ACTIVITY **REPORT** 2007-2008





Fighting disease, promoting development

ACTIVITY **REPORT** 2007-2008





INS Instituto Nacional de Saúde



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Manhiça Health Research Centre Rua 12 Manhiça Mozambique

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PREFACE

Letter from the President of the Board of Trustees of the Manhiça Foundation



Pascoal M. Mocumbi, MD Honorary Founder and President Manhiça Foundation In the name of the Board of Trustees of the Manhiça Foundation, I enthusiastically congratulate the Manhiça Health Research Centre (Centro de Investigação em Saúde de Manhiça, CISM) for the results attained during the period 2007-2008. These two years passed very quickly, but thanks to the dedicated work of its team, the CISM was able to carry out its scientific mission and, at the same time, implement the institutional transformation that led to the establishment of the Manhiça Foundation.

The Manhiça Foundation, based at the village of Manhiça, has the mission of carrying out and promoting health research and development activities with the objective of meeting the needs of Mozambique and developing national capacities in these areas. To this aim, the Foundation provides health care, carries out training activities in health-related areas and conducts biomedical research, always following the deontological norms and principles.

The Manhiça Foundation is a non-profit institution oriented towards public purposes. The Foundation aims to cooperate with the scientific and educational departments of the Mozambican central, provincial and local administrations and with other public institutions, especially universities and other scientific organizations, while maximising the social return of the use of its own resources. The research activities here reported illustrate how the Foundation contributes to catalyse the CISM to achieve its mission and to prepare itself to face future challenges.

Among the innumerable scientific activities described in this report, the first clinical trial to evaluate the safety, immunogenicity and proof-of-concept of the efficacy of the RTS,S/AS02D malaria vaccine in infants is of special relevance. The trial showed that the vaccine candidate is safe, well tolerated and efficacious against infection.

The short-term challenges are to finish the Centre's strategic plan, conclude the ongoing research activities and initiate new projects such as the phase III RTS,S/AS01E vaccine clinical trial, expected to start in the second semester of 2009.

However, I would like to call the attention of all our partners to the Foundation's largest challenge: the strengthening of its human resources without which the attainment of our ambitious objectives will not be possible.

Finally, I would like to thank all those who have been involved and supporting, in the past and present, the Manhiça Foundation. Special thanks to all those that participate in its activities.

PREFACE

Letter from the President of the Board of Governors of the Manhiça Foundation and the Director of the CISM



Pedro L. Alonso, MD, PhD President of the Board of Governors Manhiça Foundation



Eusébio V. Macete, MD, PhD Director Manhiça Health Research Centre The Manhiça Health Research Centre (Centro de Investigação em Saúde de Manhiça, CISM) was created in 1996 to promote and conduct biomedical research in priority health areas. Since its creation, the Centre has been developing its activities under a bilateral cooperation programme between the Governments of Mozambique and Spain, and with the support of the Hospital Clínic / Universitat de Barcelona (through the Fundació Clínic per a la Recerca Biomèdica). This model has enabled the CISM to grow and develop itself over the last 12 years.

In the last few years, the need to provide the CISM with a Mozambican legal structure was identified. The aim was to guarantee the long-term sustainability and autonomy of the CISM, while maintaining at the same time the involvement and commitment of the partners that created the Centre. As a response, the Manhiça Foundation (MF) was created in February of 2008.

The MF is a non-profit institution, created by the Mozambican and Spanish governments, the National Health Institute of Mozambique (INS) and the Fundació Clínic per a la Recerca Biomèdica. The MF governing bodies are the Board of Trustees, whose president is Dr. Pascoal M. Mocumbi, Honorary Founding Member, and the Board of Governors, who receive advice from the External Scientific Committee. The creation of the MF has been one of the most important milestones in the history of the Centre.

The CISM began at the end of 2008 the development of its Strategic Plan that will define the main objectives of the Centre for the next 5 years. To reach these objectives, the Centre has a multinational team, which

includes Mozambican researchers trained by the CISM and other centres. The growing number of national researchers trained by the Centre illustrates how the training efforts of the last 13 years are starting to benefit the Centre and the entire country.

Besides its young, dynamic and committed team of researchers, the CISM holds strategic partnerships with other research centres. In an open, multicultural, competitive and increasingly interconnected world, the success of the CISM will depend on our capacity to maintain a stimulating working atmosphere, to strengthen our strategic partnerships and to continue to train future researchers.

This report presents the activities carried out during 2007 and 2008. During this period, the CISM continued to contribute to research on priority diseases in Mozambique and other Sub-Saharan countries. Besides the most well-known activities on the development of malaria control tools, the Centre has been increasing its research activities on other priority diseases such as respiratory infections, diarrhoeal diseases and HIV/AIDS.

The increase in research activities has been accompanied with a strengthening of the training activities, which are key to the sustainability of the Centre. Lastly, our health care activities reflect our commitment to improve the health of the population in the Manhiça District and our partnership with the health authorities at the district and national levels.

The activities described in this report were possible thanks to the commitment and effort of our personnel, the collaboration of our partners, the trust and support of our sponsors and, above all, the collaboration and participation of the Manhiça District population in our activities. The Centre is thankful to all those who make possible the development of the CISM and the improvement of the population's health. As we look into the future, tackling global health challenges will need joint efforts from the international community. Rooted in Manhiça, a small, rural area in the South of Mozambique, the CISM will strive to continue contributing to the global health agenda.

INTRODUCTION



The CISM entrance.

The Manhiça Health Research Centre (Centro de Investigação em Saúde de Manhiça, CISM) is a research institution whose mission is to promote and conduct biomedical research in priority health areas, to promote and safeguard the health of the population.

The CISM is located in Maputo, a village that is about 80km from Maputo, in the Northern portion of the Maputo province (in the South of Mozambique). This village is located on a small plateau area near the Incomati River. The Manhiça District has a surface of 2,500 km² and close to 156,000 inhabitants.

RESEARCH

The CISM research agenda is directed at the priority health problems in Mozambique, which are also representative of other Sub-Saharan African countries.

The CISM fosters a multi-disciplinary approach to health problems to maximise the translation of results obtained in the laboratory to clinical research and the development of control and treatment tools. As a result, research projects are usually carried out by multidisciplinary teams that include expertises in areas such as immunology, molecular biology, epidemiology or social sciences.

The Centre maintains stable research collaborations with national and international centres. In this context, the Centre has a strategic partnership with the Hospital Clínic / Universitat de Barcelona and the Barcelona Centre for International Health Research (CRESIB), that have significantly contributed to the creation and development of the Centre over the last years. As a result, many research projects are carried out in collaboration with these institutions.



The Centre has three platforms (demographic, geographic and morbidity surveillance platforms) that are crucial for the development of the CISM research activities. These platforms cover a study area of 500 km² with close to 84,000 inhabitants. In this study area, houses are geo-positioned and the population is under demographic surveillance. The morbidity surveillance system collects information on all paediatric outpatient visits and admissions to the Manhiça District Hospital and other health centres in the study area on a round-the-clock basis.

In the last few years, the Centre has contributed to the development of malaria prevention and treatment tools and has gradually broadened its activities to other priority diseases. Currently the research agenda of the Centre includes an important part of the main causes of death and disease in children and pregnant women.

The research projects during the 2007-08 period presented in this report are grouped into the following areas:

- Malaria.
- HIV/AIDS and tuberculosis.
- Diarrhoeal diseases.
- Pneumonias and other invasive bacterial diseases.
- Maternal and reproductive health.
- Medical anthropology and demography.
- Other diseases.

TRAINING

Training is one of the CISM's primary activities. Mozambique, together with other African countries, has a deficit of highlyqualified human resources that also extends to the research area.

The CISM contributes to the strengthening of human resources in the country through the training of researchers and other technical personnel, which is key to guarantee the continued efforts in the fight against diseases. As a result, more than 10 researchers are currently in different phases of training, that usually lead to a Doctoral degree.

HEALTHCARE ASSISTANCE

Improving healthcare provision in the Manhiça District is one of the CISM's priorities. The Centre works in collaboration with the Manhiça Health Centre, the Manhiça District Hospital and the health authorities in Mozambique, to ensure that the community benefits from the presence of the CISM's health personnel and the research results obtained at the Centre.

STRUCTURE OF THE CENTRE

The CISM is organised into 4 areas, namely: research, services, training and administration and finance.

The **research area** includes the scientific activities of the Centre and is responsible for the coordination and follow-up of the research projects.

The **services area** includes the departments that provide services to the research projects conducted at the CISM, which include:

- The **Demography Department**, responsible for the management of the geographic platform and demographic surveillance platform.
- The Social Sciences Department, that handles the relationship of the CISM with the community and provides support to the research projects that have sociological and anthropological components.



Manhiça District.

- The Clinical Department, that manages the morbidity surveillance platform and coordinates the CISM's health care activities in collaboration with the district health authorities.
- The Laboratory Department, responsible for the management of the laboratory and provision of diagnostic services to the CISM projects and to the Manhiça District Hospital and other health facilities in the study area.
- The Data Management and Information Technologies Department, that manages the data from the morbidity surveillance platform and the different research projects. This department also manages the network and the computer and telecommunication equipment of the Centre.

The **training area** is responsible for the management of the CISM training activities and programmes as well as the relationships of the CISM with other academic institutions.

The **administration and finance area** guarantees the general functioning of the CISM and its economic-financial management. It is also responsible for the human resources management. This area is managed by the Economic-Financial Director.

MANHIÇA FOUNDATION

The CISM was created in 1996 under a collaborative programme between the Mozambican and Spanish governments. During the last few years, the need to provide the Centre with a Mozambican legal structure, to guarantee the sustainability of the Centre in the long term and its projection at the national and international levels, was identified.

As a response to this need, the Manhiça Foundation (MF) was created on the 25th of February, 2008. The MF is currently the owning institution of the CISM and is responsible for its management.

The MF is a foundation under Mozambican law, oriented towards public purposes, created by the Republic of Mozambique, the Kingdom of Spain, the National Health Institute, the Fundació Clínic per a la Recerca Biomèdica and Dr. Pascoal M. Mocumbi as honorary founding member. The MF aims to carry out and promote activities in the health, scientific and technological fields, in order to meet the needs of the country and develop the national capacities in these areas.

The governing bodies of the MF are the Board of Trustees and the Board of Governors, where the founders of the MF are represented. The MF also has an External Scientific Committee, which is a consulting organism of the Board of Trustees and the Board of Governors.



Organisational Chart of the Maniça Foundation and the CISM.

Members of the Board of Trustees		
DR. P ASCOAL M. M OCUMBI (President) Honorary Founder Manhiça Foundation	Dr. JOÃO DE CARVALHO FUMANE Director National Health Institute Mozambique	Dr. R AIMON BELENES I JUÁREZ * Chief Executive Officer Hospital Clínic Spain
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*The representative of the Fundació Clínic per a la Recerca Biomèdica can be either Prof. Ramírez or Dr. Belenes.

Members of the Board of Governors

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SECTION





Research

MALARIA

According to the the World Malaria Report 2008 from the World Health Organisation (WHO), approximately 250 million cases and 1 million deaths per year are caused by malaria worldwide. Sub-Saharan Africa is the region that is most affected by the disease, where 85% of all cases and 90% of all deaths caused by malaria occur. Children younger than 5 years old and pregnant women are the most vulnerable groups and malaria continues to be the first cause of death in African children of this age group.

Currently, the control of malaria is based on three basic strategies: (i) prompt and effective treatment of cases with artemisinin-based combination therapies and Intermittent Preventive Treatment (IPT) during pregnancy, (ii) vector control with indoor residual spraying with insecticides and (iii) decreasing the human-vector contact with insecticide-treated nets.

Malaria is one of the main research areas of the CISM, which has contributed in developing and evaluating new control strategies over the last few years, including intermittent preventive treatment (IPT) strategies (both for infants and pregnant women), the RTS,S/AS malaria vaccine candidate and new artemisinin-based combination treatments. The Centre has also developed work regarding the immunological and molecular aspects of malaria, including the study of the development of naturally acquired immunity to malaria in children and the pathogenic mechanisms involved in severe malaria and placental malaria.

EPIDEMIOLOGICAL AND CLINICAL CHARACTERISATION OF MALARIA

The CISM has been contributing to the epidemiological and clinical characterisation of malaria since the beginning of its activities. Previous projects included a study on the incidence of malaria in children in the Manhiça District (Saúte *et al., Trans R Soc Trop Med Hyg* 2003;97) and malariometric indicator surveys in this same area (Saúte *et al., Trans R Soc Trop Med Hyg* 2003;97). During 2007-2009, the Centre continued to contribute with data on the epidemiology of malaria in Mozambique and with the characterisation of clinical malaria in children, adults and pregnant women.

Epidemiology of malaria in Mozambique

Traditionally, the estimation of the burden of malaria has been primarily based on mortality and morbidity information collected from the health information systems, which in the majority of Sub-Saharan countries is inferred almost uniquely from the health services. However, the health system does not cover many rural areas, where a large part of the malaria cases occur. In Mozambique the last estimation of the prevalence of malaria in the country was done in the 1950s.

The Centre, collaborating with the National Malaria Control Programme (NMCP) of the Ministry of Health, evaluated the epidemiological situation of malaria in the country in order to determine the prevalence and intensity of infection among children younger than 10 years of age. The study was included as part of the routine surveys of the NMCP.

This survey was carried out between February 2002 and April 2003, covering 24 districts of the country and the respective homes found within them. A total of 8,816 children were recruited. Their axillary temperature was taken along with a blood sample from each one of them to determine the haematocrit and the presence of parasites in blood by microscopy.

The average prevalence of parasites in blood was 58.9%, the majority of the cases being by *P. falciparum* (89%). The prevalence of gametocytes was 5.6%. The presence of malaria was greater in coastal regions and in the Northern area of the country. The infection prevalence peak was registered during the second year of life in children and decreased with age. The average prevalence of anaemia was 69.8% and, among anaemic children, 11.5% presented severe anaemia. The highest levels of anaemia were registered in the Northern and Central regions of the country (77.9% and 79.4%, respectively).

These results confirm that malaria, principally that caused by *P. falciparum*, is endemic in the entire country. On the basis of these results, it could be estimated that 2.6 million children younger than 10 years old in the country have parasites in their blood, and that 3.8 millions are anaemic. The burden of malaria and malaria-related anaemia in children is among the most important public health problems and justifies the implementation of integrated and collaborative control interventions.

Malaria among children attending the Manhiça District Hospital

In Mozambique, as in most of Sub-Saharan Africa, the scarce health information systems are a challenge to the establishment of health policies. Aside from the epidemiological information regarding malaria obtained through household surveys (see previously described study), it is also important to define and evaluate control programmes with data on the incidence, age distribution and clinical characterisation of malaria and severe malaria. However, there are few studies published on the epidemiology of malaria in the country and there are no detailed descriptions of the different severe malaria syndromes. The hospital surveillance data, in spite of being influenced by the accessibility and health seeking behaviour, are an important source -- sometimes the only one-- of information on the most prevalent health problems in a certain community and their epidemiology.

The CISM published two articles on malaria and severe malaria in children, using data collected through the Morbidity Surveillance System at the Manhiça District Hospital (MDH) and the Maragra Health Post. These are retrospective analyses of the data collected between June 2003 and May 2005, of children attending the outpatient department and of those admitted to hospital.

A total of 94,941 children were visited at the outpatient department during these two years, of which 30.5% had malaria. Children younger than 3 years of age represented almost half of the cases, and children 5 years of age or older more than one third of the cases. Among children that presented fever or a history of fever, 37% had malaria and 13% of the malaria cases presented anaemia (haematocrit <25%). The minimum community-based incidence rates per 1,000 child—years at risk were 394 in infants, 630 in children from 1 to <5 years of age and 237 in children 5 years of age or older. These results showed that the preventive measures to control malaria should be directed at children under 3 years of age, given that this is the age group most affected by the disease. However, children between 5 and 15 years old represent more than one third of the cases and should also be included in control programmes. These results also show that the presumptive treatment of fever cases implies that many children receive treatment without needing it.

Regarding admitted patients, during the two years study period almost half of the 8,311 paediatric patients admitted



Prevalence of infection by Plasmodium in Mozambique.

to the MDH had malaria and 13% had severe malaria. Children younger than 2 years of age represented almost 60% of all cases. The case fatality rate of malaria was 1.6% and that of severe malaria rose to 4.4%. Almost 19% of the total intra-hospital deaths were due to malaria.

The most prevalent syndromes among severe malaria cases were prostration (55%), respiratory distress (41%) and severe anaemia (17%). Severe anaemia and not being able to look for the mother's breast were independent risk factors for death in children younger than 8 months old with malaria. In children between 8 months and 4 years of age with malaria, risk factors for death included malnutrition, hypoglycaemia, indrawing, inability to sit and a history of vomiting.

