Dr. Betuel Sigauque, ensures independent review of the ethical aspects of the research proposals and protocols submitted.

The **Community Advisory Board**, chaired by Mr. Abílio Amanso Mahumana, serves as a bridge between the centre and the community. Twice a year meetings are held at which CISM and community representatives share information and make their views known.

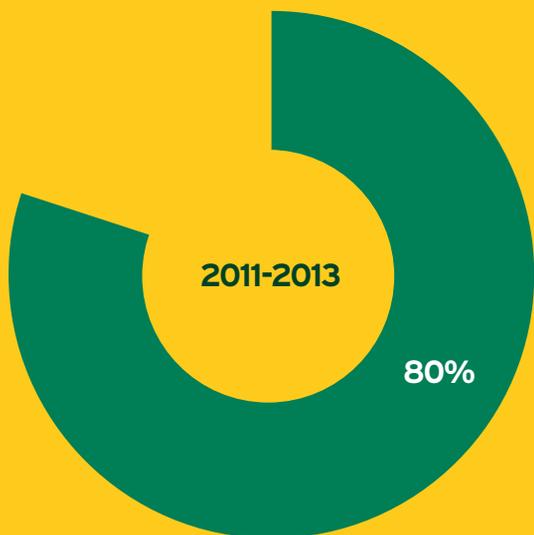
**ORGANISATIONAL
CHART OF CISM**



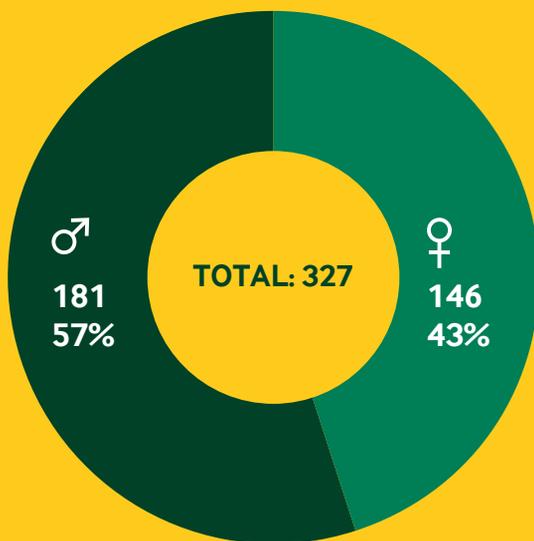
NUMBER OF PUBLICATIONS



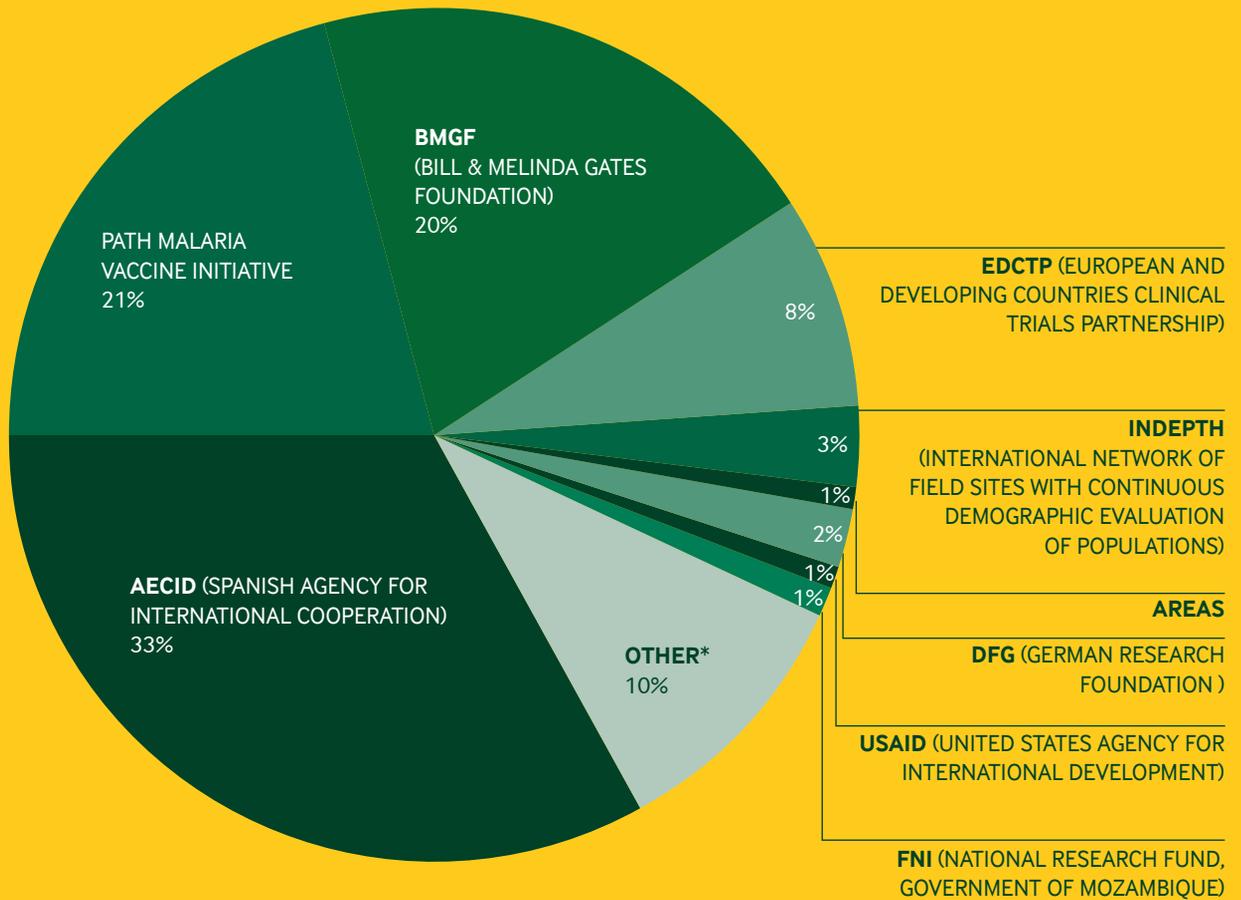
PERCENTAGE OF PUBLICATIONS IN SCIENTIFIC JOURNALS



NUMBER OF STAFF 2011 -2013



MAIN FUNDERS



* INCLUDING THE MOZAMBIKAN MINISTRY OF HEALTH

BUDGET

2011 \$5,811,154
2012 \$ 5,567,958
2013 \$ 4,496,006

CISM promotes and carries out biomedical research in priority health areas, with a major focus on diseases that cause most of the deaths in the world, especially in low-income countries. Its research agenda prioritises health problems that have a significant impact in Mozambique and are also relevant to other countries in sub-Saharan Africa. These include malaria, HIV/AIDS, tuberculosis (TB), diarrhoeal diseases, acute respiratory infections, invasive bacterial diseases, as well as maternal, infant and reproductive health.

The research activity is carried out through three key platforms. The geographic and demographic platforms are managed by the Demography Department. The morbidity surveillance platform is managed by the Clinical Department. Altogether they cover a study area of 500 km² with approximately 95,000 inhabitants. Our intention is to extend this coverage in 2014 to 160,000 inhabitants.

This infrastructure generates scientific evidence that can be used to inform the creation and updating of health policies in Mozambique and the world in general. CISM has recently been involved in projects with major national impact, such as the clinical trial of the RTS,S malaria vaccine candidate, the introduction of a vaccine against *Haemophilus influenzae type b* (Hib), the introduction of the pneumococcal vaccine, the human papillomavirus (HPV) vaccine demonstration project, and monitoring of antimalarial drugs.

RESEARCH AREAS

MALARIA

RESEARCHERS

Alfredo Mayor, Ariel Magallon, Augusto Nhabomba, Azucena Bardaji, Clara Menéndez, Carlota Dobaño, Diana Quelhas, Esperança Sevene, Eusébio Macete, Gemma Moncunill, Nélia Manaca, Jahit Sacarlal, John Aponte, Joseph Campo, Pedro Aide, Pedro Alonso, Quique Bassat, Raquel González

Malaria is still one of the priority health issues in sub-Saharan Africa. It affects over 100 countries worldwide and is the leading cause of death and morbidity in Mozambique. Since CISM was created, malaria has been one of its main areas of research, and the centre has contributed to the control of this disease by developing, implementing and evaluating innovative strategies. Our internationally recognised team of researchers plays a central role in the institute's global development, consolidating its position among leading malaria research centres.

After an initial phase dedicated exclusively to describing malaria and collecting information concerning the burden of the disease, CISM is now also contributing to the development of new malaria control instruments.

MAIN RESEARCH LINES

- Descriptive clinical and epidemiological studies. Using existing research platforms, CISM is monitoring malaria morbidity and mortality as well as the intensity of transmission. This data will be used to assess trends over time and the impact of control interventions.
- Clinical trials of vaccines and drugs. In recent years, CISM has carried out clinical trials on both the treatment and prevention of malaria:
 - Phase III trial of the RTS,S malaria vaccine candidate



- Study of the effectiveness, safety and pharmacokinetics of a new paediatric formulation of dihydroartemisinin-piperazine

- Immunology and pathophysiology studies. In this line of research, CISM has focussed on innate and acquired immunity to malaria in childhood, the role of the maternal immune response in early and mid pregnancy, and biomarkers of immunity and susceptibility to malaria in individuals exposed to *Plasmodium* infection, including immunopathologic markers of severe and placental malaria. Studies have also been undertaken on the impact of malaria control (intermittent preventive treatment and indoor residual spraying) on the development of naturally acquired immunity in children and pregnant women. Others areas of study are the development of multi-parameter and functional immunological assays, the impact of changes

in malaria infection trends on antimalarial immunity, the fundamental molecules that contribute to parasite sequestration, and host biomarkers for severe malaria.

- Programme for the elimination of malaria in Mozambique: This project was launched jointly in 2013 with Mozambique's National Malaria Control Programme. The preparatory phase is an intellectual exercise that involves designing a strategy for coordinating activities and (re)directing efforts to eliminate malaria in Mozambique. The scientific component of the programme includes a number of studies to assess the effectiveness of drugs that could interrupt parasite transmission and operational research undertaken to develop the best strategies for malaria elimination.

MAIN FINDINGS

CISM continues to be one of the most active and leading institutions in the development of the malaria vaccine. The latest study showed that RTS,S, the most clinically advanced malaria vaccine candidate, continues to protect young children and newborn babies against clinical malaria for up to 18 months after vaccination. The findings indicated that at 18 months RTS,S reduces by almost half the number of cases of malaria in young children (5 to 17 months of age at first vaccination) and by around a quarter the number of cases in infants (aged between 6 to 12 weeks at first vaccination).

