PROJECT FINAL REPORT

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Section 1 - Final Publishable Summary

1.1 Executive Summary

The STOPPAM project addressed the strategic objective HEALTH-2007-2.3.2-4: Addressing knowledge gaps in pregnancy malaria" of European 7th Framework Program. The goals of the STOPPAM were to conduct a cohort study in pregnant women and their newborns to quantify the effects of Pregnancy-Associated Malaria (PAM) and to identify a PAM vaccine candidate. By understanding the role of *P. falciparum* variable surface antigens expressed on infected erythrocytes in binding to placenta, and assessing whether the specific immune response against this antigen reduces the effect of PAM during latter pregnancies, STOPPAM aimed at making it possible to develop a new preventive strategy based on the enhancement of this specific response.

To achieve this goal, STOPPAM has performed two cohort studies in 2 endemic areas (West and East Africa), as the mechanisms and the resulting effects may vary with transmission. The Consortium was composed of seven partnering organisations (5 from 4 EU countries, and 2 from Benin and Tanzania) with a combined history of high class, internationally-recognized research in malaria. All EU teams have huge experience of collaboration with malaria endemic countries institutions and with studies related to malaria in pregnant women that are routinely conducted by the 2 African beneficiaries.

The objective was to recruit and follow-up 1 000 pregnant women in each study site. **In Benin**, 1,037 women have been included and 891 mothers have given birth in the health centres. **In Tanzania**, the required sample size of enrolling 1000 pregnant mothers was met and 928 women in the cohort had given birth within the project timeframe. As for the children cohort, 218 infants have been included and followed-up in Benin. Blood samples have been collected from all pregnant women and infants, processed and sent to the laboratories for analysis. Plasma samples have been frozen, in order to longitudinally assess inflammatory activity during pregnancy in women from the two cohorts. Placentas were also collected from delivering women for further quantification of placental alterations in the two groups of pregnant women. Venous blood samples with parasitaemia > 0.1% were also collected.

The ultimate goal of STOPPAM was to identify the most immunogenic epitopes of VAR2CSA (the major variable surface antigens of *P. falciparum* parasites infecting the pregnant women). For this purpose, several tools have first been implemented. We have generated substantial data on *var2csa* sequence from placental parasites. The sequence database comprises a minimum of 27 sequences encoding the DBL2X, DBL3X, and DBL5ε domains respectively, and 13 sequences encoding the DBL6ε. Forty PCR products covering the DBL4 domain have been cloned. Specific primers for *var2csa* real-time PCR studies have been designed. 88 VAR2CSA proteins and 4 control PfEMP1 domains have been produced. We also initiated the production of antibodies (against 4 DBL5ε variants from placental parasites) reagents using DNA immunization technique. Set of Luminex beads has been coupled with VAR2CSA recombinant constructs, and have been developed.
Multiplex quantitative real time PCR (qRT-PCR) method using these primers and a hydrolysis probes targeting the *18S rRNA* parasite was used to detect the presence of malaria parasites on the placental blood samples in both field sites. During the follow-up, RDT positive samples from pregnant women were preserved for use in qRT-PCR analyses. Venous blood samples with parasitaemia > 0.1% were maturated *in vitro* and stored in for flow-cytometry and inhibition binding assays. Placental isolates have also been obtained and preserved in glycerolyte from the deliveries. Analyses of VAR2CSA expression by *P. falciparum* on the surface of infected erythrocytes were performed and consistent expression of the protein was shown.

The measurement of the anti-Var2CSA antibodies response has been also studied. All plasma samples coming from the field sites were tested by Luminex to measure the levels of anti-VSA antibodies. Plasma samples of selected women with increased levels of anti-VSA between enrolment and delivery have been also tested for antibody maturation in binding inhibitory activity during pregnancy.

The assessment of inflammatory response and other factors have been analyzed in samples from subgroup pregnant women from Tanzania and Benin, during the course of their pregnancy. All malaria positive women were matched to uninfected controls based on age, gravidity and gestational age. Infected pregnant women indentified as thick smear positive were matched.