The minimum community-based incidence rates per 1,000 child-years at risk were 27 in infants, 23 in children from 1 to <5 years of age and 2 in children aged 5 years or older. These results confirm that malaria continues to be the first cause of hospital admission in the Manhiça area, affecting mostly small children, which are also those that have the highest risk of dying. Measures directed at protecting children during the first two years of life are fundamental to have a significant impact to reduce this trend.

Malaria in adults

There are few epidemiological studies on adult malaria in endemic areas. Therefore, more information is needed on the natural history of malaria affecting adults, to understand the dynamics of malaria infection and its interaction with the immune system. To do this, the CISM carried out a study to evaluate the clinical, parasitological and haematological status of adults that are exposed to malaria and to characterise the parasites of these individuals that progressively acquire protective immunity against malaria.

A cross-sectional study involving 249 adults was carried out in the study area. Information regarding clinical, parasitological and haematological status was collected. The presence of sub-microscopic and multiple infections were also analysed using the Polymerase Chain Reaction (PCR). From the study carried out, the prevalence of infection by *P. falciparumby* microscopy was 14%, and by PCR 42%, decreasing progressively with age. Submicroscopic infections increased with age and multiplicity of infection decreased. Anaemia was only related with the parasitaemia detected by PCR.

These data suggest that adults develop a non-sterilising protective immunity against malaria. There seems to be little specificity in the signs and symptoms of malaria in adults (none of the adults presented fever despite the presence of parasitaemia), which implies a need to propose a more sensitive malaria definition for adults, including, on top of the presence of parasitaemia, other signs and symptoms such as diarrhoea or headache.

Malaria in pregnancy

See Maternal and reproductive health section.

CLINICAL DEVELOPMENT OF DRUGS, VACCINES AND OTHER CONTROL TOOLS

Clinical development of the RTS,S vaccine

The RTS,S vaccine formulated with adjuvants from the AS0 family from GlaxoSmithKline (GSK) is currently the most promising malaria vaccine candidate. It is a pre-erythrocytic vaccine against *P. falciparum* that contains a recombinant-protein of the circumsporozoite and the hepatitis B surface antigen. The CISM has been working on the clinical development of this vaccine since 2002 in collaboration with PATH Malaria Vaccine Initiative (MVI) and GSK Biologicals. During this period the Centre has carried out various phase I, I/IIb and IIb trials.

In 2003 the Centre carried out the first Phase IIb trial in children 1 to 4 years of age that demonstrated that the RTS,S reduces the risk of infection by *P. falciparum* (45.0%) and of non-complicated malaria (35.3%) and severe malaria (48.6%) during a period of at least 18 months after the last vaccine dose.

Development of malaria prevention strategies at the CISM

The CISM has been involved in intense activities regarding the development of new prevention and treatment strategies for malaria in children and pregnant women. Some of the most important results from the Centre are listed below:

- First proof-of-concept trial done in children aged 1 to 4 years old of the RTS,S/AS02A malaria vaccine. The trial showed vaccine efficacy against clinical malaria (35.5%) and severe malaria (48.6%) during a minimum of 18 months (Alonso *et al., Lancet* 2004; 364, Alonso *et al., Lancet* 2005; 366).
- Development of Intermittent Preventive Treatment (IPT) as a malaria control strategy in infants. This strategy showed a reduction in the incidence of clinical malaria of 22.2% and in hospital admissions of 19% during the first year of life (Macete *et al., J Infect Dis.* 2006; 194).
- First trial of the RTS,S/AS02D malaria vaccine in newborns. The trial showed vaccine efficacy against infection (65.9%), providing evidence for the first time that it is possible to protect newborns with a malaria vaccine (Aponte *et al., Lancet* 2007; 370).
- First trial to evaluate the combined efficacy of two malaria control strategies in pregnant women: insecticide-treated nets and IPT (Menéndez *et al.*, *PLoS ONE* 2008; 3).
- Contribution to the registration of the dispersible form of Coartem[®] for paediatric use (Abdulla *et al., Lancet* 2008; 372).

The Centre foresees, during 2009, the initiation of new studies on the development of malaria control strategies, namely the Phase III trial of the RTS,S/AS01E malaria vaccine and a trial to evaluate the use of new drugs to prevent malaria in pregnant women by means of IPT.

Children younger than one year of age are those that have the highest risk of suffering severe malaria. Moreover, the Expanded Programme on Immunisation (EPI) has been key at increasing vaccine coverage during the first year of life. For these reasons, the objective of the clinical development of the RTS,S is to register the vaccine for its use in infants, together with the rest of the EPI vaccines.



Tent used for the trials of antimalarial drugs.

The CISM carried out the first clinical trial to evaluate the safety, immunogenicity and proof of concept of the efficacy of RTS,S/AS02D in infants. The results of this phase I/IIb clinical trial, published in 2007, demonstrated that the RTS,S/AS02D is safe and well tolerated. The candidate also induced high titles of antibodies against the circumsporozoite and the adjusted efficacy of the vaccine against infection was 65.9% (95% CI 42.6–79.8%, p<0.0001).

Another trial carried out in Tanzania with the same vaccine confirmed these results on safety, immunogenicity and efficacy. All of these studies have generated enough evidence to be able to continue with the clinical development into phase III trials.

The Centre is also developing studies to evaluate the immune markers of the pre-erythrocytic and asexual blood stages of *P. falciparum* that may be associated with the sustained protection in children vaccinated with the RTS, S/AS02A.

The CISM will participate in the multicentre phase III trial of the RTS, S/AS01E vaccine candidate, which is foreseen to start in 2009. To prepare for this trial, the Centre has carried out studies to evaluate and improve the MDH Morbidity Surveillance System to detect severe malaria and other pathologies in children of the same age group that will participate in the upcoming trial. The CISM has also evaluated different methods to quantify the densities of *P. falciparum* in peripheral blood and other diagnostic tools.

Efficacy and safety of the dispersible paediatric formulation of Artemether-Lumefantrine

Coartem[®] (Artemether-Lumefantrine) is currently the second line treatment against malaria in Mozambique. The tablets that currently exist are difficult to administer to children and they must be crushed. The Centre was involved in a randomised clinical non-inferiority trial to evaluate the efficacy, safety, tolerance and pharmacokinetics of a paediatric-suitable dispersible formulation of Coartem[®]. These dispersible tablets for oral suspension were compared to the crushed tablets in children weighing between 5 and 35 kg with uncomplicated *P. falciparum* malaria.



Kaplan-Meier Curves that show the accumulated percentages of participants with at least one episode of infection by malaria during the phase I/IIb trial of RTS,S/AS02D.

MALARIA

This clinical trial is part of the clinical development plan for this formulation to be used in children, and was funded by Medicines for Malaria Venture (MMV) and Novartis. The study was carried out in 5 countries (Benin, Kenya, Mali, Tanzania and Mozambique) and included 899 children. The results demonstrated that Coartem[®], administered in six doses with the new paediatric formulation, is as effective as the crushed tablets that are currently being used.

Clinical development of DHA+PPQ

The CISM participated in a multicentre clinical trial on the clinical development of Eurartesim[®] (Dihydroartemisinin (DHA) + Piperaquine (PPQ)). Five African centres (Burkina Faso, Mozambique, Kenya, Uganda and Zambia) and a total of 1,500 participants from 6 to 59 months of age with uncomplicated *P. falciparum* malaria were involved in this phase III study, and followed-up for the first 42 days after treatment. During the trial, participants were randomly allocated to receive Eurartesim[®] or Coartem[®], with the principal objective to demonstrate that Eurartesim[®] was not inferior (with a non-inferiority margin of 5%). Data are being analysed and results prepared for publication and delivery to the regulatory authorities during the year of 2009.



Microscopists at the CISM laboratory

Study to compare the efficacy of 4 possible artemisinin-based combination treatments

The CISM is participating in a multicentre, randomised, non-blind, phase IV multi-arm study, designed to compare the efficacy of 4 possible anti-malarial drug combinations, all of them including an artemisinin derivative, for the treatment of uncomplicated malaria. The study is funded by the EDCTP and is being done in 10 sites located in 7 African countries (Burkina Faso, Gabon, Mozambique, Nigeria, Rwanda, Uganda and Zambia), with the East African Network (EANMAT) responsible for monitorisation.

The objective of the study is to establish the safety and efficacy of these new combinations during 28 days after treatment and to determine the rate of reinfection and need for re-treatment during the 6 following months. The CISM recruited 500 children aged 6 months to 5 years with uncomplicated malaria, who were treated with one of the combinations. Afterwards, children were followed-up using active detection during 28 days and passive case detection up to 6 months after treatment.

Malaria prevention in pregnant women

See Maternal and reproductive health section.

IMMUNITY AGAINST MALARIA

Age of exposure to *P. falciparum* and development of immunity against malaria in infants

People living in regions of Sub-Saharan Africa where malaria is endemic and that are repeatedly exposed to infections by *P. falciparum* from birth, develop a naturally acquired immunity (NAI) against the parasite.

In areas with annual and stable transmission, there are almost no cases of severe malaria nor deaths associated with malaria after 5 years of age, and the incidence of clinical malaria, along with the prevalence and the density of infection decrease with age. In high transmission areas, the acquisition of NAI takes place at younger ages. The acquisition of NAI depends on the age as well as the transmission intensity, but until today, it has been difficult to determine the contribution made by these two variables in an independent manner.

The development of NAI against *P. falciparum* is still fairly unknown. Previous studies about continuous or intermittent prophylactic treatment against malaria in infants suggest that the age of the first exposure to *P. falciparum* during the first year of life could be important to determine the development of NAI. Deepening knowledge in this area is key for future strategies to control malaria and, specifically, for malaria vaccines.

The CISM is carrying out a study to evaluate the effect of the age of first exposure to *P. falciparum* in the development of NAI in infants. The study is part of the AgeMal Consortium funded by the European Union.

The study is a randomised double-blind placebo-controlled trial with three arms where the age of exposure to *P. falciparum* is controlled by administering chemoprophylaxis to

participants during different periods of the first year of life. The risk of clinical malaria and anaemia during the second year of life and the type and quality of immune responses will be compared between the different groups. The role of oxidative stress and host genetic factors will also be evaluated regarding the development of naturally acquired immunity. The study will be finished during the year of 2009.

The effect of intermittent preventive treatment in infants in the development of immunity

In areas with a high malaria transmission, infants carry the burden of disease. Therefore, this age group is one of the principal targets of prevention strategies.

Intermittent Preventive Treatment in infants (IPTi) consists in administering anti-malarial drugs at specific time points in the first year of life, through the Expanded Programme on Immunisation (EPI) visits, and has demonstrated to be effective in the prevention of malaria in children.

One of the important issues regarding the implementation of malaria preventive strategies, such as IPTi, is to evaluate their impact on the development of naturally acquired immunity (NAI). Recent studies have demonstrated that the use of chemoprophylaxis in children may jeopardize the development of NAI. However, studies carried out in Tanzania and in Mozambique indicated that IPTi not only reduced the risk of malaria without interfering in the development of NAI, but could also enhance its development. Nonetheless, there are no studies on the evaluation of the immune responses to *P. falciparum* in the context of IPTi.

The CISM carried out a study to evaluate the development of immunity against *P. falciparumin* the context of a randomised, double-blind placebo-controlled trial to assess the efficacy of IPTi with sulfadoxine-pyrimethamine (SP) administered at 3, 4 and 9 months of age through the EPI. The study showed that IPTi is efficacious against clinical malaria, reducing the risk of clinical malaria by 22.2% during the first year of life. Antibodies against *P. falciparum* erythrocytic-stage antigens MSP-1, AMA-1 and EBA 175 were used to measure the immune responses. These antigens play a critical role during the invasion of the erythrocytes and are used in the development of malaria vaccine candidates.

The study showed that IPTi with SP did not modify the antibody levels against antigens of the *P. falciparum* erythrocytic-stage during the first two years of life, indicating that the intervention does not negatively affect the acquisition of antibodies against malaria. These results contrast with those found in the context of the use of continuous prophylaxis, where there is a negative clinical and immune effect. The analyses indicate that the antibody levels of the



Participant of the AgeMal study receiving study treatment.

group that received placebo were not higher than those of the group that received SP. The results were obtained from analyses that took into account the confounding effects of other variables, such as previous episodes of clinical malaria or parasitaemia at the time of the visits.

Currently, analyses are being carried out to investigate the effects of IPTi with SP on other antibody responses that are thought to be involved in the acquisition of immunity, such as the variant surface antigens (VSA) and the growth-inhibiting antibodies.

The effect of IPT during pregnancy in the development of immunity

Within the clinical trial of Intermittent Preventive Treatment in pregnancy (IPTp) with Sulfadoxine-pyrimethamine (SP) that was carried out at the CISM (see Maternal and reproductive health section), a study was initiated to evaluate the impact of IPTp with SP on the immunological status of the mothers at the moment of delivery and their babies during the first year of life.

A subgroup of 300 women with their respective babies participated in this study, during which blood samples were analysed from the mothers and their babies to determine the type and level of different antibodies against various parasite antigens. The analysis of these data is expected to be finished during 2009.

MALARIA



Activation of T-cells induced by P. falciparum-infected erythrocytes.

MOLECULAR BIOLOGY

Adhesion phenotypes of *P. falciparum*-infected erythrocytes

Only 1 to 2% of the *P. falciparum* malaria cases lead to a severe episode, that could present itself in the form of different syndromes, including deep coma (cerebral malaria), severe anaemia, respiratory distress with metabolic acidosis and, less frequently, multi-organic failure. Any of these different syndromes may be fatal, or cause important sequelae in patients that recover. However, the causal relationship between the symptoms and the underlying pathogenic process is not well-established and continues to be a controversial topic, partially due to the scarce clinical-pathological correlations of severe malaria.

Therefore, the CISM has been trying to ascertain whether *P. falciparum* isolates have intrinsic properties of cyto-adherence that are correlated with clinical severity, and which is the contribution of specific human receptors in this adhesion phenotype. To this effect, the cyto-adherence properties, the formation of rosettes and the agglutination capacity of *P. falciparum* parasites will be compared among parasites isolated from children with mild malaria with those isolated from children with severe malaria.

The role of the gC1qR, CD36 and ICAM1 receptors in terms of in vitro cyto-adherence profiles of isolated parasites from children with mild and severe malaria will also be evaluated is order to determine whether the adhesion to endothelium cells or platelet-mediated agglutination via gC1qR is associated with severe malaria.

Phenotypic, antigenic and transcriptional characterisation of *P. falciparum* placental isolates

In malaria endemic areas, the prevalence, density and severity of *P. falciparum* infection are greater in pregnant women than in the same women before they get pregnant or in other women that are not pregnant. The susceptibility to infection and the severity of the clinical manifestations are determined by the level of immunity before pregnancy, which fundamentally depends on the intensity and stability of malaria transmission.

Therefore, in areas where transmission is stable and the level of acquired immunity against malaria is high, primiparous mothers are usually more affected by malaria than those that have had previous pregnancies (multiparous).

Nonetheless, the mechanisms involved in the susceptibility of women to malaria during pregnancy remain unknown. One hypothesis suggests that an excessive exposure to proinflammatory cytokines (IFN-g, IL-2 and TNF-a) could induce the complications associated with malaria during pregnancy. The mechanical hypothesis claims that organs would be affected depending on the number of infected erythrocytes (IE) captured in their tissues. This would imply that during pregnancy, the sequestration of IEs in the placenta negatively affects the function of this organ, interfering in the maternal-foetal exchange by generating hemodynamic alterations, hypoxia and inflammatory reactions such as chronic intervillousitis.

In this context, the Centre is researching the molecular mechanisms involved in the adhesion of *P. falciparum* to the placenta, in order to identify antigens that could be used to develop vaccines against malaria during pregnancy. To this effect, a study is being carried out on the phenotypic, antigenic and transcriptional characteristics of the parasites that are captured in the placenta, comparing them with the isolated parasites in the peripheral blood of adult men, adult women that are not pregnant and women in the postpartum period.

The correlation of the adhesion phenotype of these parasite populations with their antigen profile and with their transcriptional pattern will enable the identification of the proteins of the parasite involved in the adhesion to the placenta, giving some insights on potential mechanisms for reducing the adverse effects of malaria during pregnancy.

Molecular markers of resistance in the context of IPTi and IPTp with SP

Intermittent Preventive Treatment in Infants (IPTi) and pregnant women (IPTp) with Sulfadoxine-pyrimethamine (SP) are innovative strategies to control malaria. However, concerns have arosen regarding the possible impact that these strategies could have on the increased resistance of *P. falciparum* to SP, as well as the impact that these emerging resistances could have in the effectiveness of the IPT strategy per se.