The results show that over 18 months of follow-up there were 46% fewer cases of clinical malaria among children who received their first RTS,S vaccination between 5 -17 months of age compared to children immunised with a control vaccine. An average of 941 cases of clinical malaria were prevented over 18 months of follow-up for each 1,000 children vaccinated in this age group (note that a child can contract more than one case of malaria).

- Immunological studies related to the malaria vaccine indicate that vaccination with RTS,S modestly reduces blood stage and pre-erythrocyte stage antigens as well as anti-AMA-1 and anti-MSP-1 antibodies in Mozambican children. Other immunological results can be found in the publications listed below.
- With regard to disease control measures, CISM, both alone or in collaboration with international partners, has contributed to monitoring the effectiveness of antimalarial drugs. Studies carried out in recent years on the antimalarials artemether-lumefantrine and artesunate-amodiaquine found very high efficacy for both treatments, confirming their position as the first and second line treatments for malaria, respectively.

KEY PUBLICATIONS

- Zhang G, Manaca MN, McNamara-Smith M, Mayor A, et al. "Interleukin-10 (IL-10) polymorphisms are associated with IL-10 production and clinical malaria in young children". *Infect Immun.* 2012; 80: 2316-2322.
- Quelhas, D., L. Puyol, L. Quinto, et al. "Intermittent Preventive Treatment hit Sulfadoxine-Pyrimethamine does not modify plasma cytokines and chemokines or intracellular cytokine responses to *Plasmodium falciparum* in Mozambican Children." *BMC Immunol.* 13.1 (2012): 5.
- Dobaño, C., D. Quelhas, L. Quinto, et al. "Age-Dependent IgG Subclass Responses to *Plasmodium falciparum* EBA-175 are Differentially Associated with Incidence of Malaria in Mozambican Children." *Clin Vaccine Immunol* (2012): Feb;19(2):157-66.
- Campo, J. J., C. Dobaño, J. Sacarlal, et al. "Impact of the RTS,S Malaria Vaccine Candidate on Naturally Acquired Antibody Responses to Multiple Asexual Blood Stage Antigens." *PLoS One.* 6.10 (2011): e25779.
- Campo, J. J., J. J. Aponte, A. J. Nhabomba, et al. "Feasibility of flow cytometry for measurements of *P. falciparum* parasite burden in endemic malaria studies using bidimensional assessment of YOYO-1 and autofluorescence." *J Clin Microbiol.* 49.3 (2011): 968-74.
- Mayor A, Kumar U, Bardaji A, Gupta P, et al. "Improved pregnancy outcomes in women exposed to malaria with high antibody levels against *Plasmodium falciparum*." *J Infect Dis.* 207. 11 (2013): 1664 -1738.
- Nanche, D., E. Serra-Casas, A. Bardaji, et

al. "Reduction of Antimalarial Antibodies by HIV Infection Is Associated With Increased Risk of *Plasmodium falciparum* Cord Blood Infection." J Infecta Dis. 205.4 (2012): 568–577.

- Mayor A, Moro L, Aguilar R, et al. "How hidden can malaria be in pregnant women? Diagnosis by microscopy, placental histology, polymerase chain reaction and detection of histidine-rich protein 2 in plasma." Clin Infecta Dis. 54.11 (2012):1561-1568.

- Menendez, C., E. Serra-Casas, M. D. Scahill, et al. "HIV and Placental Infection Modulate the Appearance of Drug-Resistant *Plasmodium falciparum* in Pregnant Women who Receive Intermittent Preventive Treatment." Clin Infecta Dis. 52.1 (2011): 41–48.

- Mayor, A., A. Hafiz, Q. Bassat, et al. "Association of severe malaria outcomes with platelet-mediated clumping and adhesion to a novel host receptor." PLoS One. 6.4 (2011): e19422.

RESEARCHERS

Maria Rupérez, Raquel González, Inácio Mandomando, Lucia Pastor, Clara Menéndez, Sónia Maculúwe, Durval Respeito, Celia Serna, Cinta Moraleda, Emili Letang, Betuel Sigáúque, Khátia Munguambe, Denise Nanihe

Mozambique is one of the countries in the world most affected by HIV/AIDS, and CISM is located in an area where the prevalence and incidence of HIV is high. In 2007, over 25% of pregnant women seen in antenatal consultations in Manhica were HIV positive. Since the establishment in 2005 of the HIV day hospital, now integrated into the normal consultation schedule, CISM has carried out several research projects in this area.

MAIN RESEARCH LINES

- HIV and mother and child health
- HIV epidemiology studies to inform future HIV prevention interventions
- Characterisation of acute and early HIV infection
- Treatment and care for people living with HIV infection

MAIN FINDINGS

Work is still ongoing on characterising the HIV/AIDS epidemic in Mozambique, and although there is evidence to suggest that the situation is stabilising, more precise data on the dynamic of this disease in the country's three principal regions is still needed. CISM has contributed data from Manhica District, which serves as a reference for the country's southern region, providing valuable evidence to inform the technical debate.

- The results indicate that the overall prevalence of HIV was 39.9% in 2010 and that the age cohort with the lowest HIV prevalence was young adults (18–27 years of age). These trends reflect the critical situation of the HIV epidemic in southern Africa and the need for innovative strategies to strengthen HIV prevention.

- A study of early or initial HIV infection showed that approximately 12% of the people who sought counselling and testing in Manhica Hospital in southern Mozambique had a recent HIV infection (contracted less than 6 months earlier).

- With respect to the implementation of clinical management strategies for reducing 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. Research at the Manhica District Hospital found a prevalence of 26.5% of IRIS in patients starting highly active antiretroviral therapy.

KEY PUBLICATIONS

- González R, Munguambe K, Aponte J, et al. "High HIV prevalence in a southern semi-rural area of Mozambique: a community-based survey." (2012) *HIV Medicine*. (10):581-8.
- Serna-Bolea C., de Deus, N., Acácio S., Muñoz J., Nhalungo D., Letang E., Alonso P., Nanihe D.. "Recent HIV-1 infection: identification of individuals hit high viral load setpoint in a voluntary counselling and testing centre in rural Mozambique." (2012) *PLoS One* 7(2): e31859.

- Naniche D., Letang E., Nhampossa T., David C., Menendez C., Alonso P. “Alterations in T cell subsets in Human Immunodeficiency virus-Infected adults hit co-infections in Southern Mozambique.” (2011) *American Journal of Tropical Medicine and Hygiene* 85(4): 776-81.
- Perez-Hoyos, S., D. Naniche, E. Macete, et al. “Stabilization of HIV incidence in women of reproductive age in southern Mozambique.” *HIV Med.* 12 (2011): 500–505.
- Letang, E., J. M. Miro, T. Nhampossa, E. Ayala, J. Gascon, C. Menendez, P. L. Alonso, and D. Naniche. “Incidence and predictors of immune reconstitution inflammatory syndrome in a rural area of Mozambique.” *PLoS One.* 6.2 (2011): e16946.

TUBERCULOSIS

RESEARCHERS

Alberto Garcia-Basteiro, Elisa López-Varela, Jahit Sacarlal, Kizito Gondo, Orvalho Joaquim, Durval Respeito, Oscar Fraile, Tasmiya Ira, Hélder Buló

TB is one of the leading causes of death worldwide, and Mozambique is one of the 22 countries most affected by this disease. According to the WHO's 2013 Global Report on Tuberculosis, there were 8.6 million new TB cases in 2012 (13% co-infected with HIV) and 1.3 million people died from the disease. The same report estimates that children under 15 years of age account for between 15% and 20% of these cases. In 2012, there were an estimated 530,000 new cases and 74,000 deaths among HIV-negative children worldwide.

MAIN RESEARCH LINES

CISM's research activities in TB during the period 2011-2013 focussed principally on strengthening clinical and laboratory capacities in a Phase IIb clinical trial of a TB vaccine candidate in children and on estimating the incidence of TB in children under 3 years of age. This period also saw the start of several new studies aimed at characterising the disease in adults and particularly in patients undergoing retreatment.

- Clinical epidemiology and burden of TB disease
 - Minimum community incidence of TB in children aged <3 years (ITACA Study)
 - Determining the clinical, microbiological and sociological characteristics of patients undergoing retreatment (TE-SA-TB Study)
 - Enhanced TB surveillance project to study the burden of TB in Manhiça District (TOSSE Study)

- Evaluation of new TB vaccine candidates
 - Evaluation of a TB vaccine candidate: Phase II multicentre study of AERAS-402 Vaccine in African children.
- Community perception of childhood TB and its association with care-seeking behaviour in Manhiça District (ITACA SOC-II)

MAIN FINDINGS

- The objective of the ITACA study was to determine the incidence, clinical characteristics, and consequences of TB in children under three years of age. The results showed that the incidence of TB is high in the study area and provided initial estimates of TB incidence for this age group in Mozambique. The study also revealed the heavy burden of TB in the country and the problems involved in diagnosing childhood TB within the national health service. A high prevalence of non-tuberculosis mycobacteria (NTM) was observed in pulmonary samples obtained by induced sputum or gastric lavage, but the clinical implications of these findings are, as yet, unclear.
- In November 2010, as part of the AERAS-402 tuberculosis vaccine trial, CISM introduced—as a temporary replacement—the BCG vaccine (Copenhagen strain) in Manhiça District. This was done in collaboration with the District's Expanded Vaccination Programme. During the project, which lasted almost two and a half years, 64,000 doses of the vaccine were imported and distributed. Passive and active vaccine surveillance was implemented and cases of adverse events with a suspected association with the BCG vaccine were notified by those responsible for the expanded programme, mother and child health, or the pharmaceutical aspects of the study. The temporary replacement of the vaccine finished in March 2013.

TOTAL NUMBER OF PUBLICATIONS:

2

- Preliminary results of the AERAS-402 vaccine study were presented at the Third Global Forum on TB Vaccines held in Cape Town in March 2013. The first publication of definitive results is expected to take place in 2014.

PUBLICATIONS

- Hatherill M, Verver S, Mahomed H, et al. Stop TB Partnership Working Group on TB Vaccines. "Consensus statement on diagnostic end points for infant tuberculosis vaccine trials." *Clin Infect Dis*, 15; 54(4) (2012): 493-501.
- Lienhardt, C., S. V. Cook, M. Burgos, et al. "Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial." *Jama*. 305.14 (2011): 1415-1423.