The assessment of PAM-induced cellular immunity on the sample collected was also done, using recombinant VAR2CSA DBL5ε & cryopreserved iRBC/uRBC. Samples collected at inclusion, from both RDT+ and matched RDT- mothers have been processed for cytometric measurements. The first 3-month and 6-month post-natal follow-up cellular immunology samples have also been processed from selected number of infants. In Tanzania, since the frequency of RDT+ has unexpectedly remained low (~3%), only few numbers of RDT+ samples were analysed.

Local databases for gathering all data obtained have been designed in each study sites according to the mother surveillance form. A central database has been designed and setup to provide a reliable support for data storage, and a unique data warehouse to easily share consolidated data between European partners. All data for the various studies undertaken in STOPPAM was consolidated for statistical analysis. The entry of all data gathered is still in progress.
Interesting data have been collected from these STOPPAM studies, or will be available in a very near future. All the findings will help questioning and improving the current strategy for the treatment and prevention of PAM in the endemic areas.

This report documents briefly the main findings of the project and provides an easily accessible overview of the main achievements and their impact. The first section 1.2 briefly introduces the wider context of the project and respective scientific and technological objectives that the project set out to address. Section 1.3 briefly presents the key project achievements. Section 1.4 presents evidence of the initial impact of the project outcomes, providing details on dissemination and exploitation activities carried out by the project partners.

1.2 Summary description of the project context & objectives

Pregnancy-associated malaria (PAM) is a major public health priority for women and children (two overarching issues of strategic importance in FP7) in developing countries. *Plasmodium falciparum* is the only lethal form of malaria, responsible of 95 % of attacks in sub-Saharan Africa where 90% of world specific mortality occurs. Moreover, impact of PAM is obvious with a very large expected impact of its prevention, particularly in primigravidae. Recent introduction of intermittent preventive treatment during pregnancy in endemic areas allows an improvement of PAM prevention but clearly depends on drug resistance spread. Because of the very complex interactions network, control of a particular stage of host-parasite relationships offers a more pragmatic aim that infection control for a vaccine. Moreover, this innovative is independent of drug pressure, and make possible to develop a long-term tool to prevent PAM.

Effects of PAM on the pregnant woman (placental infection and anaemia), the offspring (birth weight reduction), and the infant (increased morbidity and mortality) are well known. Studies

underlined the role of *P. falciparum* variable surface antigens expressed on infected erythrocytes in binding to placenta. A specific immune response against this antigen reduces the effect of PAM during latter pregnancies, making possible to develop a new preventive strategy based on the enhancement of this specific response. STOPPAM proposed to conduct a cohort study in pregnant women and their newborns to quantify the effects of PAM and to identify a PAM vaccine candidate. The goals have been addressed through conducting cohort studies in two geographically separated areas where malaria is endemic (West and East Africa), in order to determine whether the pathological mechanisms and their resulting effects vary with parasite strains and/or transmission patterns. Biological samples have been collected during pregnancy and infancy in order to dissect the pathological and immune mechanisms involved in PAM, as well as to characterize phenotypically and genetically the infecting parasites, to provide a structural basis for an anti-PAM vaccine design.