Erythrocytes infected by P. falciparum trophozoites.

Parasites that are selected by SP in vitro usually present mutations in genes, codifying the dihydropholate reductase (dhfr) and dihydropteroate synthase (dhps) enzymes. However, there are studies that show that the presence of such mutations is not well correlated with the efficacy of these drugs in areas with high malaria transmission.

The CISM carried out a study to evaluate the levels of resistance to SP in the context of two randomised, double-blind studies designed to evaluate the efficacy of the IPTi and IPTp strategies. Regarding IPTi, the frequency of clinical episodes of malaria with mutations in dhfr and dhps was compared among the children that received SP or placebo. Mutations analysed were point mutations on the bases 108, 51, 59 and 164 in dhfr and 437 and 540 in dhps. Codon 76 mutations of the pfcrt (associated to chloroquine resistance) and codon 86 mutations of pfmdr1 (associated to multi-resistance) were also analysed.

The study demonstrated that IPTi was associated to changes in the prevalence of genotypes involved in the resistance against SP. Having said so, SP showed a high level of efficacy in the prevention of episodes of malaria in children, indicating that the prevalence of mutations may not be a reliable indicator to predict the efficacy of SP in prevention strategies. The study of mutations in the context of IPTp is being currently assessed.



Genotypic profile of isolates of P. falciparum obtained in the study area.



Collection of mosquitoes in the study area.

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HIV/AIDS AND TUBERCULOSIS

In 2008, the HIV epidemic affected more than 35 million individuals in the world, with Sub-Saharan Africa as the most affected region accounting for close to 70% of the cases registered worldwide, according to the World Health Organization (WHO).

Mozambique is one of the countries of the world that is most affected by HIV/AIDS, and according to data from the Ministry of Health of Mozambique (MISAU), the estimated prevalence of infection by HIV in pregnant women in 2005 was 9% in the North and 27% in the South of the country. Data from the Vertical Transmission Prevention Programme of 2007 in Manhiça showed that more than 25% of the pregnant women observed in antenatal visits were seropositive for HIV, which reflects the severity of the situation in this area of the country.

Tuberculosis (TB) is one of the principal causes of death worldwide, and Mozambique is one of the countries that is most affected by this disease. Data from the WHO reveal that almost 8 million new cases of tuberculosis occur every year and 1.6 million deaths are caused by this disease. The estimation of the annual incidence of new cases of tuberculosis in Mozambique, in 2008, was 443 new



Researchers in the immunology laboratory.

cases/100,000 habitants, and the annual mortality rate was 117/100,000 habitants.

There is a critical association between tuberculosis and HIV in Africa. The annual incidence of tuberculosis is 10% in HIV-infected individuals, and up to 30% in HIV-infected adults with severe immunodeficiency.

The research activities in HIV/AIDS and TB developed by the CISM during the 2007-2008 period aimed to study mother-child transmission of HIV, the characterisation of the infection by HIV and the response to Anti-Retroviral Treatment (ART) in adults, as well as the development of prevention tools for both diseases. Medical-anthropological studies developed in this area are presented in its respective section of this report. Finally, all of these activities are carried out in the context of a collaboration with the National Tuberculosis Control Programme and the National STI/HIV/AIDS Programme in the Manhiça District

MOTHER-CHILD TRANSMISSION OF HIV

Despite decreasing rates of mother-child transmission (MTCT) of HIV in more industrialised countries, MTCT continues to be an alarming public health problem in Sub-Saharan Africa. This is mainly due to the fact that the majority of the women give birth without knowing their HIV status. Additionally, the women of this region of the world rarely have access to MTCT prevention programmes.

A newborn can be exposed to HIV by different routes. Firstly, in the uterus the foetus can come into contact with HIV through the placenta and several mechanisms

HIV/SIDA E TUBERCULOSE

have been suggested that describe the trans-placental passage of HIV. Secondly, during birth the baby is exposed to the cervical and vaginal secretions that contain the virus. Finally, in a population that predominantly breastfeeds, the lactating baby is also exposed to HIV.

Evaluation of HIV negative children exposed to the virus during pregnancy

Many studies have analysed the specific and general immune responses to HIV in non-infected adults that have been exposed to the virus, but there are few studies assessing HIV exposure in HIV negative children born to HIV positive mothers in Africa. As a consequence, there is little knowledge about the haematologic and immune responses in this age group.

In order to cover this gap, the CISM started a study to characterise the immunological state as well as HIV-specific immune responses of these children and to better understand the impact of maternal HIV on the risk of morbidity in these children during their first year of life.

The effect of malaria prevention in the prevention of vertical transmission of HIV

HIV/AIDS and malaria are the two biggest public health problems in the Sub-Saharan Africa region and the interactions between both diseases can be especially relevant during pregnancy, potentially affecting both the mother and the child. The impact of malaria and other infections such as syphilis and intestinal parasites on MTCT of HIV has been debated in existing literature. With regards specifically to the role of placental malaria in MTCT of HIV, studies carried out have observed conflicting results and shown that it may be a very complex issue.

The WHO recommends that pregnant women in areas of stable malaria transmission receive Intermittent Preventive Treatment (IPTp) during pregnancy with Sulfadoxine-Pyrimethamine (SP) and that they use insecticide-treated mosquito nets (ITN).

The Centre carried out a trial to evaluate the efficacy of IPTp with SP in the context of the use of mosquito nets, and within this trial, a study was carried out in order to evaluate the impact of placental malaria on MTCT of HIV.

The study showed that there was no significant difference in MTCT of HIV between the mothers that received IPT during pregnancy and those that received placebo. The results of the study suggest an association between placental malaria, anaemia and MTCT of HIV.



Personnel from the Manhiça Health Centre counselling before voluntary HIV testing.

CHARACTERISATION OF HIV INFECTION IN ADULTS AND RESPONSES TO ART

Molecular characterisation of HIV in women in the CISM study area

There are studies that suggest that different HIV subtypes can have different biological characteristics that influence transmission and progression of the disease. The constant variation of the virus and its capacity for recombination also leads to generation of resistance to existing antiretroviral drugs, and increases HIV immune evasion. Therefore, the molecular information of the virus that circulates in a specific area could have great importance to improve the success of treatment and the measures used for control.

In general, the subtype C virus is responsible for more than 56% of the infections in the Southern region of Africa. However, there is little information on the molecular epidemiology of the virus in Mozambique. Therefore, the Centre carried out a study to characterise the genetic diversity, the molecular evolution and the molecular patterns of the viruses that circulate in women in Manhiça. HIV obtained in 1999 and in 2004 were analysed and compared. The regions of the genome corresponding to the Long-Terminal Repeat (LTR) U3, the envelope (env) C2V3C3 and the protease (pr) were sequenced. The phylogenetic analysis revealed that all of the sequences were of the subtype C and most viruses were CCR5-tropic (R5), although CXCR4-tropic (X4) variants were also identified (13%).



Researchers discussing flow cytometry data in the immunology laboratory.

Phylogenetic analysis including sequences from neighbouring countries showed a high level of relatedness. Sequences from HIV circulating in 2004 showed greater genetic diversity than those isolated in 1999. The results indicate an important diversification of the subtype C virus in this area.

Identification and characterisation of acute infection by HIV in adults

For HIV prevention activities to be effective, it is important to detect the infection as early a possible. The natural history of HIV, without treatment, follows three different phases of infection: acute, chronic and AIDS-defining. The diagnosis of HIV infection is routinely performed by serology, detecting HIV-specific antibodies produced at the beginning of the chronic phase of infection. Acute infection precedes antibody production. However, growing evidence suggests that the transmission potential of HIV in the acute phase of infection is dramatically increased due to extremely high levels of viral load in the plasma and genital tract. Following acute HIV infection (AHI), HIV viral load is stabilised during the first year to a set-point value at which it remains over the chronic phase.

The characterisation of acute infection and the viral load set point in the population is important in order to define the dynamics of transmission and provide important information for the design of HIV prevention interventions including vaccine trials. The Centre is currently conducting a study to evaluate the clinical, immunological and viral parameters of acute HIV infection. This study is performed in the context of the African-European HIV Vaccine Development Network (AfrEVacc).

Evaluation of the reconstitution of the immune system after starting ART

In order to design innovative antiretroviral treatment (ART) strategies specific for the African context, it is crucial to obtain baseline information on the kinetics of immune restoration after ART initiation as well as on the dynamics of opportunistic diseases.

The CISM has thus carried out a study to evaluate the immunological parameters of patients initiating ART over the first two years of treatment. The current study includes the estimation of the prevalence of Immune Restoration Inflammatory Syndrome (IRIS) associated with different diseases, such as Kaposi's sarcoma, tuberculosis etc. IRIS is defined as a paradoxical clinical worsening of symptoms in patients who show good response to ART including decrease in HIV viral load and increase in CD4 counts. In these patients, it is suspected that the rapid restoration of functionally active cells may have an immune-pathological effect. IRIS is related to a growing number of infectious, auto-immune and tumour manifestations. The project also included the evaluation of the dynamics of restoration of a functional immune system after starting ART.

The results regarding the risk factors for the development of Kaposi's sarcoma-associated IRIS have already been presented and the analysis of the study will be finished in 2009.

DEVELOPMENT OF TOOLS FOR TREATMENT AND PREVENTION

Development of Microbicides

Although the consistent and correct use of condoms is the most effective protection against HIV in heterosexual intercourse, women do not always have the power to negotiate their use with their partners. In this context, the microbicides (vaginal gels that protect against infection by HIV) are a tool that enables women to protect themselves from infection in those cases where it's not possible to negotiate the use of a condom. Studies show that a microbicide, even if it only has partial effectiveness, could prevent up to 6 million infections.

The CISM participates in the Microbicides Development Programme (MDP) network, whose objective is to develop microbicides. The research developed until now has been centred in the evaluation of the acceptance and feasibility of trials with microbicides (see *Medical anthropology and demography section*). The Centre aims to participate in the phase III clinical trials to evaluate the effectiveness of microbicides in the next few years.



Use of a HIV diagnosis kit.

Training for the development of HIV/AIDS vaccines

As in the case of other infectious diseases, a safe, effective and accessible vaccine would be a key tool to control HIV/AIDS, especially in less-industrialised countries. Therefore, the CISM aims to contribute to the development of new vaccines for HIV.

Recently, the Centre became integrated into the African-European HIV Vaccine Development Network (AfrEVacc) funded by the EDCTP. AfrEVacc aims to develop a joint network between the European Centres and those in Africa, using the data and knowledge of each centre to improve the capacities to carry out HIV vaccine trials in Mozambique, in South Africa and in Tanzania.

This network works in parallel with another network that prepares centres to carry out HIV vaccine trials (TamoVac Network), which also includes Tanzania and Mozambique. The network will collaborate with other international networks, such as the EUROPRISE Consortium, the Global HIV Vaccine Enterprise and the International AIDS Vaccine Initiative.

The activities in the context of the AfrEVacc Network in the CISM are going to include the conduct of studies to characterise the incidence and prevalence in the area, as well as to evaluate the feasibility of the vaccine trials. To do so, the CISM laboratory will be upgraded in order to carry out cellular immunology techniques that are necessary for the development of vaccine trials. The network will aim to conduct a phase I trial to evaluate the safety and immunogenicity of a HIV vaccine candidate.

Training for the development of tuberculosis vaccines

The only commercialised vaccine against tuberculosis (TB) is the Bacillus Calmette-Guérin (BCG). Despite the heterogeneous results of the analyses, the BCG seems to provide only partial protection against severe forms of TB during childhood. However, it seems scarcely effective against common forms of pulmonary tuberculosis. The increase of TB mostly in African countries with an elevated prevalence of HIV/AIDS has worried health authorities, in spite of the widespread use and high coverage of BCG. This makes the creation of a new vaccine against TB necessary and urgent.

In the last decade, various TB vaccine candidates have been developed and some have already advanced to phase I and, more recently, to phase IIa trials.

The CISM is involved, since 2007, in an international network called TBVACSIN that aims to develop capacities in African research centers for the conduct of clinical trials for TB vaccines. Currently, 4 African centres are involved in the network, namely: the University of Makerere (Uganda), KEMRI/CDC in Kisumu (Kenya), SATVI in Cape Town (South Africa) and the CISM. This year, the network hopes to begin a project funded by the EDCTP, that aims to reinforce the capacities of the CISM to carry out vaccine clinical trials and to conduct a phase IIb trial of a TB vaccine candidate in children.

Evaluation of a fixed combination of four drugs for the treatment of tuberculosis

The use of drugs in Fixed Combined Doses (FCD) for the treatment of TB was recommended by the International Union Against Tuberculosis and Respiratory Diseases (The Union) and by the WHO. The advantages of drugs in FCD include the prevention of drug resistance due to mono-therapy, the reduction of the risk of incorrect dosing, the simplification in the prescription, the improvement of adherence to treatment and the facilitation of the Direct Observation of the Treatment (DOT). Recent studies of the bio-availability of formulas with four drugs in FCD demonstrated satisfactory results, although there is still little information on the effectiveness of this strategy compared to the use of separate tablets.

The CISM is participating in a multicentre study promoted and funded by The Union, to evaluate a fixed combination of four drugs for the treatment of TB. The study tests the effectiveness of this compound, when administered in the intensive initial phase of the treatment of new cases of pulmonary TB with positive baciloscopy, in which the treatment phase will be followed during 4 months with 2 FCD drugs –rifampicin and isoniazid. The clinical follow-up phase of the patients has already been finished and data are currently being analysed.



Poster in the hospital with information about tuberculosis.

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DIARRHOEAL DISEASES



Plaque with antibiogram.

Diarrhoeal disease is one of the principal causes of morbidity and mortality in children under 5 years of age, especially in developing countries, with an average of 3.2 episodes per child. The WHO categorises diarrhoeal disease as the second major cause of mortality in children under five years of age in the world. Data from 2000-03 estimate that diarrhoea contributes with almost 18% of the 10.6 million deaths that occur yearly in this age group, with the majority of these taking place in developing countries.

In spite of the fact that morbidity caused by diarrhoeal diseases is still high in these countries, the mortality is decreasing, principally because of improved clinical management. In Sub-Saharan Africa, the mortality caused by acute diarrhoea varies from 1.9% to 37%, depending on the country.

Recent reports indicate that in the capital of Mozambique – Maputo these diseases make up the third cause of death in children from 0 to 14 years of age. In Manhiça, diarrhoea represents close to 20% of paediatric hospital admissions and the fourth cause of death in children from 12 to 59 months old. Different pathogenic agents, including bacteria, viruses and parasites, cause diarrhoea. The most frequently isolated pathogenic agents include *Escherichia coli, Rotavirus, Salmonella spp, Shigella spp, Campylobacter jejuni, Entamoeba histolytica* and *Giardia lamblia*.

EPIDEMIOLOGY, CLINICAL PRESENTATION AND ETIOLOGY OF DIARRHOEA

Etiology of diarrhoea in children

Results published during 2007-08 describe the etiology of diarrhoea in children younger than five years old admitted to the Manhiça District Hospital during 2000-01, as well as the profile of antibiotic resistance of the isolated bacterial agents. Diarrhoeogenic *Escherichia coli* was isolated in 22.6% of the samples and is the most frequent agent, followed by *Ascaris lumbricoides* (9.3%), *Salmonella spp.* (2.5%) and *Giardia lamblia* (2.5%). A. *lumbricoides* and *Strongyloides stercolaris* were the most frequent isolated pathogens in children over 12 months old. Resistance to trimethoprim-sulfamethoxazole and ampicillin was high.

The epidemiology and clinical presentation of shigellosis in children under 5 years old were also described. Shigellosis causes approximately 163 million cases per year in developing countries. The estimated incidence of shigellosis in the study area in children from 12 to 47 months old was 488.4/100,000 child-years at risk. The most frequent clinical presentations were fever and dysentery, and the most frequent serotypes were *Shigella flexneri* 2, *S. sonnei* and *S. flexneri* 6.

The Centre also analysed the levels of antibiotic resistance of *V. cholera* 01 serotype Ogawa. This is the strain that is most frequently isolated in the epidemics of cholera in the Manhiça District and treatment with antibiotics is recommended for the severe cases.

Global study of the etiology of diarrhoea

Many studies have been carried out in different countries to identify the etiology of diarrhoeal diseases and to estimate its global burden. With few exceptions, the available data suffer from notable deficiencies. On one hand, the appropriate epidemiological methods are rarely used. On the other hand, the majority of the study designs are cross-sectional and they do not capture the sequelae, which are very important to understand the rate of co-morbidities. Another restriction comes from the fact that the studies do not generally distinguish between the relative contributions of the clinical syndromes of the disease. Finally, the contribution of the various bacterial, viral and parasite agents that may cause diarrhoea have still not been completely elucidated.