DIARRHOEAL DISEASES

RESEARCHERS

Inácio Mandomando, Tacilta Nhampossa, Delfino Vubil, Sozinho Acácio, Marcelino Garrine, Eva Dora, Nilsa de Deus, Maria Pons, Joaquim Ruiz, Pedro Alonso

Diarrhoeal Diseases are still a major public health problem worldwide, accounting for around 10% of deaths in children under five years of age. Between 2011 and 2013, CISM's work in this field was focussed on continuing the study of the aetiology of diarrhoea started in 2007. The objective was to describe the burden of disease, aetiology, and sequelae of diarrhoea in children aged under five in Mozambique and other African and Asian countries. As CISM is located in an area where the prevalence and incidence of HIV is high, a sub-study was conducted in parallel with the main study to investigate the relationship between diarrhoeal diseases and HIV in children.

MAIN RESEARCH LINES

While sufficient information is available on the aetiology of diarrhoea in developed countries, the data is still scarce or flawed in developing countries. In recent years, CISM has contributed to a better understanding of the chief causes of diarrhoea and the role of HIV in an area with a high incidence of HIV infection. The research has focussed on the following aspects:

- Clinical epidemiology of diarrhoeal disease
- Role of HIV co-infection on the burden and aetiology of diarrhoea, particularly with respect to rotavirus diarrhoea
- Molecular characterisation of the most relevant enteric pathogens

MAIN FINDINGS

- Our findings on the epidemiology and aetiology of diarrhoea showed that most of the cases of moderate to severe diarrhoea (MSD) in Manhiça were caused by four pathogens: rotavirus, *Cryptosporidium*, *Shigella* and enterotoxigenic *Escherichia coli* heat-stable enterotoxin (ETEC_ST). Rotavirus and *Cryptosporidium* were responsible for approximately 27.8% and 14.6%, respectively, of all cases of MSD among infants. The incidence of MSD was higher in younger infants and decreased with increasing age. Even one episode of MSD had a significant impact on a child's growth and risk of death. After two months follow-up, the risk of death was 13.4 times higher for children diagnosed with MSD than children who were not, and the affected children also grew much less during the two-month period.

- Comparison of epidemiological data on rotavirus from rural (Manhiça) and urban (Mavalane) areas revealed a very similar pattern of infection, although the frequency of infection is higher in the urban area (Mavalane). Molecular characterisation of rotavirus strains revealed the high diversity of the circulating strains in Manhiça and Mavalane, a predominance of unusual strains, and a high prevalence of untypable rotavirus strains. These findings may be relevant to the possible impact of the rotavirus vaccine scheduled for introduction in 2015.

- The data and findings of the Global Enteric Multi-Center Study (GEMS) have provided important information that can serve as a basis for the development of strategies for the prevention and control of diarrhoeal diseases in Mozambique. The data were used by the Ministry of Health to support the implementation of rotavirus vaccination in the country.

TOTAL NUMBER
OF PUBLICATIONS:

4



PUBLICATIONS

- Kotloff, K. L., J. P. Nataro, W. C. Blackwelder, et al. "Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study." *Lancet*. 382.9888 (2013): 209–222.
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PNEUMONIA AND OTHER INVASIVE BACTERIAL DISEASES

RESEARCHERS

Betuel Sigatque, Sozinho Acácio, Delfino Vubil, Sérgio Massora, Óscar Fraile, Inácio Mandomando, Abel Nhama, Miguel Lanaspa, Lola Madrid, Quique Bassat, Eva Dora, Helio Mucavel, Jorge Uqueio

Pneumonia remains the leading cause of morbidity and mortality in children under five years of age worldwide, particularly in developing countries. For the creation of prevention programmes, local epidemiological data are necessary to inform decisions makers and public health policies. CISM has worked for years to characterise the burden and clinical presentation of pneumonia and other invasive bacterial diseases and to identify the circulating strains. This data is essential for any evaluation of the impact and effectiveness of available prevention tools, such as vaccines.

MAIN RESEARCH LINES

During the period 2011-2013, activities in this field have been focussed on evaluating the impact of Hib, measuring the burden of pneumococcal disease with a view to influencing policy decision makers concerning the need to introduce vaccination, and preparatory work on the evaluation of the impact of pneumococcal vaccines. During the same period, research was also undertaken to discover biomarkers that can be used to differentiate between most common diseases in children (bacterial and viral infections and malaria).

- Evaluating disease burden and describing the clinical and epidemiological characteristics of pneumonia and invasive bacterial infections
- Monitoring and evaluating the impact and effectiveness of preventive strategies implemented to control target diseases

- Improving diagnostic tools by identifying biomarkers that can differentiate between the most common paediatric diseases causing respiratory distress (viral and bacterial infections and malaria)

- Evaluating antibiotic use and antimicrobial resistance

MAIN FINDINGS

As part of the clinical epidemiology study, we assessed pneumococcal carriage in children under five years of age in a pre-vaccine context in Mozambique.

- A high prevalence of nasopharyngeal carriage of *Streptococcus pneumoniae* was observed in children under five years of age. Pneumococcal carriage was common, with little variation by geographic region or HIV status. Serotype coverage of PCV10, which was introduced in Mozambique in April 2013, was lower than that of PCV13. Owing to the low prevalence of β -lactam resistance, those agents continue to be useful first-line antibiotics for treating pneumococcal disease in HIV-infected children in Mozambique.

- The surveillance platform was used to evaluate the impact of Hib conjugate vaccine introduction on invasive Hib disease and pneumonia. Our findings demonstrate important reductions in invasive disease and pneumonia following Hib conjugate vaccine introduction. In children under one and under five years of age, we observed significant reductions in rates of invasive Hib disease (91% and 85%, respectively) and very severe pneumonia (29% and 34%, respectively). The incidence of radiologically-confirmed pneumonia fell significantly (33%) in children under two years of age. The incidence of severe pneumonia did not decline.

TOTAL NUMBER OF PUBLICATIONS:

7

• The research undertaken to identify biomarkers that would differentiate between the diseases that most frequently cause respiratory distress in children yielded promising preliminary results showing that the expression pattern of RNA transcription may reliably help us distinguish between the overlapping etiologies of respiratory distress in children (bacterial pneumonia, viral pneumonia and malaria). Further analyses are underway, including proteomics discovery and validation. The ultimate goal is to use such biomarkers or biomarker signatures as the building blocks of a rapid point of care diagnostic test.

CISM's data were used to inform the Ministry of Health's decisions on the introduction in 2013 of the new pneumococcal conjugate vaccines.

KEY PUBLICATIONS:

• Sigauque, B., D. Vubil, A. Sozinho, et al. "Haemophilus influenzae Type b Disease among Children in Rural Mozambique: Impact of Vaccine Introduction." *J Pediatr*. 163.1 Suppl (2013): S19–24.

• Selva, L., R. Benmessaoud, M. Lanaspá, et al. "Detection of and Type B by Real-Time PCR from Dried Blood Spot Samples among Children with Pneumonia: A Useful Approach for Developing Countries." *PLoS One*. 8.10 (2013): e76970.

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• Díez-Padrís N, Bassat Q, Morais L, et al. "Procalcitonin and C-reactive protein as predictors of blood culture positivity among hospitalised children with severe pneumonia in Mozambique." *Trop Med Int Health*. 17.9 (2012): 1100–7.

• Bassat, Q., S. Machevo, C. O'Callaghan-Gordo, B. Sigauque, L. Morais, N. Díez-Padrís, J. L. Ribo, I. Mandomando, T. Nhampossa, E. Ayala, S. Sanz, M. Weber, A. Roca, and P. L. Alonso. "Distinguishing Malaria from Severe Pneumonia among Hospitalized Children who Fulfilled Integrated Management of Childhood Illness Criteria for Both Diseases: A Hospital-Based Study in Mozambique." *Am J Trop Med Hyg*. 85.4 (2011): 626–634.

MATERNAL, INFANT AND REPRODUCTIVE HEALTH

RESEARCHERS

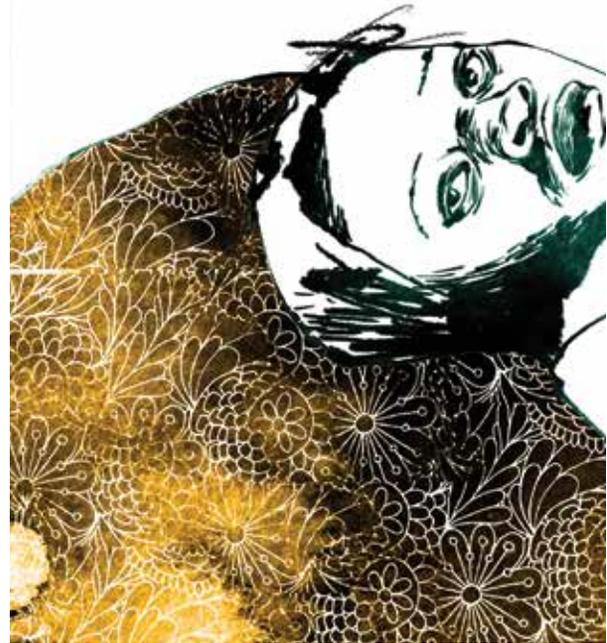
Clara Menéndez, Raquel González, Anífa Valá, Esperança Sevene, María Rupérez, Sónia Maculhwe, Nélia Manaca, Eusébio Macete, Pedro Alonso, Ruth Aguilar, Cinta Moraleda, Montse Renom, Augusto Nhabomba

About 287,000 women die every year as a result of complications related to pregnancy, childbirth or postpartum conditions, and almost all (98%) of these preventable deaths take place in developing countries. CISM is committed to the fifth Millennium Development Goal of improving global maternal health and has carried out studies on maternal and reproductive health since its early years of operation. This research programme is related mainly to the centre's Malaria and HIV/AIDS areas.