1.3 Work performed, and main S&T results/foregrounds

In general, the progress of the work has been in line with the project planning, however some delays were encountered due to difficulties in procuring different equipment and consumables from abroad. As a consequence, the inclusion of pregnant women was delayed in Korogwe (Tanzania) until September 2008 and in Comé (Benin) until June 2008. **In Benin**, 1,037 women have been included by the 31st of January 2010, and 891 mothers have given birth in the health centers. The prevalence of *P. falciparum* infection, as indicated by rapid diagnostic test (RDT), was 16.7% at inclusion and 11.9 % at delivery. **In Tanzania**, the required sample size of enrolling 1000 pregnant mothers was met by the 5th of March 2010 (In total 1005 women were included), and from all the women included in the cohort, 928 had given birth by the 1st of October 2010. The malaria prevalence rates as detected by RDT remained low; overall malaria prevalence at all visits was 1.7% based on venous blood samples. Inclusion and follow-up of the babies began in November 2008, in Benin, and 211 infants have been included. The infant follow-up lasted until late March 2011. Ending the project, 17% of the infants were tested RDT positive.
Blood samples have been collected from all pregnant women. Plasma samples have been frozen, in order to longitudinally assess inflammatory activity during pregnancy in women from the two cohorts. Placentas were also collected from delivering women for further quantification of placental alterations in the two groups of pregnant women. All blood samples were spotted on Whatman filter paper. Red blood cells pellets and whole blood samples with positive RDT (n =225 in Benin, 11 in Tanzania) were stored in Trizol for use in rt-PCR. Venous blood samples with parasitaemia > 0.1% were successfully matured *in vitro* and stored in glycerolyte for flow-based and binding inhibition assays. Regarding the infants, If RDT positive, peripheral blood was taken immediately for parasitaemia assessment and immunological assays.
The follow-up in both sites has generated a lot of clinical data and biological specimens that are ready for laboratory analyses. In Benin, a total of 5,211 venous, 676 cord and 568 placental blood samples (plasma and cells) have been collected. 7 016 blood samples were collected in Tanzania.

In order to assess the immunopathological effect of *P. falciparum* in PAM, several tools have been implemented. We have generated substantial data on *var2csa* sequence from placental parasites. The sequence database now comprises a minimum of 27 sequences encoding the DBL2X, DBL3X, and DBL5ε domains respectively, and 13 sequences encoding the DBL6ε. Forty PCR products covering the DBL4 domain have been cloned. Specific primers for *var2csa* real-time PCR studies to be used in the work on the molecular characterization of placental parasites have been designed. 88 VAR2CSA proteins and 4 control PfEMP1 domains have been produced by IRD and UCPH. 84 of these proteins were used to immunize rabbits and/or rats, allowing to generate 300 anti-VAR2CSA sera. We also initiated

the production of antibodies reagents using DNA immunization technique. Antibodies against 4 DBL5ε variants from placental parasites have been produced and immunizations with constructs comprising multiple domains from the FCR3 strain and a placental isolate have been achieved. A first set of Luminex beads has been coupled with VAR2CSA recombinant constructs, and validated. Finally, a mechanical 96 well plate based adhesion assay has been developed.

The assessment of the inflammatory responses and other factors has been analyzed in a subgroup of 121 pregnant women from Tanzania, during the course of their pregnancy, using standard cytometric bead array and ELISA. All malaria positive women (both by rapid diagnostic tests (RDT) and by microscopic examination) were matched to uninfected controls based on age, gravidity and gestational age. In Benin similar inflammatory mediators have been analyzed in a subgroup of 152 pregnant women at inclusion and 134 pregnant women at delivery using standard cytometric bead array and ELISA. Infected pregnant women indentified as thick smear positive were matched. In **Tanzania**, results show that P. falciparum infection during pregnancy affects the plasma levels of various inflammatory markers, characterized in particular by transient but significant increases in IL-10 and IP10 regardless of gestational age. In addition, the levels of IL-6, IL-8 and RANTES were significantly decreased, while the levels of MIG, MCP-1, IP-10 and suPAR were significantly increased in venous plasma of infected women compared to uninfected controls. No differences were seen for any of the factors in cord blood between RDT+ and RDT- women. In **Benin**, results at inclusion show that levels of cytokines IL-6 and IL-10 were increased in malaria-positive pregnant women as compared to uninfected controls. No differences were seen for the interferons, Angiopoiteins, uPAR or VEGF/Flt1. For the chemokines, levels of MIG and IP-10 were increased in malaria-positive women compared to their matched controls. At delivery, malaria-positive women showed increased levels of IL-6 and IL-10 as seen at inclusion and levels of the chemokines MCP-1, MIG and IP-10 were also increased in malaria-positive women as compared to controls.
Analyses of the histopathological alterations were also performed. 192 and 237 slides from formalin and finefix preserved biopsies collected in Tanzania have been read. The results were compared with birth weight as part of preliminary analysis. No correlation was seen for any of the histological alterations. In Benin analysis are still in progress: so far 466 have been read and 177 have had their second reading at IRD (France). All slides are currently being read in France. The results from France will be used to classify the women as exposed or not exposed to malaria.