Researcher in the bacteriology laboratory.

The majority of the studies carried out did not search for etiologic agents in the controls, which means that the relative pathogenicity of the agents in this population cannot be determined. This omission is especially worrisome in highly endemic areas, where many children carry enteropathogens without symptoms. As a result, the risk of disease attributed to these pathogenic agents could be overestimated in these studies.

Also, few studies measure the economic cost of diarrhoea for the families and for the National Health System, to obtain a detailed picture of the disease burden.

Finally, the use of homogenised serologic and molecular tests for diagnosis is important to be able to compare data from different studies.

To answer these questions, the Global Enterics Multi-Center Study (GEMS) was designed. The CISM participates in this study together with other research centres around the world.

The GEMS study, funded by the Bill and Melinda Gates Foundation (BMGF) and coordinated by the Center for Vaccine Development, University of Maryland School of Medicine (United States), aims to determine the burden, the microbiological etiology and the clinical presentation and sequelae of moderate and severe diarrhoea in children between 0-59 months of age in Sub-Saharan Africa and in Southern Asia. The overarching goal of the project is to serve as an orientation for the development and implementation of vaccines and other interventions. The deaths and sequelae caused by diarrhoea will be determined through a 60 day follow-up period of the patients. The direct and indirect costs caused by severe diarrhoea episodes will also be evaluated.

Researchers

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PNEUMONIAS AND OTHER INVASIVE BACTERIAL DISEASES

Acute respiratory infections and invasive bacterial diseases are responsible for an important number of deaths in the paediatric population. The last report from UNICEF/WHO estimates that pneumonia is responsible for 19% of deaths at the global level in children under 5 years of age. An important proportion of the pneumonia cases and deaths are caused by bacterial agents, among which *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) are the most prevalent. Other causes of pneumonia include viruses, the principal agent being the Respiratory Syncytial Virus (RSV).

The activities of the CISM in this area are focused on three aspects: epidemiologic surveillance (including studies on antibiotic resistance), improvement of diagnosis and the evaluation of control strategies.



Mother with her child in the outpatient department.

EPIDEMIOLOGICAL SURVEILLANCE

The epidemiological surveillance of pneumonias, bacteraemias and meningitis is a key tool to evaluate the burden and associated mortality of each of the pathogenic agents responsible for these diseases. Moreover, monitoring the levels of resistance to the most frequently used antibiotics in the country is necessary to evaluate current treatment strategies.

Since 1998, the CISM has been working in an Epidemiological Surveillance project focused on pneumonias, bacteraemias and meningitis in children in the Manhiça District Hospital (MDH).

In 2006, the Centre reported data on the epidemiology of pneumococcal invasive disease in children under 5 years of age, (Roca *et al.*, TM&IH 2006; 11) that showed an incidence of 416/100,000 child-year at risk (reaching 779/100,000 in children under 3 months of age), with a case fatality rate of 10% (rising to 56% in children with meningitis caused by this microorganism).

During this period, the Centre continued the surveillance of acute bacterial meningitis and bacteraemias, identifying the different bacterial etiologies. The CISM also carried out a specific evaluation of the burden of invasive *H. influenzae* type b (Hib) infections. The Centre also initiated studies on the molecular epidemiology of *S. pneumoniae* and *Neisseria meningitidis* that are described below.

Bacteraemias and acute bacterial meningitis

Bacteraemias in children under 15 years of age diagnosed during the period from 2001 to 2006 were reviewed and analysed. Results showed that as many as 8% of the children admitted to the hospital had bacteraemia and that the most prevalent pathogens were *Salmonella* non-typhi (NTS) and pneumococcus (26% and 25%, respectively). In children under one month of age, *S. aureus* and *streptococcus* group B were the most prevalent (39% and 20%, respectively). The minimum community-based incidence rates were 1,730/100,000 child-years at risk in children under one year of age, 782/100,000 child-years in children between 1 and 4 years of age and 49 per 100,000 child-years in children 4 years and older. The overall case fatality rate of bacteraemias was 12%. These results will be published during 2009.

More recent data on acute bacterial meningitis in children show that the most frequent pathogenic agents are Hib, pneumococcus, and *N. meningitidis*. The overall incidence rate of paediatric bacterial meningitis was estimated at 85/100,000 child-years at risk, peaking in children between 2 and 12 months of age (1,078/100,000 child-years at risk). The overall case fatality rate for meningitis was 24%. These data suggest that an important proportion of the cases of bacterial meningitis could be prevented using currently available conjugate vaccines against pneumococcus and Hib. These results will be published during the year 2009.

Characterisation of the invasive infection by Hib

*H. influenza*e type b (Hib) still causes over 3 million clinical episodes each year, and close to half a million deaths, the majority of them in developing countries. In order to evaluate the benefit of introducing the available conjugate Hib vaccine in a given country, it is crucial to have information on the burden of Hib disease. However, in Sub-Saharan Africa, diagnostic capacities are limited and the burden of Hib disease has been underestimated. The CISM carried out a study to characterise the epidemiology, clinical presentation and microbiology of invasive Hib disease in children less than five years of age.

The study was done by analysing samples obtained in the Centre during the period of 2001-05. During this period, 106 episodes of disease by Hib were described, with a minimum community incidence rate in children under 5 years of age of 125/100,000 child-years at risk. Data showed that 56% of the cases were found in children between 3 and 12 months old. The case fatality rate of Hib invasive disease was 21%, and isolates showed a high resistance to the most frequent-ly used antibiotics in Mozambique (39%, 35% and 74% for chloramphenicol, ampicillin and co-trimoxazole, respectively)



Courtesy of the Bill & Melinda Gates Foundation/Prashant Pa

Preparation of a slide for gram staining of a positive blood culture.

These results showed a burden of Hib disease that justifies the introduction of the vaccine in the country. These data were used by Mozambique in its application to the GAVI Alliance for funds to introduce the vaccine.

Molecular epidemiology of S. pneumoniae

S. pneumoniae is one of the principal bacterial etiologies of pneumonia and meningitis in children. The pneumococcus has more than 90 serotypes, of which more than 20 can be invasive. The distribution of invasive serotypes presents variations depending on the geographic area. In the meantime, the most effective vaccines against pneumococcus in children (the age group most affected by the severe forms of the infection) only include a certain number of serotypes and, thus, its potential coverage depends on the local serotype distribution.

The Centre is currently characterising the serotypes of the invasive strains isolated in the last 8 years, to evaluate the potential coverage of the existing vaccines. For this purpose, molecular diagnosis technology previously developed at the Centers for Disease Control and Prevention (CDC) of the Unites States of America, was transferred to the CISM.

Moreover, the Centre is currently genotyping the invasive isolates in a collaborative project with the *Universidade Fiocruz de Salvador de Bahia* (Brazil). These analyses will contribute to the understanding of the clonal transmission mechanisms of invasive pneumococcus.

Molecular epidemiology of N. meningitidis

The surveillance of bacterial meningitis carried out by the CISM since 1998 and reinforced in the year 2006 revealed that *N. meningitidis* is the third cause of meningitis among children admitted to the Manhiça District Hospital. Recent data reveal a significant increase in the number of meningitis cases diagnosed in the last few years, resulting in high incidence rates. The W-135 sero-group is the most prevalent, similarly to what has been observed in neighbouring countries like South Africa over the last few years.

The molecular epidemiology of the *N. meningitides* isolates obtained from invasive samples during the last 10 years and the pattern of resistance to antibiotics are being studied, using the molecular characterisation of the bacteria and the determination of the minimum inhibiting concentrations for the antibiotics used in the treatment of meningitis in Mozambigue.

IMPROVEMENT OF DIAGNOSIS

Differential diagnosis of pneumonia and malaria

In endemic areas, the majority of the malaria cases are diagnosed and treated based on the presence of fever or history of fever without laboratory confirmation of parasitaemia. On the other hand, malaria in children frequently provokes respiratory distress that, together with fever, is also very frequently present in pneumonia cases.

Due to this overlap in signs and symptoms, misdiagnosis of pneumonia and malaria is frequent in areas with scarce diagnostic resources. Poorly diagnosed patients could be either under treated or over treated, using resources that are limited and accelerating the development of resistance to antibiotics in the community.

At the end of the year 2007, the CISM completed a study that aimed to characterise the signs and symptoms of children with a clinical presentation compatible with pneumonia and malaria, so as to improve the differential diagnosis between the two diseases. These data are being analysed and will be published during the year 2009.

Biomarkers for the diagnosis of the most frequent infections

The differential diagnosis of bacterial and viral diseases, as well as malaria, is difficult in cases where the clinical presentation is very similar and where diagnostic resources are limited.



X-ray image of a child with pneumonia.

This project, developed by the CISM, aims to provide evidence to support the development of new simple, inexpensive and minimally invasive diagnostic tools, that could be used in rural health centres in Africa to determine the etiology – *P. falciparum*, bacterial and viral – of infectious diseases in children. This will be done by exploring the use of various biomarkers to distinguish between malaria, bacterial and viral infections in children that present with fever and other unspecific symptoms to the Manhica Health Centre.

Determination of the bacteria that cause bacterial meningitis using the Real Time Polymerase Chain Reaction (real-time PCR)

Acute bacterial meningitis is one of the most serious diseases in Sub-Saharan Africa, which as a region registers more than one million cases yearly. There are three main bacteria responsible for this disease: Hib, *S. pneumoniae* and *N. meningitidis*.

The incidence of meningitis caused by each one of these bacteria is frequently underestimated. Previous use of antibiotics before collecting cerebral spinal fluid (CSF) greatly complicates isolation and, consequently, the identification of bacteria. Molecular diagnosis technology could significantly improve the diagnosis of Acute Bacterial Meningitis (ABM) in negative CSF culture samples. Techniques such as real-time PCR are capable of detecting minimal quantities of bacterial DNA with a specificity higher than 95% to discriminate between Hib, *S. pneumoniae* and *N. meningitidis*, providing a more exact estimation of the incidence rate of the disease caused by each one of these bacteria.

The CISM is implementing the diagnosis of ABM using realtime PCR techniques, as a complement to the traditional microbiological diagnostic methods. This will also allow measuring the effect of the administration of antibiotics before collecting cerebral spinal fluid on the rate of isolation of the bacteria using cultures.

PNEUMONIAS AND OTHER INVASIVE BACTERIAL DISEASES

EVALUATION OF CONTROL STRATEGIES

Evaluation of the effectiveness of the Hib vaccine in Mozambique

Invasive Hib infection used to be the predominant cause of meningitis and pneumonia in developed countries before the conjugate Hib vaccine was introduced. This vaccine is approximately 98% effective against Hib invasive disease and its use has practically eliminated this disease in many countries. Data obtained at the CISM on the burden of Hib disease were used by the Ministry of Health of Mozambique to request financial support to introduce the vaccine in the country. The introduction of the vaccine is expected for 2009.

The CISM has initiated a project that aims to monitor the effectiveness of the immunisation with the Hib vaccine within the Expanded Programme on Immunisation (EPI). This monitoring of the impact of the vaccine is of capital importance for the country itself and also for the international community.

The effectiveness of the vaccine will be evaluated within the study area using the Morbidity Surveillance System at the

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Sample of cerebral spinal fluid in a bacterial meningitis case.

CISM to compare the incidence of Hib invasive disease, before and after the vaccine introduction, and also by concomitantly carrying out a specific case-control study to assess risk factors for Hib invasive disease.

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MATERNAL AND REPRODUCTIVE HEALTH

The improvement of maternal and reproductive health is one of the priorities of the international community and it is considered key for the social and economic development of low-income countries. A study carried out in 2005 by the WHO and other international organisms estimated that there were 536,000 maternal deaths on a global level. Of these, 99% took place in developing countries and 50% in Sub-Saharan Africa.

In this section, the Centre's research lines that are focused on maternal and reproductive health are presented. The projects developed during this period were carried out in five areas, namely: (i) maternal mortality, (ii) malaria during pregnancy, (iii) monitoring the safety of antimalarial and antiretroviral drugs during pregnancy, (iv) Human Papilloma Virus and (v) HIV/AIDS.

Research in HIV/AIDS (study on the vertical transmission and development of prevention tools) is presented in the *HIV/AIDS and tuberculosis* and the *Medical anthropology and demography* sections.



Placenta with parasites.

MATERNAL MORTALITY

Maternal mortality continues to be one of the most serious problems in developing countries. Recent estimations indicate that close to half a million women die every year from complications related to pregnancy and giving birth, half of them in Africa. As a consequence, more than one million children become orphans.

However, there is little information about the causes of these deaths. One of the Millenium Development Goals (MDG) is to reduce mortality by three fourths by 2015, but in order to do this, information is needed about the causes of maternal deaths in developing countries. In these countries, the principal sources of information are hospital files and verbal autopsies, that can provide important information regarding the causes of maternal deaths to guide public health policies. Nonetheless, these two sources present limitations.

On the other hand, the available information during the last years suggested that obstetric complications are the principal cause of death in developing countries. However, the impact of the HIV/AIDS epidemic, as well as of malaria, on maternal mortality in the last two decades has scarcely been researched.

The CISM carried out a descriptive study to determine the causes of maternal death in the Central Hospital of Maputo (CHM) -a tertiary hospital- that included complete autopsies during the period 2002-04. Maternal mortality during the study period was 8.47 per 1,000 live births. Obstetric complications were responsible for 38.2% of the deaths, with bleeding as the most frequent cause.

Non-obstetric diseases were responsible for 56.1% of the deaths. Infectious diseases, principally HIV/AIDS, pyogenic broncho-pneumonia, severe malaria and pyogenic meningitis, were responsible for more than half of the deaths (56.1%), even after effective measures were given for their treatment. These results clearly showed the need to implement preventive strategies that are accessible and effective, such as IPT during pregnancy and insecticide-treated nets, antiretroviral treatment for HIV/AIDS, and vaccines and antibiotics for pneumococcal and meningococcal diseases.



Woman showing a mosquito net placed in her house.

MALARIA DURING PREGNANCY

Clinical characterisation of malaria in pregnant women

There is a generalised opinion, based on a small number of information sources, that in areas with stable malaria transmission, the majority of women with an infection by *P. falciparum* do not present symptoms. The CISM carried out a study that aimed to clinically characterise malaria in pregnant women and to evaluate the clinical management strategies.

The study was done between August of 2003 and November of 2005 in the antenatal clinic of the Manhiça District Hospital. A total of 3,129 visits to the hospital were used in the analysis. The study showed that in 77.4% of the visits, women had symptoms suggestive of malaria, 23% of them during the first trimester. Parasitaemia was confirmed in 26.9% of the visits. The most frequent symptoms were headache (86.5%), arthromyalgia (74.8%) and a history of fever (65.4%), but the positive predictive values for the presence of parasites in blood were low (28%, 29% and 33%, respectively).

The study concluded that the presence of symptoms suggestive of malaria are frequent in pregnant women in a stable malaria transmission area. However, less than a third of the women had parasites in blood. In the context of absence of a microscope or rapid diagnosis tests, an important proportion of women, including women in their first trimester of pregnancy, may receive treatment unnecessarily, in some cases with drugs that may not be safe during pregnancy. These results highlight the need to develop diagnostic tools and safe drugs to be used in pregnant women.

Intermittent Preventive Treatment (IPT) during pregnancy and Insecticide-treated Nets

Every year, close to 50 million women get pregnant in areas where malaria is endemic, half of them in Africa. Malaria during pregnancy is associated to maternal and foetal morbiditiy, mortality from maternal anaemia and low birth weight and premature births. Malaria prevention during pregnancy is, therefore, one of the public health priorities, mainly in Sub-Saharan Africa.

In spite of the fact that the Intermittent Preventive Treatment (IPT) during pregnancy and the use of insecticide-treated nets have separately shown to be effective in reducing the consequences of malaria during pregnancy, there was no information about the safety and efficacy of the two interventions when used together.

The CISM carried out a randomised, double-blind study to evaluate the safety and efficacy of the IPT during pregnancy with Sulfadoxine-Pyrimethamine (SP) administered together with the use of insecticide-treated nets in pregnant women. The aim was to create evidence to guide public health policies for malaria prevention during pregnancy.

A total of 1,030 women participated in the study and were randomised to receive two doses of SP or placebo. All of them received an insecticide-treated net during their antenatal visit. The primary endpoint was the reduction of low birth weight.