MAIN RESEARCH LINES

One of the Ministry of Health's top priorities is to reduce maternal and infant mortality. CISM's research efforts in this area have a cross-cutting focus and seek to reduce the impact of various diseases that threaten the lives of mothers and children. The centre has carried out a number of different studies in the following areas:

- Evaluation of alternative drugs for Intermittent Preventive Treatment in pregnancy (IPTp)
- Mother-to-child transmission of HIV and interactions with malaria
- Childhood anaemia
 - Aetiology of and risk factors for anaemia in children
 - Diagnosis of iron deficiency in children exposed to a high prevalence of infections
 - Mechanisms underlying malaria-related erythropoiesis suppression and its peripheral blood biomarkers using novel flow cytometric analysis and a transcriptional profile based on erythroblastoid-specific gene expression
- Breast milk
 - Influence of malaria parasites and haemozoin on bone marrow
 - Detection of immature gametocytes of *Plasmodium falciparum* in bone marrow using molecular techniques
- Breast milk
 - Breast milk microbiota and its interaction with HIV
 - Studies on breast milk concentrations of dichlorodiphenyltrichloroethane (DDT) and related compounds
- Pharmacovigilance
 - Safety of new drugs and vaccines before commercialisation and in the early postmarketing years
 - Development of the WHO Pregnancy Registry





MAIN FINDINGS

- CISM concluded the Malaria in Pregnancy Prevention Alternative Drugs (MiPPAD) study whose objective was to evaluate the efficacy and safety of alternative medicines to prevent malaria in HIV positive and HIV negative pregnant women. Two multicentre studies enrolled over 1,700 pregnant women between 2009 to 2013 in the CISM study area. Data analysis is underway and it is anticipated that the results will be published in results will inform WHO guidelines and provide guidance for public health strategies for the prevention of malaria in pregnancy in countries where this disease is endemic

- Women with HIV RNA in their breast milk were found to have a different pattern of microbiological composition, a finding suggestive of a specific immunopathological phenomena in HIV-infected women.

- With regard to DDT exposure in pregnant women, number of births was found to be associated with significant differences in the concentrations of DDT and related compounds in breast milk, with higher levels occurring in primiparae than multiparae.

- Studies showed that malaria infection, wasting, prealbumin and albumin deficiencies, HIV infection and iron deficiency were the main causes of anaemia in Manhiça. In contrast to similar studies, iron deficiency accounted for more than half of anaemia cases. Bone marrow examination showed that iron deficiency was extremely common in children exposed to an environment characterised by a high prevalence of infections. Haemozoin in bone marrow was independently associated with decreased haemoglobin concentration and was more common in dyserythropoietic bone marrow; this finding suggests that haemozoin in bone marrow plays a role in the pathogenesis of malarial anaemia through ineffective erythropoiesis.

TOTAL NUMBER OF PUBLICATIONS:

9

- Preventing iron deficiency could have a significant impact by reducing the burden posed by iron deficiency in HIV-care settings. Effective treatment and strategies for the prevention and management of these conditions need to be reinforced.
- A retrospective study of drug exposure during pregnancy showed that exposure to drugs (including drugs with recognised potential for risk during pregnancy) was high in this rural area of southern Africa. The association of stillbirths with drug exposure may have been a consequence of the disease that prompted drug administration, but it cannot be excluded that the drugs themselves were the direct cause. These findings highlight the need to reinforce pharmacovigilance systems in rural Africa, especially—or at least—in pregnant women. We participated in the development of the WHO Pregnancy Registry, a tool that improves health outcomes and facilitates the timely assessment and management of newborn infants and the collection of reliable clinical data. While improving maternal and neonatal care, the registry also provides much-needed information on the safety of medicines in pregnancy.

KEY PUBLICATIONS

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RESEARCHERS AND LABORATORY TECHNICIANS

Khátia Munguambe, Rui Anselmo, Helena Boene, Maria Maixenchs, Carolina Mindu, Lina Fiosse, Elpidia Pedro, Elisa Sicuri

CISM has contributed greatly to the assessment of the efficacy of innovative disease control interventions. However, the effectiveness of interventions is also determined by acceptability, access, uptake, cost and equity issues.

MAIN RESEARCH LINES

- Community perceptions of health and illness
- Determinants of care-seeking behaviours
- Acceptability of interventions
- Social determinants of health and the demand for health care services

MAIN FINDINGS

On perceptions of febrile and respiratory illness:

- Chest conditions are considered to be chronic and hereditary, and an acute respiratory infection (ARI) episode is seen as an attack (an exacerbation of a chronic illness).
- When a person has a chest condition, fever is the only symptom that triggers care-seeking behaviour at the hospital. Interventions promoting health should take these contradictory beliefs into account when explaining ARIs in the context of behaviour related to care-seeking for children. Explanations should use lay interpretations and terms to emphasise the importance of seeking hospital care for all conditions considered locally to be chest illnesses, and the importance

of seeking care for any exacerbation of an already-diagnosed chest condition.

- Health messages about ARIs should therefore be ongoing and evidence-based, even when ARIs appear to be well understood.

Concerning malaria control through community-based interventions (the case of indoor residual spraying):

- Beneficiaries do not fully appreciate the contribution of indoor residual spraying to malaria and mosquito control, preferring instead other cost-effective interventions such as insecticide-treated nets.
- Adherence to indoor residual spraying was found to be influenced by socio-political factors.
- Community awareness-raising approaches need to be redefined to make indoor residual spraying a genuinely participatory, acceptable and sustainable programme.

On perceptions of malaria in pregnancy and the acceptability of malaria control through intermittent preventive treatment in pregnancy:

- Low awareness of the risks and adverse consequences of malaria in pregnancy did not seem to affect the acceptability or uptake of the various malaria prevention interventions.
- Perceived convenience, the delivery method chosen, and type of care provider were key factors. Through antenatal care services, pregnant women can be vehicles for the distribution of insecticide-treated nets in communities and can help to improve overall coverage.

TOTAL NUMBER
OF PUBLICATIONS:

6

- Knowledge about neonatal health and malaria needs to be improved to increase the uptake of interventions delivered through channels other than health facilities.

KEY PUBLICATIONS

- Bassat Q, Ordi J, Vila J, Ismail MR, Carrilho C, Lacerda M, Munguambe K, Odhiambo F, Lell B, Sow S, Bhutta ZA, Rabinovich NR, Alonso PL, Menéndez C. Development of a post-mortem procedure to reduce the uncertainty regarding causes of death in developing countries. *Lancet Global Health*. (2013).
- Munguambe K, Pool R, Montgomery C, Bavo C, Nhacolo A, Fiosse L, Sacooc C, Nhalungo D, Mabunda S, Macete E, Alonso P. What drives community adherence to indoor residual spraying (IRS) against malaria in Manhica district, rural Mozambique: a qualitative study. *Malar J*. (2011) 10:344.
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DEPARTMENTS

DEMOGRAPHY

Director: Charfudin Sacoor

The Demographic Surveillance System (DSS) is a crucial component of our health care research. It provides demographic indicators as well as reliable and accurate data, allowing us to measure the impact of interventions, to locate and follow-up study participants, to monitor demographic trends in the population, and to create accurate disease distribution maps of the study area.

The DSS currently covers an area of approximately 500 km² and follows a population of about 95,000 inhabitants living in some 20,000 households. All the houses in the study area are identified by GPS coordinates and every resident is identified by a unique identification number.

Demographic information is collected through three basic procedures: household visits, maternity and morgue visits to collect data on births and deaths, and contact with key community informants.

In 2012, the Demography Department introduced a mobile biometric solution for gathering demographic data. This new system reduces the number of paper forms required, automates data collection processes, and introduces useful new variables such as children's immunisation status and the origin and destination of migrations. These devices use fingerprint readers and GPS coordinates for identification.

In 2013, the department reduced the number of household visits from two to one per year. In order to ensure data reliability, the number of visits to health units and key informants in the community was increased. This year CISM has also introduced automated computerised coding and assignment of cause of death for verbal autopsies, a task previously performed by the centre's medical staff.

TOTAL NUMBER OF PUBLICATIONS:

3

Like other centres in the INDEPTH network, CISM's Department of Demography published demographic data for the past several years in June 2013 (www.indepthshare.org/indepthstats).