As part of the molecular characterization of the placental parasites**,** several analyses have been performed on the samples collected from all pregnant women. **In Benin**, the malaria prevalence was quite high. A multiplex quantitative real time PCR (qRT-PCR) method using primers and a hydrolysis probes targeting the *18S rRNA* parasite was used to detect the presence of malaria parasites from the placental blood samples. Using this technique that proved more sensitive than RDT and microscopy, the prevalence rate of placental infections was estimated at 25%. During the follow-up, RDT positive samples from pregnant women were preserved for qRT-PCR analyses. Venous blood samples with parasitaemia > 0.1% were maturated *in vitro* and stored in flow-cytometry and inhibition binding assays. Placental isolates have also been obtained and preserved in glycerolyte from the deliveries. Analyses of VAR2CSA expression by *P. falciparum* on the surface of infected erythrocytes were performed and consistent expression of the protein was shown. On the other hand **in Tanzania**, the malaria prevalence rates as detected by rapid diagnostic test (RDT) remained low. Of the entire cohort 7.4% (75/1005) were tested positive at least once for malaria parasite antigen based on venous blood RDT. Hence, all the RDT and microscopically positive samples have been included in the analyses. From all the blood samples collected (7,016), the same number of filter spot blood on Whatman number 3 were collected for DNA extraction and parasite genotyping for assessing the multiplicity of infection and markers of

SP resistance whilst 91 red blood samples from the RDT positive individuals were preserved in trizol for later transcriptional analyses using qRT–PCR. Out of the 91 RDT positive samples, 43 (47%) had malaria parasites after blood slide reading and were put into cultures. Trough all these analyses, we have noticed that in most of the samples tested, parasite isolated from pregnant women either from peripheral or placental blood expressed VAR2CSA on the surface of iRBCs. However no expression was found in parasites collected from non-pregnant individuals from Benin. Most of the var2csa expressing parasites that were further tested in binding inhibition assay were highly inhibited by specific antibodies to DBL1-2 and DBL4 of VAR2CSA. Thus, we have been able to define 2 major subtypes of var2csa that are transcribed by both peripheral and placental parasites isolated from pregnant women: the 3D7 type and the FCR3 type.
We also pursued our investigations on the quantification of the clone number and proportion per infection in order to identify multiplicity of infection among the pregnant women of our cohort, and we found out that overall, most infections were polyclonal, exceeding 60% in both sites. The determination of parasite genotypes related to SP resistance, revealed us that that there is a high prevalence of both the Pfdhfr triple and Pfdhfr/dhps quintuple mutations in Tanzania, whereas triple (Pfdhfr) mutations and Pfdhfr/dhps quadruple mutations are predominant in Benin. All the data generated from these studies were incorporated into the clinical and laboratory databases for subsequent statistical analyses.

All plasma samples coming from the field sites were tested by Luminex to measure the levels of anti-VSA antibodies. Plasma samples of selected women with increased levels of anti-VSA between enrolment and delivery have been also tested for antibody maturation in binding inhibitory activity during pregnancy. Antibody levels in the tested plasma samples can be associated with clinical outcomes and other parameters collected during the study. Preliminary results obtained allowed the identification of some linear epitopes exposed in the VAR2CSA protein using a peptide-array. These epitopes were conserved and recognized by both FCR3 and 3d7 antibodies. The two most predominant peptides identified were synthesized, coupled to KLH and immunized in rats. The anti-peptide antibodies were able to induce antibodies in rats and were tested to be surface reactive on parasites and thereby confirmed to be surface exposed in the native VAR2CSA protein. Besides, it was found that constructs containing the N-terminal domains of VAR2CSA and constructs containing the DBL4 VAR2CSA domains induced antibodies that were broadly cross reactive and inhibited binding.
When the VAR2CSA construct that mediated specific high affinity binding has been identified it was attempted to develop assays to measure to which degree plasma from pregnant women inhibited the binding. Unfortunately, we found a very high inhibitory effect in many of the control plasma from non endemic donors' women who never had been pregnant. Thus it was not feasible to use the assay to access the inhibitory capacity of the plasma of pregnant women. However when the plasma samples were assessed on the binding of infected erythrocytes, it appeared that increased plasma inhibitory ability was associated with protection against placental infection at delivery, and this ability was correlated with the level of anti-VAR2CSA IgG. In addition, it was demonstrated that antibody response to N-terminal var2csa is associated to parity women, while antibody avidities are observed among primigravidae. The affinity of the antibodies was quite high and characterised by low of rates. Longitudinal analyses of anti-var2csa antibody avidities will help understand any implication in acquired protection to malaria in pregnancy. The statistical analyses of all the measurements done are still in progress.