The study demonstrated that the intervention with SP was safe and well-tolerated, even with the high prevalence of HIV/AIDS in the study area, and that it reduced the incidence of clinical malaria by 40%. The intervention reduced certain indicators such as clinical malaria, peripheral parasitaemia and placental infection, but these



Preparation of a slide to determine parasitaemia.

improvements did not have a significant impact on birthweight or prematurity.

New drugs for IPT during pregnancy

The emergence of resistance to SP particularly in Eastern Africa, caused concern regarding the use of this anti-malarial drug for IPT during pregnancy in the mid and long term. On the other hand, HIV infection increases susceptibility to malaria and could reduce the effectiveness of current interventions. Therefore, there is an urgent need to evaluate new anti-malarial drugs that could be used for IPT in both HIV negative and positive women. Among the anti-malarial drugs that are currently available, mefloquine (MQ) is the one that offers more advantages.

The CISM is participating in a consortium that involves centres in Benin, Gabon, Kenya and Tanzania, that aims to evaluate the use of MQ for IPT during pregnancy. The study will be a randomised, multicentre, double-blind trial to evaluate the safety and efficacy of MQ compared to SP for IPT during pregnancy, in the context of insecticide-treated nets that will involve 4,260 pregnant women who will be followed up until their child is one year old.

In the countries where the prevalence of HIV infection in pregnant women is greater than 10% (namely Kenya, Mozambique and Tanzania), MQ will be compared with a placebo in women infected by HIV receiving prophylaxis with co-trimoxazole (1,070 pregnant women followed up until their baby is two months old).

The CISM will be responsible for the data management for all the trials and will later coordinate the analysis of the data. These trials will be done in the context of the Malaria in Pregnancy Consortium, an international consortium that aims to improve the prevention and treatment of malaria during pregnancy.



Card used in the pharmacovigilance study.

MONITORING THE SAFETY OF ANTI-MALARIAL AND ANTIRETROVIRAL DRUGS DURING PREGNANCY

There is currently little information about the incidence of adverse reactions produced by drugs (Adverse Drug Reactions – ADR) in Mozambique, and especially about the use of anti-malarial and antiretroviral drugs in pregnant women. Mozambique is making efforts to establish a pharmacovigillance system, but the system has yet to be able to capture the maximum amount of information regarding ADR. ADR are an important cause of mortality in many countries, and they can even reach levels of 10% in hospitalised patients. In the context of the introduction of new treatments against malaria and HIV/AIDS and of the large presence of co-morbidities by these two diseases, having information about the ADR of these drugs during pregnancy is of vital importance.

The CISM is implementing a study to evaluate the safety of different anti-malarial and antiretroviral drugs used during pregnancy. All of the ADR that take place during pregnancy are registered in questionnaires during the antenatal visits, and immediately after birth, the health status of the babies is also evaluated including the existence of congenital malformations. Children are also evaluated between 2 and 12 months of age to detect any anomalies that were not diagnosed at birth. The ADR are later evaluated to determine the existence or not of a causal relationship between the ADR and the use of drugs during pregnancy.

The recruitment phase of the study will end in February of 2009 and follow-up will be continued until the year 2010. A total of 1,224 women were recruited from the antenatal clinic at the Manhiça Health Centre and the Maragra Health Post. This project will complement the information generated by the other surveillance systems and will inform the Ministry of Health about the safety of these drugs when used during pregnancy.

HUMAN PAPILLOMA VIRUS (HPV)

In countries like Mozambique, where there is a high incidence of invasive cervical cancer but there are no effective screening programmes, the vaccine against the Human Papilloma Virus (HPV) could be a very effective strategy to fight this disease. However, there is little information about the distribution of the genotypes of the HPV in women with and without cervical cancer in Africa. This information is crucial to estimate the potential impact of the HPV vaccine. Preliminary evidence indicates that vaccines against the HPV genotypes 16/18 could also protect against infections from the genotypes 31 and 45. Understanding the contribution of these genotypes would allow the evaluation of the implementation of a HPV vaccine in Mozambique.

The CISM participated in a study to estimate the burden of HPV infections by genotype, analysing cervical samples of women with and without cervical cancer. The study confirmed the potential of the current HPV vaccines to reduce the invasive cervical cancer incidence in rural areas of Mozambique. The study showed also the relative importance of genotypes 51, 52, 45 and 35 as cause of cervical cancer, which could have implications regarding the development of future polyvalent vaccines.

HIV/AIDS

See HIV/AIDS and tuberculosis and Medical anthropology and demography sections.

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Woman receiving a mosquito net in the antenatal visit.

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MEDICAL ANTHROPOLOGY AND DEMOGRAPHY

Any health intervention that involves individuals needs to and must take into account the values, attitudes and beliefs of the target population. As such, social studies must understand and explain these phenomena using systematic scientific methodologies (quantitative, qualitative or mixed).

In the context of biomedical research, the social science approach offers an important additional value to the information generated by the other areas of knowledge, empowering the contribution of the CISM even more in the elaboration and implementation of health policies in the country.

The CISM research in the area of Medical anthropology and demography has the following objectives: (i) to evaluate the community perception regarding general health and the specific diseases, (ii) to describe the strategies that the communities adopt to preserve health and treat diseases, (iii) to identify the factors that determine the acceptance and adherence of specific health interventions, such as the research activities carried out by the CISM within the community and (iv) to determine the relationship of the socio-economic variables with health.

SOCIAL AND CULTURAL PROFILE OF PRIORITY DISEASES

There are 2 studies being carried out in this area that cover diseases such as tuberculosis (TB), malaria and acute respiratory infections, focusing on children.

Perception of mothers and caretakers of children under 5 years of age regarding febrile syndromes and respiratory infections

The correct and timely diagnosis is considered to be a fundamental step to reduce the mortality caused mostly by malaria and acute respiratory infections. This step depends on the recognition of febrile symptoms and respiratory problems and on the health seeking behaviour of mothers and caretakers of the children at risk.

This study aims to document the itinerary carried out by mothers and caretakers from the moment the first symptoms appear until they contact the hospital. The study also explores the interpretation that mothers and caretakers give for symptoms and which of them trigger them to seek health care. To do so, interviews were carried out with the mothers of children that were admitted for a short stay at the Manhiça District Hospital, and follow-up was carried out after the patients were discharged from the hospital. The same exercise was carried out with mothers of healthy children in the community. The data are now being analised.



Worker of the CISM at a meeting with the community.

Perception of tuberculosis (TB) and possible relationship with the practices of prevention and health care seeking in Manhiça

Undocumented evidence maintains that in certain areas of Africa, tuberculosis (TB) is seen as a disease that is acquired due to the transgressions of traditional taboos. Knowing that the choice of health providers is partially determined by the cause that the patient believes causes the disease, it is probable that many TB cases never reach the health units. In other contexts in Africa, it has been documented that



Women waiting to vaccinate their children.

60% of the patients diagnosed with TB in a health unit sought health care from alternative sources before arriving to the hospital. In these cases, the control measures for TB may not have the desired impact if the interaction between traditional and modern medicine is not taken into account.

This study aims to deeply understand the level of awareness of the community regarding TB, especially in children, and the perception of the etiology. Moreover, the study aims to understand the health care seeking behaviours in the presence of TB, in order to facilitate the efforts to find TB cases in the community, in the context of the National Tuberculosis Control Programme.

PERCEPTION AND ACCEPTANCE OF THE DISEASE CONTROL INTERVENTIONS

Anthropological studies in other regions have demonstrated that the adherence to a given therapy is socially and culturally constructed and that this dynamic adherence could depend on the perceptions and experiences of the patient, including the initial reaction of the organism to the treatment.

Perception and reaction to the ART, regarding the reconstitution of the immune system and adherence to treatment

The compliance of Anti-Retroviral Treatment (ART) and staying on it for the rest of the HIV/AIDS patient's life is crucial for it to be effective. This suggests that the patient's behaviour and attitude regarding treatment are important components for it to be successful.

Nonetheless, the restoration of the immune responses of

beneficial protection can also be accompanied by atypical opportunist infections and other associated diseases in the context of what is known as the Immune Reconstitution Inflammatory Syndrome (IRIS). These complications in the first months of treatment may influence the perception of the treatment itself. Moreover, when the patients improve after the start of the ART, they could have a false sensation of being cured, and thus an increased risk of stopping treatment.

Determining the perception of ART and its effect in the treatment compliance throughout the patient's life is important to guarantee that the design and implementations of ART programmes are sustainable, effective, accepted and easily adhered to by the target community. The work carried out by the CISM in this area aims to determine the level of understanding regarding ART, to perceive the interpretation made about the symptoms felt and its relationship with the adherence to treatment, as well as the reasons that lead to non-adherence.

Perceiving the implementation and reception of indoor spraying in Manhiça

In a recently finished anthropological study in the Manhiça District, it was observed that the community saw indoor spraying as their own strategy to control malaria. This was generally accepted, in spite of the fact that the majority of the participants and/or respondents considered that the spraying was hardly effective.

Nonetheless, it has been observed that the enthusiasm of the communities regarding spraying has decreased. This situation raises two questions: (i) how does one explain that a programme is acceptable in a community, although the community does not consider it to be effective? (ii) What factors contribute to the decrease in enthusiasm, if it is not correlated with the perception of efficacy of the programme?

The answer to these questions, that go beyond a simple question of "acceptance", requires a profound knowledge of the informal processes through which the health interventions are implemented and received in the community.

The acceptance (or rejection) of interventions such as spraying can not be adequately understood if the process of implementation is not taken into account, that alone cannot be understood without considering the broadest context of the political debates, of the coverage by the media and historical processes, at the local level as well as at the regional and international levels.

The study of current policies related with the implementation of the spraying programme in Mozambique and in the

MEDICAL ANTHROPOLOGY AND DEMOGRAPHY



Hospital worker giving a speech to mothers.

Southern African region requires, therefore, a historical analysis of political, social and cultural factors involved in the first attempt to control malaria in Mozambique through spraying with DDT. It is important to perceive the discourse used to present the current spraying strategies and the rhetoric strategies used to justify them.

The objective of this study was to understand, from a wide perspective, the development, implementation and reception of the Spraying Programme in the South of Mozambique. To do so, members of intervention-receiving family groups were interviewed along with the programme sprayers, the community leaders, those responsible for the elaboration of health policies at the national level and the opinion leaders at the international level. The data are currently being analysed.

FEASIBILITY AND ACCEPTABILITY OF CLINICAL TRIALS

Feasibility of microbicide trials

The CISM participates in the Microbicides Development Programme (MDP) network, whose objective is to develop microbicides for HIV infection prevention. A feasibility study is being carried out in order to prepare the CISM for the conduction of a phase III clinical trial to test a vaginal microbicide candidate against HIV transmission.

The study has the following objectives: (i) to evaluate the percentage of people with HIV and other Sexually Transmitted Infections (STI); (ii) to determine the level of awareness about HIV and AIDS in the community in general and more specifically in the study population; (iii) to identify sexual practices in the study areas; (iv) to evaluate the impact of the promotion of condoms and their use; (v) to determine the maximum attainable rate of recruitment and retention; (vi) to confirm if the materials to collect of information are of good quality; (vii) to evaluate if the women

respond to the study questions; (viii) to evaluate the willingness of women to participate in a future trial for Microbicides and (ix) to evaluate if women and the community are prepared to take on a new way to fight against HIV.

The study recruited and will monitor 500 HIV negative women from the areas covered by the 1 de Junho Health Centre (Maputo), and the Manhiça Health Centre. The study has 3 fundamental stages: First, the process of building awareness in the community and mobilising women to adhere to the study. Second, the recruitment and clinical follow-up of the participants using the same procedures that will be implemented in the clinical trial. Finally, sociobehavioural follow-up: This follow-up involves a sub-sample of 100 women and their partners, that are invited to participate in deeper interviews, focus group discussions and to experiment with alternative techniques for the collection of data on sexual practices.

In Mozambique, the Fundação para o Desenvolvimento da Comunidade (FDC), the INS/Ministry of Health and the CISM are the institutions responsible for the study.

Feasibility of HIV vaccine trials

This study is framed within the AfrEvacc Network, an international consortium that works to establish and fortify partnerships between African and European research institutions to create capacities to conduct clinical trials with HIV vaccines in the future.

The feasibility study has the following objectives: (i) to identify the attitudes and beliefs related with immunization in adults; (ii) to understand how people explain the concept of immunity, especially regarding HIV; (iii) to foresee the willingness to participate in future HIV vaccine trials and the factors that determine acceptance; (iv) to determine the maximum attainable rate of recruitment and retention of participants in the study.

Participants of the microbicides study.



Through this study, the CISM will gain crucial experience on the involvement of healthy adult men in clinical trials and the creation of a Community Advisory Board: a forum where representatives of the community and researchers can discuss issues to maximise the collaboration of the community with health research, as well as to adequate the procedures of the intervention studies to the local socio-cultural reality.

IMPACT OF PATERNAL MORTALITY ON CHILDREN'S HEALTH

In spite of the fact that adult mortality has increased in the last decades, especially because of HIV/AIDS, the consequences of these deaths on the children health status has yet to be adequately studied. The death of a father or a mother is associated with an increase of the vulnerability of families and a decrease in the survival of children, school drop-out, emigration and others. Therefore, improving the information on the survival of orphan children is necessary to better guide the support programmes for children in Mozambique.

To this aim, the CISM is carrying out an analysis of the relationship between paternal and maternal mortality and the health status and survival of children, using data from the Demographic Surveillance System and the Morbidity Surveillance System. This analysis will be published during 2009.



Focus group discussion on the microbicide study.

Researchers

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OTHER DISEASES

This section presents studies that do not fit in the previous sections. These projects are focused on some of the main health problems affecting children that are especially relevant to public health, such as anaemia, the effects of pesticides on health and measles.

ETIOLOGY OF ANAEMIA IN CHILDREN

Anaemia continues to be one of the most important public health problems in children in developing countries. The World Health Organisation (WHO) estimates that close to 2.000 million people in the world are anaemic. According to the report, close to 818 million women and young children suffer anaemia. For these two groups, the highest prevalence of anaemia is found in Africa, reaching 65% in children.

In children, anaemia is associated with a greater risk of death and deficiency in cognitive and motor development, growth and immune functions. Children admitted to hospitals with severe anaemia, even when they receive blood transfusions, have a mortality rate from 6 to 18%. Moreover, the majority of children at risk of severe anaemia do not have easy access to infrastructures with capacities to carry out blood transfusions.

Studies carried out in Eastern Africa showed that malaria caused by *P. falciparum* and iron deficiency are responsible for most of the cases of anaemia observed in children. Available data from the CISM show that malaria, infection by HIV (the prevalence in pregnant women is close to 25%) and malnutrition (prevalence of 56% in children attending the health services) are among the main causes of anaemia. On the other hand, there is no relevant data for the prevalence and possible contribution of micronutrients deficiency, intestinal parasites, schistosomiasis, bacteraemias and hereditary haemoglobin and erythrocyte diseases to anaemia in infants. Beyond this, little is known about the physiopathology of anaemia caused by malaria.

The CISM started a study to improve our knowledge on risk factors for anaemia and their respective contribution to cases of anaemia. This information is necessary to develop new control strategies and to better implement those that already exist. The study also aims to improve the biochem-



Collection of a sample from a child for haematocrit determination.

ical markers to diagnose iron deficiencies, as well as to investigate the mechanisms involved at the cellular and molecular level in the anaemia caused by malaria. The study is foreseen to be finished at the beginning of 2010.

STUDY OF THE EFFECTS OF PESTICIDES ON CHILDREN'S HEALTH

One of the tools to combat the transmitting vector of malaria is the use of insecticide-treated nets and the periodical fumigation of the house with pesticides. It is known that certain pesticides used for indoor spraying, like DDT, for example, pass through the placenta and breast milk and have negative effects on the health of infants. Due to the increase of scientific evidence on the effects of DDT on health and the environment, its use has been stopped, except in malaria endemic areas. In Manhiça, malaria is endemic and indoor spraying has been done with DDT.

The CISM is carrying out a study to evaluate the effect of the exposure to contaminants derived from the fumigations with DDT on the health of children in the Manhiça District, depending on the existence or not of indoor fumigations. This study involves children and their mothers and aims to determine the concentrations of organochloride pesticides in samples of breast milk, from umbilical cord blood and in the thatches of the houses, in order to evaluate their effect on the immune status of the children using immune markers.

This study is being carried out in collaboration with the Centre de Recerca Ambiental – CREAL (Spain).

EPIDEMIOLOGY AND VIRAL LOAD OF MEASLES IN THE MANHIÇA DISTRICT

Measles continues to be a health problem in developing countries, in spite of the existence of an effective vaccine. It is estimated that this disease is responsible for almost half a million deaths per year, half of them African children under 5 years of age.