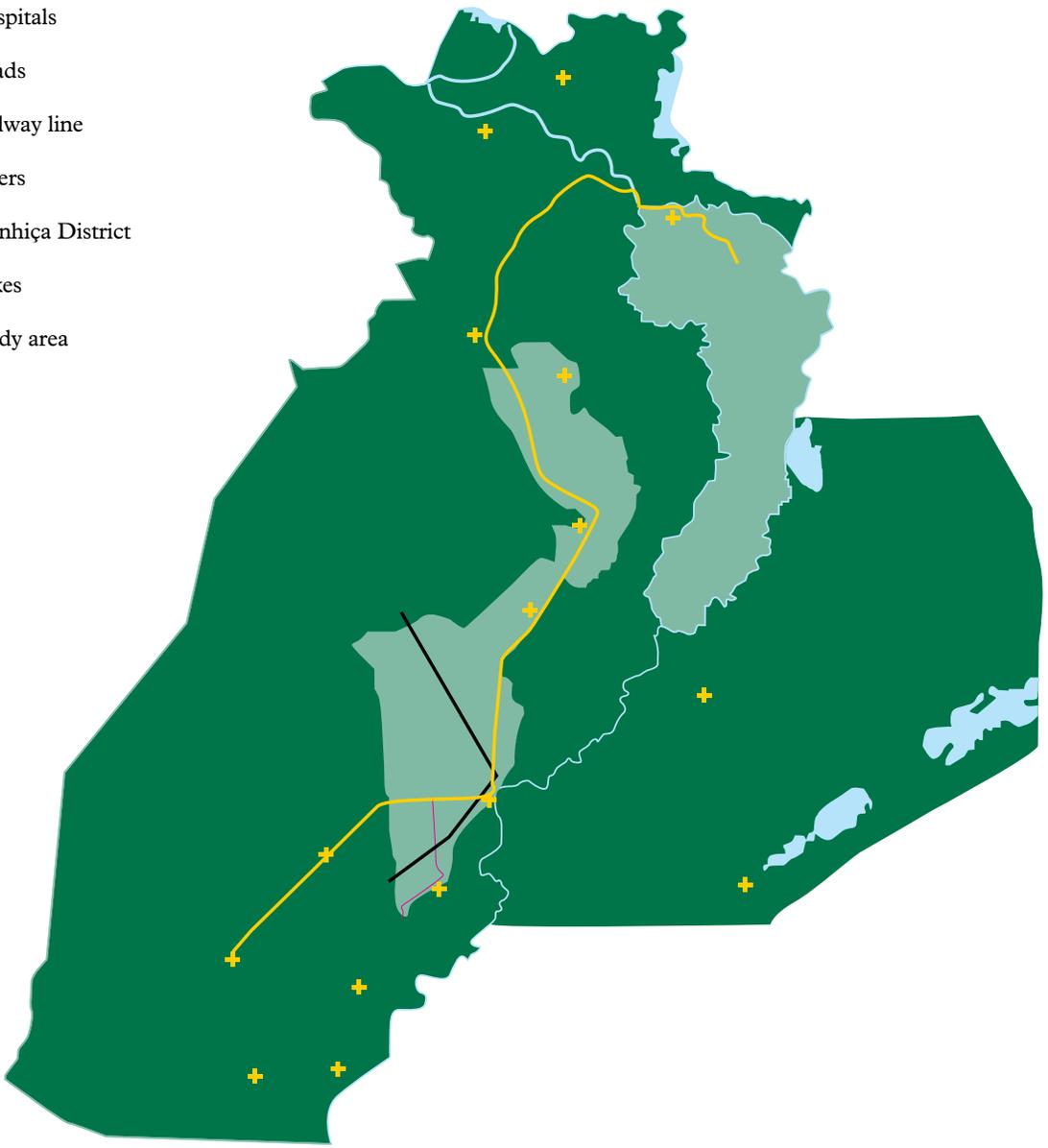
PUBLICATIONS

- Charfudin Sacoor, Ariel Nhacolo, Delino Nhalungo, John J Aponte, Quique Bassat, Orvalho Augusto, Inácio Mandomando, Jahit Sacarlal, Natu Lauchande, Betuel Sigauque, Pedro Alonso, and Eusébio Macete - Profile: Manhiça Health Research Centre (Manhiça HDSS). *International Journal of Epidemiology*: 2013; 42:1309–1318.
- Charfudin Sacoor, Orvalho Augusto, John J Aponte, Jahit Sacarlal, Ariel Nhacolo, Delino Nhalungo, Clara Menendez, Eusébio Macete, and Pedro Alonso - Using a verbal autopsy technique to determine the underline causes of maternal death in Manhiça District in Mozambique. Paper presented in the Second Global Congress on Verbal Autopsy, Rhodes (Greece), October 14 -16, 2013.
- Annette Gerritsen, Philippe Bocquier, Michael White, Cheikh Mbacké, Nurul Alam, Donatien Beguy, Frank Odhiambo, Charfudin Sacoor, Ho Dang Phuc, Sureeporn Punpuing, Mark A. Collinson - Health and demographic surveillance systems: contributing to an understanding of the dynamics in migration and health. *Global Health Action* 2013, 6: 21496.



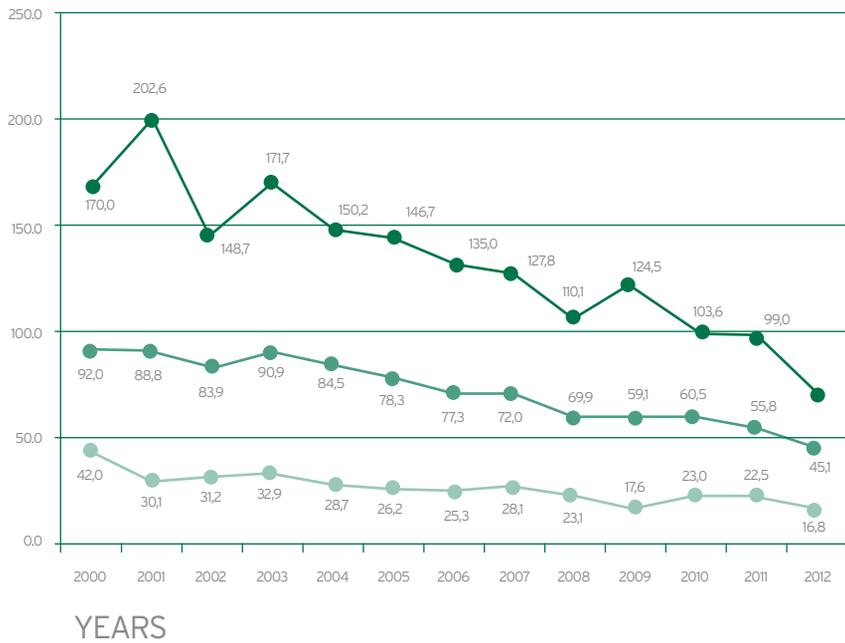
CISM STUDY
AREA

- ✚ Hospitals
- Roads
- Railway line
- Rivers
- Manhiça District
- Lakes
- Study area



MORTALITY TRENDS IN THE CISM STUDY AREA

PER 1,000 LIVE BIRTHS



- Mortality rate in infants <5
- Child mortality rate
- Neonatal mortality rate

LABORATORY

Director: Hélder Bulo

CISM's current laboratory capacity reflects our growth in recent years. The Laboratory Department is divided into four sections: Clinical Analysis (blood parasitology, haematology and biochemistry), Microbiology (general bacteriology and mycobacteriology), Immunology, and Molecular Biology. The core objectives of the department are to support research activity and contribute to the centre's clinical work by providing a testing service for patients who require laboratory analyses. The centre has been working continuously to maintain and improve its quality levels. To do this, we use international standards including the Good Clinical Laboratory Practice concept and International Organization for Standardization (ISO).

Data collected by the CISM laboratory helped the Ministry of Health to justify the introduction of new preventive tools, such as the Hib and PCV10 vaccines. The laboratory has also contributed to the training of technical personnel from the national health system and other partners, as well as to the monitoring and evaluation of a demographic health survey and studies on the effectiveness of antimalarial medicine.

NUMBER OF SAMPLES PROCESSED BY TYPE

| Type | Number of Samples Processed |
|------------------------------|-----------------------------|
| Clinical Analyses | |
| Parasitology | 185,942 |
| Haematology/ Biochemistry | 16,531 |
| Microbiology | |
| Bacteriology | 14,199 |
| TB | 13,631 |
| Immunology | 12,353 |
| Molecular biology | 8,376 |

CLINICAL ANALYSES

BLOOD PARASITOLOGY

The blood parasitology unit investigates and diagnoses parasites in the blood. The work has been focussed on diagnosing malaria using optical microscopy.

HAEMATOLOGY AND BIOCHEMISTRY

The haematology and biochemistry unit performs complete blood counts with differential using a Sysmex XT2000i (main) and a Sysmex KX21-N (secondary) analyser. Vitros E350 and E250 analysers are used to perform biochemical studies.

MICROBIOLOGY

GENERAL BACTERIOLOGY

The general bacteriology unit makes bacteriological diagnoses in various types of samples, including blood, cerebrospinal fluid, pus, urine, faeces, and other bodily fluids. Bacterial pathogens are isolated and identified in cultured samples and antibiotic-resistant profiles are determined. This unit plays an important role in the programme established in 1998 to monitor invasive bacterial infections.

TUBERCULOSIS

The TB unit, which opened in 2010, processes liquid and solid cultures to identify *Mycobacterium tuberculosis*. The unit's level III laboratory made it a pioneer in the country; a MGIT 960 mycobacterial detection system is used to grow and detect the pathogens and to perform susceptibility testing to identify treatment-resistance disease.

IMMUNOLOGY

The immunology unit works towards improving our understanding of the mechanisms of immune response to infectious agents and interventions such as vaccines and drugs. The laboratory has the capacity to conduct basic studies to assess humoral and cell-mediated immune responses. The main focus is research, although the unit also occasionally supports the national health care system in the task of determining CD4 counts in HIV positive patients at Manhiça District Hospital.

MOLECULAR BIOLOGY

The molecular biology unit performs diagnostic and molecular epidemiology studies using polymerase chain reaction assays, investigates disease outbreaks, and studies the clonality of pathogens. It also provides substantial support to the national health system in the early diagnosis of HIV infection and measuring viral load.

QUALITY ASSURANCE

The quality assurance area centralises all activities related to the control and supervision of processes, analyses, quality control, documentation management, staff training, and so on. It applies international standards such as Good Clinical Practices, Good Clinical and Laboratory Practice, and ISO.

DATA CENTRE AND INFORMATION TECHNOLOGY

Directors: Boaventura Cuna and Vivaldi Nobela

The Data Centre and the Information Technology unit are closely related in their day-to-day operation. The Data Centre manages the data from all of CISM's studies and the morbidity surveillance system that supports each project. It ensures that data from projects and the morbidity surveillance system are entered, cleaned and stored according to established protocols.

Between 2011 and 2013, the Data Centre improved its assistance to researchers by introducing new data management techniques and improving existing methods. The CISM Data Centre also coordinated the database of a multicentre study for the first time.

The Information Technology unit is responsible for the maintenance of the internal and external communications infrastructure. It is also responsible for the data backup system for the centre as a whole. To improve Internet access, a structured wireless network has been installed facilitating adequate access to CISM's entire biomedical and clinical software infrastructure to up to 600 simultaneous users.

The server infrastructure has been modernised with the installation of a structured data centre infrastructure with several multi-core servers based primarily on open-source technology. This scalable system supports a gigabit network with fibre-optic connections between the buildings. CISM is now equipped with a total of 15 servers and 150 computers.

Data capture in the centre's demographic surveillance work has been automated through the use of personal digital assistants, mobile phones and tablets. Finally, the bandwidth of the centre's Internet connection has been increased.

DATA CENTRE FIGURES

| | 2011-2012 | 2013 |
|---|-----------|---------|
| Questionnaires processed | 522,652 | 251,815 |
| Staff | 26 | 20 |
| Specialised technical staff | 3 | 2 |
| Technical staff in post-graduate training | | 1 |

CLINICAL SERVICES

Director: Sónia Maculuve

The Clinical Services Department is responsible for the centre's morbidity surveillance system and other activities that support the research being carried out by health centres in the study area. Six health centres—located in Maragra, Tanginga, Palmeira, Ilha Josina Machel and Malavele—and Manhiça District Hospital are all involved in the morbidity surveillance programme.

In the past 3 years, the epidemiological profile of major diseases such as malaria has changed considerably and this is reflected in the number of doctor's appointments and other medical care.

The medical unit provides care for the most vulnerable groups: pregnant women and children and related groups, such as malnourished individuals and patients with TB. The service has also supported the construction, rehabilitation and maintenance of the local health units mentioned above, and occasionally provides drugs when supplies have run out.

CISM has been working with the national health authorities on the implementation of national health programmes. It is currently supporting the implementation of national programmes for the control of sexually transmitted infections, HIV/AIDS and TB, an initiative supported by the Catalan Agency for Development Cooperation (Spain) and the AERAS Global TB Vaccine Foundation. The aim of these activities is to ensure the quality of information, education, communication, counselling and health testing, and to support the Vertical Transmission Prevention Programme.

The clinical units are an internship rotation point for students from the Faculty of Medicine at Eduardo Mondlane University and for trainees from countries where the diseases common to Mozambique are not present.

| Indicator | 2011 | 2012 | 2013 |
|---|-------------|-------------|-------------|
| No. of external paediatric consultations | 80,904 | 87,301 | 83,563 |
| No. of patients admitted to the paediatric ward | 2,658 | 2,475 | 2,276 |
| Intra-hospital mortality rate (children) | 4% | 3,40% | 2,89% |
| No. of deaths from malaria (age < 15 years) | 22 | 24 | 17 |
| No. of HIV tests (children and adults) | 4,247 | 3,729 | 14,747 |

Technical Assistance

Director: Sónia Maculuve

Improving health care in Manhiça District is one of CISM's priorities. The centre works with Manhiça Health Centre, Manhiça District Hospital and the national health authorities to ensure that communities benefit from its presence and research findings.

CISM works together with the Ministry of Health to combat malaria, one of the major challenges for public health and sustainable development in Mozambique. The centre's work on malaria has contributed to the development and evaluation of new control strategies. For the past 3 years, CISM has taken part in clinical trials of the RTS,S malaria vaccine, which has twice been called the scientific discovery of the year by the journal *Science* (2004 and 2011). A regulatory application will be submitted for RTS,S to the European Medicines Agency in 2014. In collaboration with Mozambique's National Programme for Malaria Control, CISM is studying the effectiveness of antimalarial medicine, new medicines for malaria prevention in pregnant women, and the first protocols outside of Manhiça District. In another project with the National Programme for Malaria Control, the centre is leading an ambitious regional initiative to eliminate malaria (zero transmissions and infections) in Mozambique, Malawi, Swaziland, South Africa and Zambia.

In addition to collaborating in the fight against malaria, over the past 3 years CISM has also worked alongside the Ministry of Health—with support from international organisations such as the Global Alliance for Vaccines and Immunisation (GAVI Alliance)—to enlarge the Expanded Programme on Immunisation. The pneumococcal conjugate vaccine, which protects against pneumococcal infection, was introduced in Mozambique as part

of this programme. This measure ensured the support of the GAVI Alliance and was made possible by surveillance data supplied by CISM research projects. The centre's morbidity surveillance system was also used to assess the impact of the introduction of the Hib vaccine on invasive diseases caused by Hib and pneumonia.

CISM is currently working with civil society organisations, research institutions, the Ministry of Health and the Ministry of Education to assess the acceptability and feasibility of implementing an HPV vaccination programme targeting 10-year-old girls in rural and urban areas of Mozambique. Because most countries lack a track record in the implementation of school-based advanced vaccine programmes, they are asked to carry out demonstration projects before the vaccine is introduced. The results of these projects enable governments to make decisions regarding the nationwide introduction of the vaccine. CISM and other institutions have supported the Ministry of Health by demonstrating the feasibility of vaccinating 10-year-old girls against HPV in Manhiça District, thereby ensuring the GAVI Alliance's support for the introduction of the HPV vaccine.

In collaboration with the National Programme for Tuberculosis Control, the South African Tuberculosis Vaccine Initiative in Cape Town (South Africa), the Kenya Medical Research Institute (KEMRI/CDC) in Kisumu (Kenya) and the Perinatal HIV Research Unit at Chris Hani Baragwanath Hospital, CISM started a Phase II clinical trial of the TB candidate vaccine AERAS-402 in children.

Director: Teresa Machai

The training of young researchers and technical staff has been a core strategic activity of CISM since its creation. Apart from being crucial to ensuring the centre's sustainability, these training activities contribute to the development of health research skills in Mozambique. The development of such skills are crucial to Mozambique's progress, especially in the areas of health and research.

CISM is dedicated to developing Mozambique's human resources by investing in the training of researchers and technical staff in collaboration with national and international academic institutions, such as Eduardo Mondlane University, the University of Barcelona, and ISGlobal.

TRAINING FELLOWSHIP PROGRAMME

The Training Fellowship Programme has been one of the most successful training initiatives run by the centre in recent years. In this programme, young graduates from Mozambique and elsewhere in sub-Saharan Africa with the potential to become researchers are trained in health care and related fields. The course is organised jointly with CRESIB, ISGlobal's research centre, where the students do their internships and attend conferences during their training.

As part of their training, the participants acquire direct experience of research methodology by participating in CISM's research projects and by doing post-graduate studies at the Master and/or PhD level at internationally recognised universities. The programme also provides students an opportunity to complete internships at international universities, research centres and other institutions.

More than 30 researchers have taken part in the Training Fellowship Programme to date; of these, 17 have obtained their masters, 14 have received a doctorate and 3 have completed their specialist training. There are currently 5 people in the programme.

POST-DOCTORAL TRAINING

CISM facilitates post-doctoral training at partner research centres for researchers who have completed a Training Fellowship and then joined the centre's research team. Between 2010 and 2012, Dr Inácio Mando-mando, a specialist in the area of diarrhoeal diseases and invasive bacterial infections, completed his post-doctoral research in the United States at the Centre for Vaccine Development, the University of Maryland in Baltimore and the University of Virginia School of Medicine in Charlottesville.

ROTATIONS AND INTERNSHIPS FOR STUDENTS AND HEALTH CARE PROFESSIONALS

CISM provides internship places for students, resident physicians, and other health professionals. The interns have the opportunity to work with CISM's teams on research projects and in health care settings. The centre has an agreement with the Faculty of Medicine at Eduardo Mondlane University to coordinate and supervise medical students during their rural and integrated internships at Manhiça District Hospital. Likewise, under an agreement with the Veterinary Faculty, CISM offers internships involving research and teaching activities to the faculty's top graduate students.

Between 2011 and 2013, CISM hosted:

- 41 international interns from various countries including Spain, the Netherlands, Germany, Australia, Brazil and the United States



- 54 student interns from the Faculty of Medicine and 2 graduate students from the Veterinary Faculty of Eduardo Mondlane University in Mozambique
- 25 students taking a Masters in Field Epidemiology and Laboratory Studies from various public institutions in Mozambique
- 2 senior technicians from the Centre for Infectious Disease Research at the Catholic University of Mozambique
- 1 pharmacy student from the Higher Institute of Science and Technology of Mozambique
- 16 technicians, of whom 9 were from the National Malaria Reference Laboratory of the National Health Institute of Mozambique
- 8 technicians from the National Health Institute who work for the Polana Caniço Health Centre

TRAINING OF TECHNICAL PERSONNEL IN SCIENCE AND HEALTH CARE

CISM trains technical personnel through on-site courses and courses at other institutions.

Between 2011 and 2013, 72 short courses were organised. The courses that took place most frequently were Good Clinical Practice, Good Clinical and Laboratory Practices, biostatistics, financial management, data management and introduction to clinical research, project management and ethics, clinical trials monitoring, laboratory techniques, and basic paediatrics. Some of these were held at CISM and others took place in Maputo, South Africa, Ghana, Botswana, Burkina Faso, Spain and the United States.

OTHER TRAINING PROGRAMMES

- CISM is a member of **Trials of Excellence in Southern Africa (TESA)**, a network of excellence sponsored by the European & Developing Countries Clinical Trials Partnership to speed up the development of new clinical interventions against HIV/AIDS,

TB and malaria. The aim of the network is to build the capacity of participating centres so that they can establish common platforms for conducting clinical trials and adopt similar quality standards, ethical procedures and good clinical practices. Since 2012, CISM has also been involved in research within the framework of the TESA I project, particularly in the field of TB. Starting in 2014, CISM will be coordinating TESA II. The centre is now preparing multi-ethnic projects to be conducted in collaboration with various TESA centres in the areas of malaria, TB and HIV/AIDS.

- **Training and Resources in Research Ethics Evaluation for Africa (TRREE for Africa).** The aim of this project is to make available tools and information on research and ethics that will facilitate the sharing of knowledge and experiences between European and African countries. Within the scope of the project, three modules (I, II and III) were created. These modules describe Mozambique's ethics and research procedures as well as the country's ethics and research laws and regulations (with translations).

- **Collaboration with IESE Business School:** A case study on CISM and the Manhica Foundation was prepared for use in business schools, universities, MBA programmes and executive education.

- **Teaching Activities:** A number of CISM researchers have lectured in undergraduate and graduate courses at Eduardo Mondlane University, the Regional Centre for Health Development in Mozambique and the University of Barcelona.

COMPLETED PHDs

- Diana Quelhas “*Impact of Intermittent Preventive Treatment with Sulfadoxine-Pyrimethamine on immune responses to Plasmodium falciparum Antigens in Mozambican Infants*”, Universitat de Barcelona, Spain (2011)
- Nélia Manaca “*Exposure to organochlorine compounds at the early stages of DDT use for indoor residual spraying in domestic environments in Manhica, Mozambique*”, Universitat Pompeu Fabra, Spain (2011)
- Pedro Aide “*Safety, immunogenicity and duration of protection of a candidate malaria vaccine in Mozambique*”, Universitat de Barcelona, Spain (2011)
- Tacilta Nhampossa, “*Epidemiologia das diarreias: determinação do peso, etiologia e sequelas das diarreias em menores de 5 anos no distrito da Manhica, Moçambique*”, Universitat de Barcelona, Spain (2013)

COMPLETED MA's

- Augusto Nhabomba, “*Infectious and immunity*”, University of Sidney, Australia (2012)
- Charfudin Sacoer, “*Population Based Field Epidemiology*”, University of Witwatersrand, South Africa (2011)
- Luis Morais, “*Biotecnologia em Saude e Medicina Investigativa*”, Centro de pesquisa Gonzalo Muniz, Fundação FIOCRUZ, Brasil (2012)
- Leonel Monteiro, “*Detecção de mecanismos moleculares de resistência aos antimicrobianos em Escherichia coli enterotoxigénica isoladas de crianças menores de 5 anos no distrito da Manhica*”, Universidade Eduardo Mondlane, Mozambique (2012)

COMPLETED UNDERGRADUATE DEGREES

- Eva Dora, “*Incidência da infecção por rotavirus e identificação dos genótipos circulantes em crianças menores de 5 anos com diarreia aguda no Hospital Distrital de Manhica*”, Universidade Eduardo Mondlane, Mozambique (2013)
- Marcelino Garrine, “*Prevalência e Sustentabilidade aos antibióticos de Escherichia Coli enterohemorrágica, enteroinvasiva e difusa-aderente em crianças com menos de 5 anos no distrito de Manhica*”, Universidade Eduardo Mondlane, Mozambique (2013)

PHDs IN PROGRESS

- Augusto Nhabomba, PhD in Medicine, University of Barcelona, Spain (2013)

MA's IN PROGRESS

- Arsenio Nhacolo, MA in Statistics, Bio-statistics, University of Hasselt, Belgium (2013)

- Delfino Vubil, MA in Cellular and Molecular Biology by the University of Coimbra, Portugal (2013)

- Helena Boene, MA in Public Health, London School of Hygiene & Tropical Medicine, UK (2012)

- Sozinho Acacio, MA in Clinical Research-specialization in International Health, University of Barcelona, Spain (2013)

CONTRIBUTIONS TO PHD STUDIES BY EXTERNAL COLLABORATORS

Within the framework of the close collaboration between CISM, ISGlobal and CRESIB (ISGlobal's research centre), several PhD theses by external researchers were written partly at CISM.