In Sub-Saharan Africa, the measles vaccine is administered in a single dose at 9 months of age as part of the Expanded Programme on Immunisation (EPI). The use of the current vaccine in children under 9 months old is limited, as it is not effective when maternal antibodies are present, until 6-8 months of age. These antibodies protect children from measles during the first days of life, leaving them susceptible when the titles of the antibodies begin to lower. The difficulty of ensuring a good cold chain in rural areas also constitutes a problem for the use of this vaccine.

Available data indicate the occurrence of measles in children before they are old enough to be vaccinated, which is associated to a high case fatality rate. The need to implement new strategies to vaccinate children under 9 months of age, in order to protect them during the so-called period of "vulnerability" is currently being discussed. In order to evaluate new vaccination strategies, more information about the epidemiology of measles in children and young adults is needed.

In this sense, the CISM carried out a study to describe the epidemiology and burden of measles in the Manhiça District. To this aim, a case-control study and two cross-sectional studies were carried out to determine the prevalence of measles antibodies in maternal plasma and breast milk in the Manhiça District.

The case-control study was carried out in the general population (children and adults), and the cross-sectional studies were carried out in children and young adults, to evaluate the sero-prevalence of specific measles antibodies (IgG) and in women between the ages of 14 and 47 while breastfeeding to evaluate the presence of specific antibodies of measles in maternal breast milk.

The results of the studies on the prevalence of antibodies showed that 53.6% of the individuals had antibody titles above the protection level (>=200mIU/mL). However, a high



Informative poster of the EPI calendar.

prevalence of individuals with non-protective antibody titles was found, including 20.5% of the people that had non-detectable titles.

From the vaccinated group, 20.7% had non-protective antibody titles. Almost all (96%) children between 6 and 8 months of age did not have protective antibody titles, suggesting a low transfer of maternal antibodies to children.

The study showed that, although recent immunisation campaigns have been carried out in the study area, a notable proportion of the population is susceptible to measles. Moreover, the study confirms the window of susceptibility in children between 6-8 months of age. The data from the case-control study is currently being analysed.

Researchers

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PUBLICATIONS

Mandomando IM, Naniche D, Pasetti MF, Valles X, Cuberos L, Nhacolo A, Kotloff KL, Martins H, Levine MM, Alonso P (2008) Measles-specific neutralizing antibodies in rural Mozambique: seroprevalence and presence in breast milk. Am J Trop Med Hyg 79(5):787–792

SECTION





Services

DEMOGRAPHY DEPARTMENT

Head of Department: ARIEL NHACOLO, BSc, MSc

ourtesy of the Bill & Melinda ates Foundation/ Prashant Panjia



Demography Department worker during a visit to update demographic data.

This department is responsible for maintaining the Demographic and Geographic Platforms, which are two of the three research platforms needed to develop the Centre's research activities.

These two platforms are key to CISM activities, as they provide information about the geographical position of houses and other relevant geographic data, as well as basic demographic information about the population of the study area, enabling the permanent surveillance of deaths, births, pregnancies and migratory movements. This information allows to establish precise and credible demographic indicators.



The CISM is a founding member of the INDEPTH Network, formed by 37 centres that use Demographic Surveillance Systems in 19 countries in Africa, Asia and Central America. This network contributes to knowledge sharing between the different centres and enables the dissemination of information, promotion of courses and internships, training and standardization of research methodologies, as well as the sharing of articles published in the centres.

The department is formed by geographers, field workers and data clerks. The Demography Department, during the 2007-08 period, strengthened its team by hiring new field workers and data clerks, and by incorporating a new geographer.

Moreover, in the technology area, the department purchased an automatic meteorological station and improved the Geographic Information System (GIS).

The CISM study area includes approximately 84,000 people (around 25,000 families) in a surface area of approximately 500 km2. In the following table, some of the basic demographic indicators of the study area are represented.

	2004	2005	2006	2007	2008
Total population (inhabitants)	73.519	79.349	81.169	82.521	84.217
Infant Mortality Rate (per one thousand live births)	83,9	77,4	71,8	70,8	55,5
Child Mortality Rate (per one thousand live births) <5 years of age	132,8	148	123,5	117,8	96,5
Maternal Mortality Rate (per one thousand live births)	6,3	8,1	6,2	8,7	7,0
Life expectancy, Males (years)	37,7	38,9	40,4	42,6	44,0
Life expectancy, Females (years)	46,7	48,4	50,1	52,8	53,7
Life expectancy, both sexes (years)	42,5	44,0	45,8	48,1	49,4

Various basic demographic indicators of the study area.

CLINICAL DEPARTMENT

Head of Department: TACILTA NHAMPOSSA, MD

The Centre works in close collaboration with the Manhiça District Hospital (MDH) and other health facilities in the study area, where the Morbidity Surveillance Platform is implemented. This platform includes the permanent registration of all outpatient visits and admissions of children under 15 years of age. The morbidity data, complemented with the data from the Demographic and Geographic Platforms, allow to monitor the priority diseases in the community and to measure the impact of health interventions.

Currently, the Centre is implementing the morbidity surveillance in four health facilities in Manhiça, Maragra, Taninga and Ilha Josina.



Mothers with their children in the Manhiça Health Centre.

The Clinical Department has the role of coordinating the Centre's activities in these health units. Activities include healthcare provision, training of personnel and preparation of case-management guidelines, principally in the maternal and paediatric areas. The Centre also supports the refurbishment and construction of infrastructures in the health facilities of the study area.

The department is also responsible, in the context of the collaboration between the CISM and the Universidade Eduardo Mondlane (UEM), for the supervision of medical students that are in their last year of medical school, during their internships at the Manhiça District Hospital.

The CISM, fulfilling its mission, has been collaborating for the last years with the national health authorities in the implementation of national health programmes. The Centre is currently providing support to the implementation to the National STI/HIV/AIDS Programme and the National Tuberculosis Control Programme.

The CISM has been collaborating with the National STI/HIV/AIDS Programme since 2005 with the support of the Agència Catalana de Cooperació al Desenvolupament (Spain). The activities have been aimed at guaranteeing the counselling and testing for HIV and vertical transmission prevention programmes, as a means to contribute to the

control of the pandemic and to give support to the different studies being carried out in this area.

The support of the Centre to the National Tuberculosis Control Programme, initiated in 2002, consists of supporting the diagnosis of patients and the identification of contacts when a new patient is diagnosed.

Lastly, the Centre is collaborating with the Manhiça District Hospital in the Malnutrition Programme, through a collaborative project funded by the NGO Africa Viva.

	2007	2008
Number of paediatric outpatient visits ¹	60.862	60.500
Paediatric admissions	3.053	3.335
Intra-hospital case fatality rate	5,1%	3,0%
Number of patients on ART ²	1.399	1.888³
Number of HIV counselling sessions	6.684	5.330

Some indicators of the clinical activity in the study area.

¹ Under 15 years of age

² ART: anti-retroviral treatment

³ of which 142 were younger than 15 years of age

SOCIAL SCIENCES DEPARTMENT

Head of Department: KHÁTIA MUNGUAMBE, BSc, PHD



The Social Sciences Department gives support to the projects with important socio-behavioural components, contributing through the adaptation of the information given to the participants and the development of social and behavioural data collection tools.

The Department has the resources needed to establish a good relationship between the CISM and the community, aiming to maximize the collaboration of the community in the research activities.

Workers of the Social Sciences Department.



Speech to the community about the Centre's activities.

In order to attain the department's objectives, the department staff engages with representatives of the social groups found in the community, to whom they provide information about the Centre's activities involving the participation of the community. Information campaigns are also carried out to inform and educate the community about the Centre's mission and activities.

The long term vision of the department is to establish appropriate and structured forums, such as the Community Advisory Boards, to facilitate and ensure a constant dialogue between the community and the CISM.

LABORATORY DEPARTMENT

Head of Department: Luís Morais, VET



Automatic Culture Equipment of the microbiology laboratory.

The laboratory is currently undergoing a reorganization process to be able to face the new challenges, in terms of the provision of services to the hospital and research projects.

The Centre started a project to make the laboratory paperfree, aiming to improve the service quality and making access to information faster. In organisational terms, a new management structure was created, with a Laboratory Manager position and Area Supervisors, which will be implemented during the year of 2009. Regarding the infrastructure, the laboratory has started works to upgrade and expand the laboratory.

The Laboratory Department works in the following areas: (i) Parasitology, (ii) Biochemistry and Haematology, (iii)

The CISM carries out research activities that require laboratory services and diagnostic services for the Manhiça District Hospital (MDH). In particular, the Laboratory Department aims to provide services and support to the researchers that need these infrastructures, guaranteeing the required quality standards.

The laboratory works under the international principles of Good Laboratory Practices (GLP) and under Standard Operating Procedures (SOP). In order to assure that the procedures carried out comply with the GLP recommendations, the Department created an Internal Auditing System and has an External Quality Control Programme.

In this sense, one of the primary activities carried out by the Department during the 2007-08 period was to reinforce the Quality Assurance and Bio-safety Unit, and start the activities towards obtaining the ISO 9001:2008 certificate.

	2007	2008
Parasitaemia	48.870	39.589
Haematocrit	37.884	39.037
Full blood count	5.669	5.308
Biochemistry	11.517	4.472
Blood cultures	3.503	2.563
Immunology tests	820	565
CSF cultures	608	482
Bacilloscopies	1.519	1.816
Other cultures	1.113	786

Samples processed during 2007-2008.

LABORATORY DEPARTMENT



Researchers and technicians in the immunology laboratory



Worker in the parasitology laboratory.

Bacteriology, (iv) Immunology and (v) Molecular Biology. Beyond these five areas, the department also has a Quality Assurance and Bio-safety Unit.

The laboratory has a specific area to prepare culture media and solutions, for sterilisation and a room for fridges and freezers. This department is also responsible for the capturing and morphological identification of mosquitoes in the study area and the estimation of the entomologic inoculation rate.

PARASITOLOGY

This area performs malaria diagnosis by optical microscopy. It provides diagnostic support to the Manhiça District Hospital and to the other health facilities in the study area, seven days a week, performing semi-quantitative and quantitative readings of the slides. Besides the malaria diagnosis, they also carry out determinations of capillary hematocrit and they provide service to the Centre's research projects.

BIOCHEMISTRY AND HAEMATOLOGY

The Laboratory Department has automatic analysers for the determination of biochemical and haematological parameters that are able to process close to 60 samples per hour. The biochemical equipment uses the dry biochemical system that makes it possible to obtain parameters using only 10 μ L of serum or plasma.

During the year of 2008, new haematological and biochemical equipment was purchased.

BACTERIOLOGY

This area has two different sections: general bacteriology and mycobacteriology.

In the **bacteriology** section, the processing of blood, fecal, cerebral spinal fluid (CSF) and other body fluid samples is done.

The laboratory is equipped with automatic incubation systems for the blood cultures, performs cultures in solid mediums and uses concentration techniques to detect parasites. The isolated microorganisms are later identified using biochemical tests, latex agglutination and specific anti-serums, among other techniques. Antibiotic susceptibility tests are carried out using the disk diffusion test.

Additionally, the minimal inhibitory concentration tests for *Streptococcus pneumoniae* and *Neisseria spp*, are performed following current protocols recommended by the CLSI (Clinical and Laboratory Standards Institute, CDC, United States of America).

The **mycobacteriology** section gives support to the National Tuberculosis Control Programme in the Manhiça District and to the research projects in the tuberculosis area. Besides the culture of the samples and the identification of isolates using biochemical tests, the laboratory has the capacity to carry out susceptibility tests to the antibiotics used to treat tuberculosis.



Room for fridges and freezers in the laboratory.

IMMUNOLOGY

The immunology area has the capacity to evaluate the immune responses (cellular and humoral) against infectious agents. This area provides services, primarily, to malaria and HIV/AIDS research projects.

In this laboratory, human immune cells are phenotyped *ex vivo*, using surface colouration for their identification by flow cytometry (BD 4-color FACS Calibur). CD4+ count can also be performed using the same system. The culture of *cells in vitro* to measure specific immune responses to specific antigens is also carried out. The production of cytokines and cytotoxicity are evaluated using the intracellular colouration of cytokines, flow cytometry and methods based on ELIspot. The ELISA and immune-fluorescence techniques are used to detect antibody responses.

The laboratory also has the capacity to carry out *in vitro* culture of *P. falciparum*, to prepare parasite antigens and other parasitological procedures, and has personnel trained to carry out the histological processing (including immunohistochemistry) of placentas.

MOLECULAR BIOLOGY

The molecular biology area offers services to research projects that have a molecular epidemiology component, primarily in the area of diarrhoeal diseases, pneumonias, meningitis and bacteraemias. The unit has the necessary equipment to extract and amplify genetic material (DNA and RNA).

This laboratory has the capacity to diagnose and identify microorganisms, to perform their genotyping and serotyping when needed, and to determine molecular markers of resistance and cloning of bacterial agents using Pulsed Field in Gel Electrophoresis (PFGE).

QUALITY ASSURANCE AND BIO-SAFETY UNIT

The Quality Assurance and Bio-Safety Unit aims to guarantee that the activities carried out by the laboratory are done following the appropriate quality regulations, applicable to the safety measures in the laboratory and in the elimination of residues from the different laboratory procedures and processes.

The unit controls and supervises the laboratory processes and manages the SOP and the internal and external quality control, which includes the equipment. It is also responsible for training personnel in quality aspects and carrying out internal audits of the laboratory, in order to monitor and guarantee that the procedures are carried out as recommended by the Good Laboratory Practices.

DEPARTMENT OF DATA MANAGEMENT AND INFORMATION TECHNOLOGIES

Head of Department: ARNALDO NHABANGA, BSc

This department guarantees the data entry and storage of questionnaires and the administration and maintenance of the Centre's Information Technologies (IT). The data entry is done using a double entry system to minimise errors. Regarding the information technologies, the Centre has access to internet and the capacity to perform videoconferences.



Workers in the Data Centre

During the years of 2007 and 2008, close to 203,000 and 218,000 questionnaires were entered in the databases, respectively, corresponding to research projects and the morbidity platform.

The Department initiated a reorganization process to face the challenges of the Centre in the coming years and to allow for the separation of data management from information technologies. To do so, a new Supervisor position was created for Information Technologies that will be responsible for the maintenance and improvement of the infrastructures and processes related with information technologies. This position will allow the Department to address IT needs like the implementation of a Remote Data Entry System.

The department has planned during 2009 for the implementation of a new data entry software that will improve the quality management and the data cleaning process. The CISM is also planning to install a wireless network that will cover the Centre and the Manhiça District Hospital, thus allowing the data transfer between the two centres.

SECTION



Training

TRAINING

Head of Training: TERESA MACHAI, ENG., MBA



The consolidation and future sustainability of the CISM depends on the existence of qualified personnel to lead, manage and participate in research projects. Beyond this, Mozambique needs the development of these capacities for its own development, especially in the health and biomedical research areas.

Since the creation of the Centre in 1996, training researchers and technical personnel has been one of the strategic areas of the CISM. The collaboration with the Universidade Eduardo Mondlane (UEM) and the Universitat de Barcelona (Spain), have been key to strengthening the research and technical capacities of the country.

A course carried out at the CISM.

The centre has various training models including:

- Research Training: Training Fellowship Programme.
- Post-graduate training programme.
- Internships and short term stays for health sciences students and professionals in the CISM.
- Training of technical personnel on health sciences topics.
- Workshops and seminars.
- Training Projects in Mozambique.

Those who benefit from the training programmes are the workers of the Centre (some of which work in collaboration with other institutions such as the School of Medicine of the UEM, Ministry of Health, etc.) and external personnel.

A summary of the training activities is presented below.

TRAINING FELLOWSHIP PROGRAMME

The Centre, as a means to support the training of researchers in the country, created some years ago the Training Fellowship (TF) Programme, aimed at training young Mozambican graduates that wish to develop their professional career as researchers in the biomedical area. The programme provides the participants with direct experience in research through their involvement in research projects carried out in the Centre, and post-graduate training (master's or doctorates) at internationally recognised universities.

The programme is implemented in collaboration with the Barcelona Centre for International Health Research (CRESIB) and the Universitat de Barcelona (Spain), where the participants of the programme carry out internships during their training.

While participating in this programme, fellows may also carry out internships at other universities, research centres or international organisations. In the case of the medical doctors, the training can include support to do a specialty.

Since the beginning of the TF Programme, 17 researchers have benefited from the research training at the Centre, 6 of which have already finished their training. Dr. Francisco Saúte, Dr. Samuel Mabunda, Prof. Mamudo Ismail and Dr. Fátima



One of the Training Fellows from the Centre during an internship at the CRESIB/Hospital Clínic.