- Celia Serna Bolea, “*Epidemiología de las fases tempranas de la infección por el VIH en pacientes ambulatorios de una zona semi-rural del sur de Mozambique*”, University of Barcelona, Spain (2012)

- Emili Letang Jiménez-de- Anta, “*Characterization of immune reconstitution inflammatory syndrome (IRIS) and Kaposi's sarcoma-associated IRIS after initiation of antiretroviral treatment in sub-Saharan Africa*”, University of Barcelona, Spain (2011)

- John Aponte Varón, “*Evaluation of tools to prevent malaria during the first years of life*”, University of Barcelona, Spain (2011)

- Eduard Rovira Vallbona, “*Malària durant l'embaràs: immunitat materna i expressió de gens implicats en la citoadhesió de Plasmodium falciparum*”, University of Barcelona, Spain (2011)

- Cristina O’Callaghan Gordo, “*Epidemiologia de les infeccions respiratòries víriques en pacients pediàtrics a Manhiça, una zona rural de Moçambic*”, University of Barcelona, Spain (2011)

- Núria Díez Padrisa, “*The use of biomarkers for the diagnosis of severe infections in rural Africa*”, University of Barcelona, Spain (2011)

MANHIÇA SENIOR RESEARCH FELLOWSHIP PROGRAMME

In order to define new models to attract and retain talent and human resources in Mozambique, CISM launched an innovative programme to provide an opportunity for top Mozambican researchers to pursue a scientific career in their own country. This programme, one of the few of its kind in Africa, is based on successful models developed in Europe and the United States. It is based on research excellence, regular external review processes and competitive salaries (a key element in preventing brain drain).

In addition, CISM has created the professional category of **Associate Senior Research Fellow**, a senior post-doctoral position affiliated with one of the institutions on the Manhiça Foundation’s Board of Governors. This category is applied to senior researchers who are partially involved in research programmes carried out at the centre.

Highlights 2011–2013

ANNUAL LECTURE ON GLOBAL HEALTH

Through CISM, the Manhiça Foundation aspires to play a key role in the generation and dissemination of knowledge related to major public health challenges at both the national and international levels. The Foundation's Annual Lecture on Global Health is organised to further this objective.

In 2011, as part of the celebration of CISM's 15th anniversary, the Manhiça Foundation organised the third edition of its Lecture on Global Health. The lecture—The Importance of Alliances in Facing Global Health Challenges—was delivered by **H.R.H. The Infanta Cristina de Borbón**, President of ISGlobal's Board of Trustees. In 2012, the 4th edition of the lecture, entitled *Miracles of Science: Vaccines and Ensuring Access for All*, was given by **Dr Seth Berkley**, CEO of the GAVI Alliance. In 2013, the fifth edition of the lecture—Addressing Unmet Needs in Global Health: Progress and Opportunities—was delivered by **Dr Trevor Mundel**, President of the Global Health Programme at the Bill & Melinda Gates Foundation.

RESULTS OF THE PHASE III STUDY OF THE RTS,S MALARIA VACCINE

A large-scale phase III study published in November 2012 in the *New England Journal of Medicine* found that the RTS,S malaria vaccine candidate may help to protect African children against malaria. The study found that children immunised with RTS,S (aged between 6 and 12 weeks at the time of the first immunisation) had one-third fewer episodes of both clinical and severe malaria than children who received the control vaccine. Both groups had similar reactions to the vaccination. The results showed the RTS,S vaccine had an acceptable safety and tolerance profile.

This trial was conducted in seven African countries at eleven research centres—including CISM in Mozambique—in collaboration with GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative with grant funding from the Bill & Melinda Gates Foundation.

11TH INDEPTH SCIENTIFIC CONFERENCE

CISM hosted the 11th INDEPTH Scientific Conference from 24 to 27 October 2011. The theme of the conference was Increasing the Productivity and Utilisation of Health and Demographic Surveillance System Data for Public Health in Low- and Middle-Income Countries. The conference brought together over 300 researchers from the network, representing 42 institutions in Africa, Asia and Oceania. It was opened by His Excellency the President of the Republic, Armando Guebuza. CISM has been a member of INDEPTH since 2011, and the director of the centre, Dr Eusébio Macete, is the vice chair of its board of trustees.

BACTERIOLOGY AND PARASITOLOGY UNITS CERTIFIED AS LABORATORIES OF EXCELLENCE

Between 2012 and 2013, CISM's Bacteriology and Parasitology units were classified as Laboratories of Excellence in the diagnosis of bacterial infections and malaria. These certificates, awarded by the NHLS National Institute for Communicable Diseases in South Africa and by the NICD National Institute for Communicable Diseases, demonstrate the quality of the data produced by the laboratory.

VISITS

During the period covered by this report, CISM had the honour of hosting several visitors interested in learning about the centre's research activities.

In October 2013, the **First Lady of Mozambique**, Dr Maria da Luz Dai Guebuza, visited CISM during the launch of the study on the feasibility and acceptability of introducing the HPV vaccine in the districts of Manhiça and KaMavota. This study was an essential precursor to the introduction of this vaccine in Mozambique.

In April 2013, 15 years after her first visit to CISM, **Her Majesty Queen Sofia of Spain** came back to witness the centre's achievements and progress to date. Her Majesty was accompanied by a delegation of approximately 30 people, including the Ambassador of Spain to Mozambique, the Secretary of State for International Cooperation and for Ibero-America, the Director of Cooperation for Africa and Asia, and the Ambassador of Mozambique to Spain.

On 9 November 2012, to mark the **Southern African Development Community (SADC) Malaria Day**, CISM had the pleasure of receiving 14 ministers and senior staff from the SADC Secretariat. The 160-person delegation was interested in learning about the centre's activities and understanding its importance in research for development.

The **Regional Director of the WHO for Africa**, Dr Luis Gomes Sambo, visited CISM on 18 September 2012. He was

accompanied by the WHO Representative in Mozambique, the National Director for Public Health of the Ministry of Health of Mozambique, and other members of the WHO team.

The centre had the privilege and honour of receiving His Excellency the **President of the Republic of Mozambique, Armando Guebuza**, on 20 May 2012.

Despite being a young institution, CISM has become a key player in the field of health research both in Mozambique and internationally. Today, it is one of Mozambique's leading contributors to the implementation of new tools to combat the diseases that affect developing countries. The centre has earned an excellent reputation and recognition from local authorities as well as national and international partners owing to its high-quality scientific output, support for health care, investment in training Mozambican human resources, and work in supporting evidence-based public health policies. This is reflected on a national level in its ability to influence the public health domain through strategic advice and partnerships and through activities for the promotion of global health.

The results achieved by CISM and the Manhiça Foundation over the past 3 years reflect their effort to improve and develop partnerships with the Mozambican government as well as with national and international institutions to promote health care, training and biomedical research.

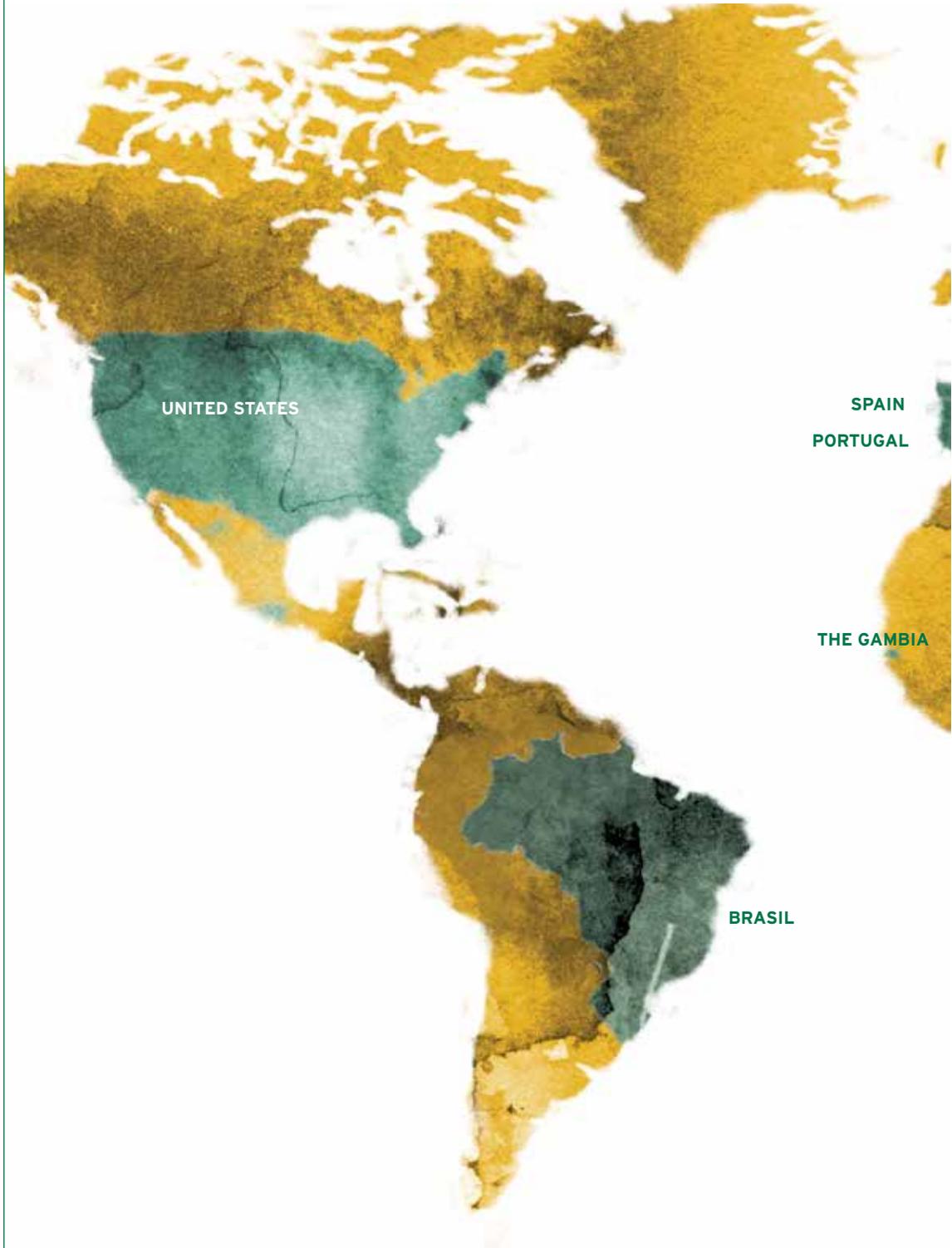
CISM collaborates with **9 national institutions and over 40 international organisations in 19 countries in Africa, Europe, the Americas, Asia and Oceania**. The centre's most important alliances are with the following institutions:

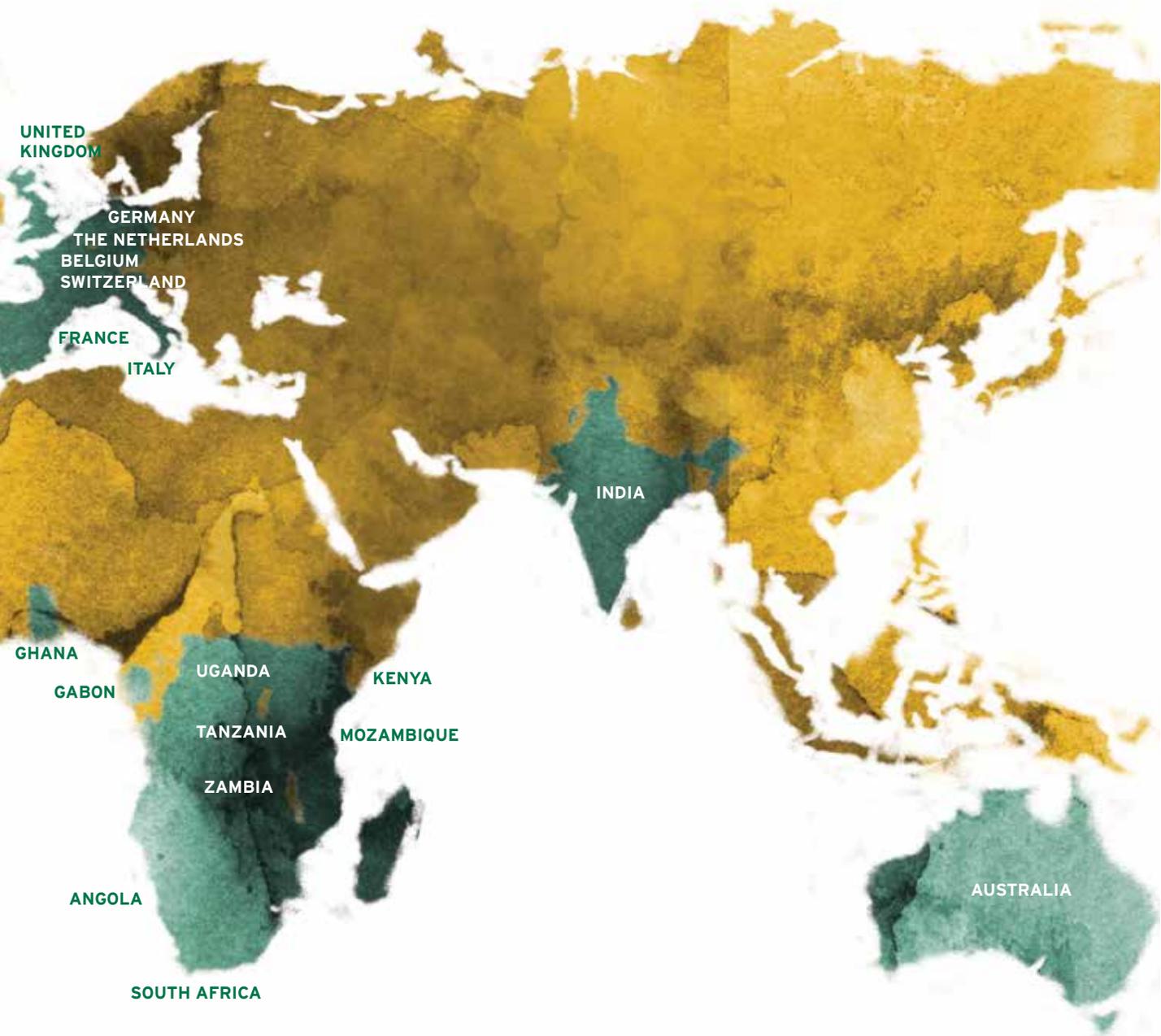
- Africa Centre for Health and Population Studies (South Africa)
- Barcelona Institute for Global Health - ISGlobal (Spain)
- Centre for Vaccine Development, University of Maryland School of Medicine (United States of America)
- Centres for Disease Control and Prevention - CDC (United States of America)
- GlaxoSmithKline Biologicals (Belgium)
- HIV Prevention Research Unit, Medical Research Council South Africa (South Africa)
- Ifakara Health Institute (Tanzania)
- Institute of Tropical Medicine Antwerp (Belgium)
- International Center for Genetic Engineering and Biotechnology (India)
- International Network of Field Sites with Continuous Demographic Evaluation of Populations – INDEPTH (Ghana)
- International Partnership for Microbicides (United States of America)
- Irsicaixa (Spain)
- Johns Hopkins Bloomberg School of Public Health (United States of America)
- Kenya Medical Research Institute – KEMRI (Kenya)
- London School of Hygiene and Tropical Medicine (United Kingdom)
- Makerere University (Uganda)
- Medical Research Council Durban (South Africa)
- Medical Research Council Unit, (The Gambia)
- Medical Research Unit, Albert Schweitzer Hospital (Gabon)
- Novartis Pharma (Switzerland)
- PATH Malaria Vaccine Initiative - MVI (United States of America)
- Sanofi Pasteur (France)
- School of Paediatrics and Child Health, University of Western Australia (Australia)
- Sigma-Tau Pharmaceuticals (Italy)
- South African Tuberculosis Vaccine Initiative - SATVI (South Africa)
- Swiss Tropical Institute (Switzerland)
- The Walter and Eliza Hall Institute of Medical Research (Australia)

CISM receives funding from a number of institutions and agencies, namely:

- AERAS Global TB Vaccine Foundation
- Africa Viva Fundació
- Agència Catalana de Cooperació al Desenvolupament (ACCD)
- Agencia Española de Cooperación Internacional para el Desarrollo (AECID)
- Agencia de Cooperación Internacional de Las Illes Balears (ACIIB)
- Bill & Melinda Gates Foundation
- European and Developing Countries Clinical Trials Partnership (EDCTP)
- European Union (EU)
- Fondo de Investigación Sanitaria (FIS), Instituto de Salud Carlos III
- Fundo Nacional de Investigaçã (FNI), Governo de Moçambique
- Ministério da Ciência e Tecnologia, Governo de Moçambique
- Ministério de Saúde, Governo de Moçambique
- Fundació “la Caixa”
- Generalitat de Catalunya
- Instituto Nacional de Saúde (INS)
- International Union Against Tuberculosis and Lung Disease
- Jomaa Pharma GmbH
- Malaria Clinical Trials Alliance (MCTA)
- Ministério da Saúde, Governo de Moçambique
- PATH Malaria Vaccine Initiative (MVI)
- PneumoADIP
- The Hib Initiative
- Trials of Excellence in Southern Africa (TESA)
- Universidad Eduardo Mondlane (UEM)
- World Health Organization (WHO)

**COUNTRIES THAT
COLLABORATE WITH CISM**





UNITED KINGDOM

GERMANY
THE NETHERLANDS
BELGIUM
SWITZERLAND

FRANCE
ITALY

INDIA

GHANA
GABON
UGANDA
KENYA
TANZANIA
MOZAMBIQUE
ZAMBIA

ANGOLA

SOUTH AFRICA

AUSTRALIA

List of Publications 2013-2011

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- Castillo, P., C. Menendez, A. Mayor, et al. "Massive *Plasmodium falciparum* visceral sequestration: a cause of maternal death in Africa." *Clin Microbiol Infect* (2013): Ahead of print.
- Chaccour, C. J., K. C. Kobylinski, Q. Bassat, T. Bousema, C. Drakeley, P. Alonso, and B. D. Foy. "Ivermectin to reduce malaria transmission: a research agenda for a promising new tool for elimination." *Malar J.* 12.1 (2013): 153.
- Clifford, H. D., C. M. Hayden, S. - K. Khoo, et al. Impact of CD14 promoter variants on measles vaccine responses and vaccine failure in children from Australia and Mozambique., 2013.
- Herrmann, M., S. Abdullah, A. Alabi, et al. "Staphylococcal disease in Africa: another neglected 'tropical' disease." *Future Microbiol.* 8 (2013): 17–26.
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- Le Polain de Waroux, O., J. R. A. Schellenberg, et al. "Timeliness and completeness of vaccination and risk factors for low and late vaccine uptake in young children living in rural southern Tanzania." *Int Health.* 5.2 (2013): 139–147.
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- Moncunill, G., A. Mayor, A. Bardaji, et al. "Cytokine Profiling in Immigrants with Clinical Malaria after Extended Periods of Interrupted Exposure to *Plasmodium falciparum*." *PLoS One.* 8.8 (2013): e73360.
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- Nasrin, D., Y. Wu, W. C. Blackwelder, et al. "Healthcare-Seeking for Childhood

Diarrhea in Developing Countries: Evidence from Seven Sites in Africa and Asia.” *Am J Trop Med Hyg* (2013): Ahead of print.

• Nhampossa, T., I. Mandomando, S. Acacio, et al. “Healthcare Use and Attitudes Survey in Cases of Moderate-to-Severe Diarrhea among Children Ages 0-59 Months in the District of Manhica, Southern Mozambique.” *Am J Trop Med Hyg* (2013): Ahead of print.

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• O’Callaghan-Gordo, C., Q. Bassat, N. Diez-Padriza, L. Morais, S. Machevo, T. Nhampossa, L. Quinto, P. L. Alonso, and A. Roca. “Lower Respiratory Tract Infections Associated with Rhinovirus during Infancy and Increased Risk of Wheezing during Childhood. A Cohort Study.” *PLoS One*. 8.7 (2013): e69370.

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- The malERA Consultative Group on Health Systems and Operational Research. "A research agenda for malaria eradication: health systems and operational research." *PLoS Med*. 8.1 (2011): e1000397.
- The malERA Consultative Group on Integration Strategies. "A research agenda for malaria eradication: cross-cutting issues for eradication." *PLoS Med*. 8.1 (2011): e1000404.
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- The malERA Consultative Group on Vaccines. "A research agenda for malaria eradication: vaccines." *PLoS Med*. 8.1 (2011): e1000398.
- The malERA Consultative Group on Vector Control. "A research agenda for malaria eradication: vector control." *PLoS Med*. 8.1 (2011): e1000401.

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