Abacassamo are among the researchers that have done their post-graduate studies at the Centre since the beginning of the programme.

Training Fellows during 2007-08

Augusto Nhabomba Ariel Nhacolo Betuel Sigaúque Diana Quelhas Eusébio V. Macete Inácio M. Mandomando José A. Machado Luís Morais M. Nélia Manaca Pedro Aide Sónia Machevo Tacilta Nhampossa

PhD degrees achieved during 2007-08

Eusébio V. Macete, "New control tools against Malaria", Universitat de Barcelona, Spain (2008).

Master's degrees finished during 2007-08

Jahit Sacarlal, "Public Health", Universitat Pompeu Fabra, Barcelona, Spain (2007).

Maria Nélia Manaca, "Public Health", Universitat Pompeu Fabra, Barcelona, Spain (2008).

Master's degrees in progress at the end of the 2008

Pedro Aide, "Epidemiology and Biostatistics", WITS University, Johannesburg, South Africa.

Internships in other institutions within the programme during 2007-08.

Eusébio V. Macete, six months internship at the World Health Organisation, Geneva, Switzerland (2007).

Betuel Sigaúque, internship at the Hospital Sant Joan de Déu (2006-08), Barcelona, Spain and during three months at the Pneumology Department of Hospital Clínic, Barcelona, Spain (2008).

POST-GRADUATE TRAINING PROGRAMME

The CISM supports post-graduate training of non-scientific personnel. Training during the 2007-08 period was focused on the areas of administration and management.

Throughout this period, 3 master's degrees carried out within this programme were finished, in the areas of human resource management and business administration.

Master's degrees finished during 2007-08

Abel Detepo, "Human Resource Management", Escuela de Alta Dirección y Administación, Barcelona, Spain (2007).

Lúcia de Deus, "Master in Business Administration (MBA)", Universitat Pompeu Fabra, Barcelona, Spain (2008).

Teresa E. Machai, "Master in Business Administration (MBA)", Universitat Pompeu Fabra, Barcelona, Spain (2007).

Master's degrees in progress at the end of 2008

Charfudin Sacoor, "Population Based Field Epidemiology", WITS University, Johannesburg, South Africa

INTERNSHIPS AND SHORT TERM STAYS FOR HEALTH SCIENCES STUDENTS AND PROFESSIONALS

The CISM receives health sciences students and professionals in the following categories:

- Pre-graduate UEM student internships.
- Internships for pre-graduate international health sciences students and professionals.
- Internships for national and international master's and PhD students.
- Internships for personnel from other centres with whom the CISM collaborates in the context of research projects, such as the MCTA, etc.

The CISM has an agreement with the School of Medicine of the UEM by which the Centre supervises the medical students during their rural and integrated internship at the Manhiça District Hospital. The coordination and supervision of these internships is done by the Clinical Department. During the 2007-08 period, the Centre supervised a total of 57 students.

The CISM also participated in the training of a Geography student from the UEM during a 3 months internship in the Demography Department of the Centre.

The CISM received during 2007-08 a total of 27 international health sciences students and professionals from countries where the most prevalent diseases in Mozambique are not endemic, such as Europe and the United States. The internships were carried out at the Manhiça District Hospital and additionally, in some cases, at the Central Hospital of Maputo.

Finally, the CISM participates in the training of national and international master's and PhD students through research projects carried out at the Centre. Currently, Dr. Esperança Sevene, a researcher from the UEM who is doing her PhD in Pharmacovigilance, is one of the beneficiaries of this programme. Her PhD will include projects carried out at the CISM, and she is expected to defend her thesis in the first months of the year 2009. PhD degrees based on projects carried out at the CISM

Cleofé Romagosa Pérez-Portabella, "Maternal Mortality in Sub-Saharan Africa: An Autopsy Study ", Universitat de Barcelona, Spain (2007).

TRAINING OF TECHNICAL PERSONNEL

The CISM contributes to the training of technical personnel through courses organised by the Centre and other institutions. The courses include training in Good Clinical Practices (GCP), Good Clinical Laboratory Practices (GCLP), Quality Management, Biomedical Diagnosis and Analysis and Systems Programming, among others. A list of the courses carried out during the 2007-08 period is found in annex 5.

Additionally, two university degrees are currently being carried out, one in general nursing and the other in paediatric nursing.

WORKSHOPS AND SEMINARS

The scientific and technical personnel participate in national and international conferences and seminars as a means to present results of studies conducted at the CISM, to develop research networks and to exchange knowledge and experience with other researchers.

Scientific sessions and journal clubs for the research and technical personnel are regularly performed at the Centre. These sessions are an essential training component for researchers and technical personnel and a means to sharing knowledge and research results among colleagues.

Finally, the Social Sciences department organised an international workshop in Maputo on qualitative data collection and analysis techniques in the context of microbicides development projects (described in the *Research* section).

TRAINING PROGRAMMES IN MOZAMBIQUE

Health Sciences Training Programme in Mozambique: Development of competencies and reinforcement of academic capacities of the School of Medicine, of the Universidade Eduardo Mondlane"

The general objective of the programme is to develop and create a collaboration between the Universidade Eduardo Mondlane (UEM) and the Universitat de Barcelona (UB, Spain) in the health sciences area, with the support of the

TRAINING



Some of the Training Fellows from the Centre during an internship at the CRESIB/Hospital Clínic.

Fundació Clínic, the CISM, the CRESIB and the "la Caixa" Foundation. Particularly, the programme is geared to identifying priorities and to designing and implementing training activities between the two institutions that lead to an improvement of the academic and research competencies and capacities of the Mozambican professionals in Health Sciences. Hopefully, with this programme, the collaboration between the two universities will be strengthened in the areas of teaching and research. The programme, funded by the "La Caixa" Foundation, was initiated in June of 2008 and it is foreseen to last until December of 2009.

The CISM supports the programme management in Mozambique, staying in close contact with the Fundació Clínic (institution that manages the programme) and participating in some of the training activities.

The Community Health, Pharmacology, Pathology and Microbiology and Parasitology departments of the School of Medicine are involved in this programme. The programme includes transversal training activities in Scientific Research Methodologies and the training of trainers. The following activities should be pointed out from this period:

- 1. Review of the Public Health Master's Programme at the School of Medicine of the UEM.
- 2. Participation of faculty from the UEM in 2 international conferences in pathology.
- 3. Seminar to review the thematic and analytical programmes in Pharmacology and Therapy, at the School of Medicine of the UEM.

SECTION





Administration and finance

ADMINISTRATION AND FINANCE

Head of Administration and Finance: JACINTO CHILENGUE, BSC

The Department of Administration and Finance guarantees the correct general functioning and economic-financial management of the Centre and its research projects. It is also responsible for the management of human resources, equipment, legal aspects, maintenance and improvement of infrastructures as well as other administrative tasks. Since the creation of the Manhiça Foundation, the Department of Administration and Finance is also responsible for the economic and financial management of the Foundation.



The Centre collaborated with the AECID in the construction of the new Manhiça Health Centre.

During the 2007-08 period, this department went through some changes, namely the arrival of a new Centre Administrator and the reinforcement of its personnel in order to improve the financial accounting and management of projects. New internal procedures that will contribute to the improvement in the management of Centre were also established.

The Centre was audited during this period by Price Waterhouse Coopers that presented a positive evaluation in their final report.

During the 2007-08 period, the Centre collaborated with the Agencia Española de Cooperación Internacional para el Desarrollo (AECID), to build the new Manhiça Health Centre (MHC), which was inaugurated in April of 2008.

The growth of the Centre and its activities, and the gradual increase of the Manhiça Foundation activity, represent a great challenge. The strategies laid out to face these challenges in the mid term include the improvement of capacities and procedures for the administrative management of the Centre and its research projects.



Relative contribution of funding institutions and agencies to the CISM budget during the 2007-08 period.



Príncipe de Asturias awards ceremony.

NEWS

SELECTION OF NEWS ABOUT THE CISM DURING THE 2007-08 PERIOD

CISM awarded the "Príncipe de Asturias" Prize

The CISM was awarded, on the 28th of May of 2008, the Príncipe de Asturias Prize for International Cooperation for the work that they have been carrying out on the fight against malaria in Mozambique. The ceremony took place in the Spanish city of Oviedo, where the Mozambican delegation was present.

The Príncipe de Asturias Prizes are given by the Foundation with the same name, that is presided by the prince of Spain and recognised internationally. The jury highlighted in their resolution the work of the Centre on the fight against malaria and other important diseases in Sub-Saharan African countries, as well as their capacity-building efforts to train technical and research personnel.

This award gives recognition to the work of the CISM to promote and conduct biomedical research in priority health areas, promoting and safeguarding the health of the population.

Other biomedical research Centres in Africa were also awarded for the work that they carry out in the African continent, namely: the Ifakara Health Institute (Tanzania), the Malaria Research and Training Centre (Mali) and the Kintampo Health Research Centre (Ghana).

The Príncipe de Asturias Foundation was created on the 24th of September of 1980,



Signature of the creation of the Manhiça Foundation.

in the city of Oviedo, Spain, with the goal to contribute to encouraging and promoting scientific, cultural and humanistic values that form part of mankind's universal heritage.

Manhiça Foundation Created

On the 25th of February of 2008, the Manhiça Foundation (MF) was created and became responsible for the management of CISM.

The MF was created to promote activities of technical-scientific development in the health area, and on a broader spectrum, to contribute to the improvement of the population health status through capacity building, research and the improvement of the quality of healthcare provision in Mozambique.

The course to formalise the Public Registration of the Manhiça Foundation was done by the Board of Trustees, constituted by the Honorary Founder and President of the MF, Pascoal M. Mocumbi, the vice-Minister of Health of Mozambique, Aida Libombo, the Director of the National Health



The Minister of Health, the Director of the INS and the Director of the CISM during the Minister of Health visit to the Centre.

Institute (INS), João Fumane, the Spanish Ambassador to Mozambique, Juan Manuel Molina Lamothe and by the President of the Fundació Clínic per a la Recerca Biomèdica and Dean of the Universitat de Barcelona, Màrius Rubiralta.

This ceremony was attended by members of the Mozambican Government, including Ivo Garrido, Minister of Health, Aiuba Cuereneia, Minister of Planning and Development, the Vice-Ministers of Education and Culture and Mineral Resources, Luis Covane and Abdul Razak, respectively, and the Governor of the Province of Maputo, Telmina Pereira.

During the co-fraternity ceremony on the 24th of February of 2008, the Minister of Science and Technology of Mozambique, Venâncio Massingue, claimed that "the creation of the Manhiça Foundation is done in the context of partnerships promoted by the Government geared towards fostering the contribution of scientific research, the innovation and transfer of technologies while searching for solutions to health problems in Mozambique".

The creation of the Manhiça Foundation is an important milestone in the collaboration between the Governments of Spain and Mozambique in the health research area, which started in 1996 through the creation of the CISM.

Minister of Health visits the CISM

The Minister of Health of Mozambique, Ivo Garrido, highlighted the quality of the projects carried out by the Centre and the importance of the results obtained to guide the design of health policies linked to the needs and the reality of the country.

Ivo Garrido gave these declarations during a visit that he made to the CISM in November of 2008. The objective of the visit was to learn more about the Centre and the projects that are being carried out.

During the visit, the Minister had the opportunity to visit all the departments of the CISM, where he received explanations about the Centre research platforms. After the visit to the departments, the most relevant research projects being conducted at the Centre were presented to the Minister.

Phase I/IIb trial of the malaria vaccine candidate against malaria shows efficacy

One of the research results with more relevance in the media during this period was the phase I/IIb trial of the RTS,S/AS02D vaccine in newborns, that demonstrated an efficacy of 65.9% during the first 6 months. This result was published in international media such as the New York Times, The Economist and the BBC.

This result revealed, for the first time, the efficacy of a malaria vaccine in this age group, and contributed to the decision making process that led to continuing the development of this vaccine candidate with the phase III trial.

The study was developed by the CISM in partnership with the CRESIB/Hospital Clínic (Spain), PATH Malaria Vaccine Initiative (MVI) and GSK and was funded by MVI. The RTS,S vaccine is being developed by GSK.

ANNEX 1: CISM PERSONNEL 2007-08

DEMOGRAPHY DEPARTMENT

Ariel Nhacolo Head of Department

Charfudin Sacoor Demographer

Delino Nhalungo Demographer

Leonildo Felisberto Demographer

Gertrudes Jacinto Mutola Community assistant

Adelaide Agostinho Give Vaccination assistant

Agibu Mahamade Bapú Supervisor

António Sousa Francisco Macamo Supervisor

Armando Eduardo Dimande Supervisor

Carlos Pereira Machava Supervisor

Farida Sultane Omar Supervisor

Salomão Augusto Mucocana Supervisor

Samuel Armando Simbine Supervisor

Sérgio José Bento Supervisor

Acrísio Nelson Maleane Field worker

Alfredo Paulino Sitoe Field worker

Angelina Luís Macamo Field worker

Armando Silvestre Chemana Field worker

Atanásio Joaquim chirinze Field worker

Atanásio Judite Matusse Field worker Aurécia da Gina Manguele Field worker

Beatriz Estévão Macaringue Field worker

Benedito António Jeco Field worker

Benício Vicente Chongo Field worker

Daúde Cassamo Ussemane Chitará Field worker

Dulce Alberto Mazive Field worker

Elias Silvestre Baloi Field worker

Elina José Chavango Field worker

Fátima Odete Mabote Field worker

Felicidade António Nhantumbo Field worker

Felisberto Victorino Mondlane Field worker

Felix Carlos Timana Field worker

Fernando Assício Matabula Field worker

Fernando Mondlane Junior Field worker

Ferreira Fernando Timana Field worker

Francisco Gomes Field worker

Francisco Morais Magaia Field worker

Gilda José Nhantumbo Field worker

Horácio Fernando Tamele Field worker

Ilda Fernando Xerinda Field worker **Isabel José Manganhe** Field worker

João Gabriel Nhassengo Field worker

Joaquim Casimiro Machava Field worker

José Luis Cossa Field worker

Julio Carlos Chavana Field worker

Júlio Paulo Mulhanga Field worker

Laurinda João Nwendzana Field worker

Lina António Timana Field worker

Lisete Francisco Mawelele Field worker

Lucas André Nhantumbo Field worker

Luís Titos Massimbe Field worker

Luisa Agostinho Mandlate Field worker

Luisa André Meque Manhiça Field worker

Luísa Vasco Dgedge Field worker

Maria Clara Sambo Field worker

Mário Albino Bila Field worker

Matias Salvador Bate Field worker

Milagre António Chisseve Field worker

Moisés Tomás Tembe Field worker

Mónica Gabriel Mimbirre Field worker Moniz José Simango Field worker

Narciso Francisco Macamo Field worker

Noa Felimone Mulhanga Field worker

Paixão Miguel Chilengue Field worker

Paulo Manuel Roldão Field worker

Pedro José Melembe Field worker

Rafael Armando Cumaio Field worker

Salomão António Mimbir Field worker

Santos Alfredo Melembe Field worker

Sérgio Fernando Xerindza Field worker

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Vasco Viriato Mahumane Field worker

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Zeca Júlio Matsinhe Field worker

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António Fernando Timana Transcriber

Bento Adriano Nhancale Transcriber

Ernesto Maximiano Mandlate Transcriber

Fanuel Maximiano Mandlate Transcriber João Campos Justino Mucasse Transcriber

Juvêncio Manuel Elias Joaquim Transcriber

Ventura Lourenço Amâncio Transcriber Arsénia Melita Mbeve Data clerk

Gina Carmina Firmino Data clerk

Isabel Langa Parruque Data clerk Julieta Laurinda Massango Data clerk

Lucinda Afonso Soto Data clerk

Sandra Paulino Sitoe Data clerk

CLINICAL DEPARTMENT

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Catarina David Medical doctor

Jahit Sacarlal Medical doctor

Pedro Aide Medical doctor

Sónia Machevo Medical doctor

Emili Letang Medical doctor

Jose Muñoz Medical doctor

Nayra Gutiérrez Medical doctor

Cinta Moraleda Medical doctor

Montse Renom Medical doctor

Quique Bassat Medical doctor

Iolanda Alice Júlio Manhiça Medical officer

Madalena Ripinga Medical officer

Adelina André Malembe Medical assistant

Ana Eugénia Matavel Medical assistant

Angélica Armando Chissano Medical assistant

Arminda Justina Lourenço Medical assistant

Berta Francisco Juga Medical assistant

Elsa Alfredo Banze Medical assistant Ester Lucas Matsimbe Medical assistant

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Inácio Ernesto Armando Noreno Medical assistant

Issufo Juma Aly Medical assistant

Jorge Alfredo Uqueio Medical assistant

Linda Elias Hamela Nhalucue Medical assistant

Lino Alexandre Guambe Medical assistant

Martinho Dzindichoque charles Medical assistant

Palmira Agostinho Monteiro Migi Medical assistant

Sérgio Roque Medical assistant

Telma Posseca Ngomane Medical assistant

Felicia Julio Boane Nurse

Manuel Muamede Nurse

Amónica Anita Filipe Ferrão Nurse

Ângela Mateus Chipera Lugenda Nurse

Apolinário Bartolomeu Nzango Nurse

Celina Judite António Lucas Nurse

Edmundo Fernando Calisto Nurse Felismina Alberto Cossa Nurse

Fortunato Romão Nurse

Helena Moreira Nurse

Idalina Alexandre Chicane Nurse

Jaime Carlos Lumbela Nurse

Jaime Julio Machai Nurse

Joana Ângelo Manhiça Nurse

Joaquina Mário Pinto do Rosário Nurse

Jorcelina José Rungo Nurse

Lídia Laço Majombole Nurse

Marilia Esperança Gonçalves Nurse

Melina Fabião Cuambe Nurse

Núria Alcária Abdul Gafur Nurse

Olívia Paulo Nhatsave

Recifal Sali Iaço

Nurse

Roque Singaril Vilanculo Nurse

Sérgio Marques Juliano Nurse

Vicente Salomão Monjane Nurse

Violeta Chiluane Ubisse Nurse **Maria Madalena Luciano Almeida** Midwife

Armindo Francisco José Lumbelane Community assistant

Filipe Arone Community assistant

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Eugénia Bilana Counsellor

Lucinda Fernando Xerinda Counsellor

Olívia António Macana Counsellor

Albertina Eduardo Manhiça Field worker

Alice Augusto Chithango Field worker

Humberto Dias Manuel Justino Mucasse Field worker

Júlia Da Silva Machava Field worker

Marta Marcos Macamo Field worker

Zumilde Arão Boca Field worker

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Irene Celestino Nhantumbo Receptionist

Isabel António Nguenha Receptionist

Maria Helena Xirindza Receptionist Maria Moisés Siúta Receptionist

Paulina Carolina Chipanga Receptionist

Teresa Jorge Chilaúle Receptionist

Isália Marta Salvador Boa Cook

Ancha Iracema Ricure Assistant

Belinda Simão Pelembe Assistant

Celeste Elias Chambal Assistant

Emília Ofélia Manhiça Assistant

Eunice David Chicuamba Assistant

Inácia de Lurdes João Mazutulelo Assistant

Latifa Ussumane Momade Assistant

Luísa Boaventura Mutevule Assistant

Rosa João Mboa Assistant

Rosalina Cochombane Massingue Assistant

Tânia Orlando Nhantumbo Assistant

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Head deputy

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Project assistant

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Lina Fiosse Social sciences assistant

Rui Anselmo Social sciences assistant

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Zeca Júlio Alseu Matsinhe Social assistant

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Carolina Mindú Community officer

LABORATORY DEPARTMENT

Inácio Mandomando Head of Department (until 2007)

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Hélder Bulo Laboratory manager

María José López Laboratory management and Quality Assurance

Lucinda Araújo Quality Assurance

Roberto Álvarez Warehouse and Bio-Safety manager

Amândio Chilengue Bio-Safety assistant

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Diana Quelhas Researcher

Dinis Jaintilal Researcher

José Machado Almeida Researcher

Maria Nélia Manaca Researcher

Mauricio Rodríguez Researcher

Nilsa de Deus Researcher

Ruth Aguilar Researcher

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Zita Jorge Sidumo Mhula Research assistant

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Esperança da Conceição José Lázaro Laboratory technician

Eugénio Sultane Mussá Laboratory technician

Mariano Sitaúbe Laboratory technician

Samira Ismael Sirage Laboratory technician

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Fernando Alfredo Zita Laboratory assistant

Lázaro Mussacate Quimice Laboratory assistant

Nelito Ernesto José Laboratory assistant

Salvador Aliasse Atibo Laboratory assistant

Salvador Fernando Mesa Laboratory assistant

Alfredo Fernando Zunguene Microscopist

Alzenda Amélia Bata Microscopist

Américo Sidónio Matusse Microscopist

Ana Motácia Dimande Microscopist

António Moisés Simango Microscopist

Augusta Adelaide Tembe Microscopist

Austrino Dos Santos Manhiça Microscopist

Carlinda Francisco Monche Tsucana Microscopist

Cecília Justino Zita Microscopist

Cidália da Graça Macuacua Microscopist

Guerreliwa Márcia Ribeiro Paulino Microscopist

Guilherme Lima Aníbal Sucamer Microscopist

Janeta Simão Vilanculo Microscopist

José Alexandre Gomes Microscopist

Laura José Cumbe Microscopist

Luísa Quitéria Francisco Manganhelas Microscopist

Pedro Alexandre Dimande Microscopist

Rita Mahigo Bambo Microscopist

Vânia Marta Moises Simango Microscopist

Vitória Justino Zita Microscopist

Elpídia Narciso Pedro

DATA MANAGEMENT AND INFORMATION TECHNOLOGIES DEPARTMENT

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Arsénio Nhacolo Statistician

Orvalho Augusto Software consultant

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Sérgio Tamele IT assistant

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Jossias Silvestre Sueia Warehouse manager Alice Pedro Melembe Data clerk

Helena André Cowana Data clerk

Lee João da Fonseca Data clerk

Orlando Carlos Tamele Data clerk

Abílio Almeida Data clerk

Albertina Lurdes Matabela Data clerk

Almirante Alberto Mulhovo Data clerk

Carlos Alberto Da Costa Correia Data clerk

Daniela Victor Alberto Data clerk Edna Das Dores Humberto António Data clerk

Eleutério Amone Chiau Data clerk

Erasmo Carlos Tamele Data clerk

Helena Armando Chavana Data clerk

Isabel Jorge Matlombe Data clerk

Isabel José Tsandzana Data clerk

Joaquim Paulino Sitoe Data clerk

Laura Janete Daniel Data clerk Madalena Boaventura Mutevue Data clerk

Nelson Jorge Machel Data clerk

Nicolau Pedro Massingue Data clerk

Sónia Manuel Matimele Data clerk

TRAINING AND COMMUNICATION

Teresa Eduarda Machai Head of Training and Communication (since August 2008) Salut Renom Head of Training and Communication (until July 2008)

ADMINISTRATION AND FINANCE

Jacinto Francisco Chilengue Head of Administration and Finance (since April 2008)

Sergi Noguera Head of Administration and Finance (until March 2008)

Emílio Aniceto Fernando Dava Project management

Mário Hermínio Djedje Internal auditor

Fernando Pizzabiocche Controller

Abel Alberto Detepo HR manager

Rosária de Jesus Paulino HR assistant

Ana Aguilera Project manager

Mário Alexandre Gomes Accountant Abel Carlos Massingue Accountant assistant

Sheila Geraldo Machevo Secretary

Carmina Camal Logistics

Constância Isaca Uamusse Logistics

Humberto Victor Poio Logistics

Isaura Armando Ngovene Logistics

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Palmira Gomes Lucas Warehouse assistant

Fernando António Dimande Maintenance manager Raimundo Alexandre Miambo Electrician

Celso Francisco Matola A/C technician

Ernesto Aurélio Mbeve Maintenance assistant

Pedro José Cossa Maintenance assistant

Araújo Ruface Cuamba Maintenance assistant

Pinto Jonasse Dimande Maintenance assistant

Fausa Baptista Mandlate Driver

Germano Adelino Matsimbe Driver

Joaquim Francisco Cossa Driver José Maiate Jeremias Nhabanga Driver

Júlio Matias Mpfumo Driver

Rafael Francisco Manhiça Driver

Sebastião Abílio do Espírito Santo Ouana Driver

Telmo Aldino Maússe Driver

Frederico Bernardo Chongo Mechanic

Sérgio Fernando Dimande Mechanic

Silvestre Dimande Mechanic

Boaventura António Mandlate Mechanic assistant Michael Armindo Muchanguana Mechanic assistant

Rudes Mundau Mandlate Security manager

Adriano Ernesto Mulhanga Security

Alberto Artur Macumbe Security

Alberto Zefanias Inguane Security

Américo Rafael Dimande Security

André Faustino Mandlate Security

António Miguel Mazanalo Security

António Vasco Chuva Security

Armando Anselmo Lipangue Security

Armando Juizo Melembe Security

Bernardo Chongo Security Carlos Duzenta Mutisse Security

Constantino Isac Maússe Security

Ernesto Mahache Muthombene Security

Ernesto Paulo Ubisse Security

Francisco Lázaro Nhabanga Security

Jacinto Macuacua Security

Joaquim Machava Security

Jorge António Jeco Security

Juca José Bulande Security

Júlio Ernesto Sousa Chicuamba Security

Manuel Henrique Malhongo Security

Mário Fernando Timana Security Moisés Vasco Mucachua Security

Pereira Luís Sitoie Security

Samuel Mazuva Macuácua Security

Sebastião Combo Muchanga Security

Sérgio António Sitoe Security

Sérgio Sebastião Muchanga Security

Silvestre Castigo Justino Zita Security

Xavier Ângelo Langa Security

Alexandre Luis Manhiça Gardener

Amone Nataniel Massango Gardener

Adélia Bernardo Nhassengo Housekeeping

Carmila Sofia José Norberto Come Housekeeping Delfina Alberto Macie Housekeeping

Ester Melita Mbeve Housekeeping

Gertrudes Adriano Maluvele Housekeeping

Guilhermina da Glória Buque Housekeeping

José Bachavana Cossa Housekeeping

Lurdes Gabriel Matsimbe Housekeeping

Maria Inês Mabote Housekeeping

Maria Raquel Francisco Utui Housekeeping

Nirma José Nhantumbo Housekeeping

Rabeca José Langa Housekeeping

ANNEX 2: COLLABORATING INSTITUTIONS

A large part of the projects and activities carried out by the CISM would not be possible without the collaboration of other institutions and organisations. The following list presents the principal collaborators of the Centre:

Aeras Global TB Vaccine Foundation (United States of America)

Africa Centre for Health and Population Studies (South Africa)

Medical Research Unit Albert Schweitzer Hospital (Gabon)

Center for Vaccine Development, University of Maryland School of Medicine (United States of America)

Centers for Disease Control and Prevention – CDC (United States of America)

Barcelona Centre for International Health Research – CRESIB (Spain)

Centre for Poverty-Related Communicable Diseases (Holland)

Centre Hospitalier Universitaire Vaudois, Division of Immunology and Allergy (Switzerland)

Contract Laboratory Services – CLS (South Africa)

Direcção Provincial de Saúde de Maputo – DPS (Mozambique)

Division of Infectious Diseases, University of Colorado Health Sciences Center (United States of America)

EuroVacc Foundation (Switzerland)

Fundação para o Desenvolvimento da Comunidade – FDC (Mozambique)

GlaxoSmithKline Biologicals – GSK (Belgium)

HIV Prevention Research Unit, Medical Research Council South Africa (South Africa)

Hospital Central de Maputo (Mozambique)

Hospital Clínic (Spain)

Ifakara Health Institute (Tanzania)

Imperial College London (United Kingdom)

Institute for Medical Microbiology and Hygiene, Universität Regensburg (Germany)

Institute of Tropical Medicine Antwerp (Belgium)

Instituto Nacional de Estadística – INE (Mozambique)

Instituto Nacional de Saúde – INS (Mozambique)

Instituto Superior de Ciências de Saúde – ISCISA (Mozambique)

International Center for Genetic Engineering and Biotechnology – ICGEB (India)

International Network of Field Sites with Continuous Demographic Evaluation of Populations – INDEPTH (Ghana)

International Partnership for Microbicides (United States of America)

Johns Hopkins Bloomberg School of Public Health (United States of America)

CDC/Kenya Medical Research Institute – KEMRI (Kenya)

KNCV Tuberculosis Foundation (Holland)

London School of Hygiene and Tropical Medicine (United Kingdom)

Makerere University (Uganda)

Mbeya Medical Research Programme (Tanzânia)

Medical Research Council – MRC (United Kingdom)

Ministério de Ciência e Tecnologia (Mozambique) Ministério da Saúde (Mozambigue)

MRC/Uganda Virus Research Institute Programme on AIDS (Uganda)

Novartis Pharma (Switzerland)

PATH Malaria Vaccine Initiative – MVI (United States of America)

Pneumonia Accelerated Development and Implementation Plan – PneumoADIP (United States of America)

Reproductive Health and HIV Research Unit, Chris Hani Baragwanath Hospital (South Africa)

Reproductive Health Research Unit, University of Wittswatersrand (South Africa)

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 – STI (Switzerland)

The Walter and Eliza Hall Institute of Medical Research (Austrália)

Universidade Católica de Mozambique (Mozambique)

Universidade Eduardo Mondlane (Mozambique)

Universitat de Barcelona (Spain)

Università di Torino (Italy)

University of Oxford (United Kingdom)

University Teaching Hospital (Zambia)

ANNEX 3: FUNDERS

The CISM appreciates the trust deposited in the Centre by the following funding institutions and agencies:

Africa Viva Fundación Agència Catalana de Cooperació al Desenvolupament (ACCD) Agencia Española de Cooperación Internacional para el Desarrollo (AECID) Bill & Melinda Gates Foundation European and Developing Countries Clinical Trials Partnership (EDCTP) Fondo de Investigación Sanitaria (FIS), Instituto de Salud Carlos III Fundació "la Caixa" GlaxoSmithKline Biologicals International Union Against Tuberculosis and Lung Disease Malaria Clinical Trials Alliance (MCTA) World Health Organization (WHO) PATH Malaria Vaccine Initiative (MVI) Pathfinder International PneumoADIP The Hib Initiative **European Union**

ANNEX 4: CISM PUBLICATIONS 2007-08

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Number of publications during the 2004-2008 period.

ANNEX 5: COURSES

Courses and workshops done by the CISM technical and research personnel during the 2007-08 period.

Date	Course, training session, seminar	Place
March 2007	Training in the management of Standard Operations Procedures (SOPs)	CISM
April 2007	Training in the management of Standard Operations Procedures (SOPs)	CISM
May 2007	Training in the management of Standard Operations Procedures (SOPs)	CISM
May 2007	Basic Course on Good Clinical Practices (GCP)	CISM
May 2007	Capacity-building in paediatric radiology	CISM
May – July 2007	"Strategies to Combat Social Exclusion at the local level" Course	Fundação para o Desenvolvimento da Comunidade (FDC) Maputo (Mozambique)
July 2007	Course on Good Clinical Practices (GCP)	Maputo (Mozambique)
August 2007	Training in PCR techniques, Iso-Hay and TV In Pouch	South Africa
August 2007	Review Course for field workers of the Demography Department	CISM
August 2007	Course in "Focalised Ethnographic Methods"	CISM
September 2007	Training in the correct use and maintenance of the Millipore water- purifying system, for internal use in the laboratory	CISM
September – December 2007	English Course	British Council, Maputo (Mozambique)
October 2007	Training in the management of Standard Operations Procedures (SOPs)	CISM
October 2007	Data Management Workshop (part of the EDCTP project "Ifakara, Lambaréné & Manhiça Partnership")	CISM
October – December 2007	Training in laboratory techniques including the splicing and prepa- ration of microscope slides from tissues fixed in formaldehyde, pre- paration of tissues, reading and identification of parasites, malaria pigments, inflammatory cells and in vitro cultures	Hospital Clínic (Spain)
February – March 2008	STATA Course	Barcelona Centre for International Health Research (CRESIB, Spain)
May 2008	Course on Good Clinical Practices (GCP)	Kumasi (Ghana)
June 2008	Patient Care Forum Training for Phase III Malaria Vaccine Lead Physicians	Brussels (Belgium)
March – July 2008	English Course	CISM
March – June 2008	Measurement of antibodies against P. falciparum variable surface antigens (VSA) in infected erythrocytes using flow cytometry	Barcelona Centre for International Health Research (CRESIB, Spain)
July 2008	Training on scientific writing	Livingstone (Zambia)
July 2008	Basic Course on Good Clinical Practices (GCP)	CISM
July 2008	Course on Good Clinical Practices (GCP)	CISM
September 2008	Radiology Training for the Phase III malaria vaccine trial	Nairobi
November 2008	Radiology Training	Cape Town (South Africa)
December 2008	Basic Course on microbiological diagnosis	Maputo (Mozambique)
December 2008	Basic Course on Good Clinical Practices (GCP)	CISM