The assessment of PAM-induced cellular immunity has been done as well, using recombinant VAR2CSA DBL5ε & cryopreserved iRBC/uRBC were prepared on time. In Benin, 152 samples at inclusion, from both RDT+ (74) and matched RDT- mothers (77), have been processed for cytometric measurements. A total of 152 maternal samples from delivery have been processed for cytometric analyses, so as 86 samples of cord blood. The first 3-

month and 6-month post-natal follow-up cellular immunology samples have been processed from 26 and 9 infants, respectively. In Tanzania, the frequency of RDT+ has unexpectedly remained low (~3%). The long rains due to start in March 2009 did lead to the predicted upswing in RDT+ samples in general during May-July 2009.
A multiplex real-time quantitative PCR method using primers and a hydrolysis probe targeting the *18S rRNA* gene of the parasite detected the presence of malaria parasites. Using this technique, the prevalence of placental infections was estimated at 25%. Analyses of VAR2CSA expression by *P. falciparum* on the surface of infected erythrocytes demonstrated consistent expression of the protein. CMI in pregnant women was completed by the 2nd quarter 2011, and data have been integrated in the databases. Analyses are still ongoing. In analyses completed to date in samples from both enrolment and delivery, the following significant cellular changes were observed in P. falciparum-infected women: lower DC, NK cell and Treg frequencies in *P. falciparum*-infected women, and Impaired HLA-DR expression on APC. These results suggest 1) an impaired systemic innate and cell-mediate immune response in mothers with PAM and 2) a possible migration of immune cells to placenta. Analyses are still ongoing, but the results obtained up to date suggest that significant cellular changes were observed in P. falciparum-infected women. This information could be very important with respect to vaccine development, since natural boosting of vaccine-induced responses is likely to be pivotal with respect to protective efficacy.
In analyses completed to date, in the preliminary assessment of infant CMI, we observed an impact of gestational malaria at delivery on the orientation of the immune response during the first year of life reflected in significantly higher cytokine responses of dendritic cells to TLR ligands and frequencies of Treg. Dendritic cells and Treg are both implicated in the control, the development and the maintenance of adaptive immunity to infection as malaria. Our findings suggest that P. falciparum infection in pregnant women can modulate innate immune responses of newborns in the first months of life; the time of mother's infection during the pregnancy also influences the APC responses via TLR. Hypersensitivity to TLR stimulation could be induced by the passage of *P. falciparum* soluble antigens in utero. Increased of pro-inflammatory, innate responses in children from mother with PAM may contribute to altered adaptive immune responses. This finding could have important implications for malaria vaccination of children residing in endemic areas.
Our data have also revealed higher VAR2CSA-specific immune memory in multigravidae suggesting that T cell-mediated responses may contribute to anti-PAM immunity, providing help for B cell responses but possibly also activating phagocytes for destruction of infected erythrocytes.

Local databases (for capturing all clinical and epidemiological data) in each study site have been designed according to the mother surveillance form. Two additional databases were also built, tested and consolidated: one for laboratory data collection, the other for infant follow-up data collection. Satellite databases for immunological, pathological and CMI studies were also created. These satellites database were merged with the biological database after validation. A central database has been designed and setup to provide a reliable support for data storage, and a unique data warehouse to easily share consolidated data between European partners. The transfer of all local databases to the central database was also started. The training of data management team has been done, both in Tanzania and Benin. Data entry is almost completed in both sites. Corrections and consolidation have started in February 2009, and completion is expected by December 2011.

1.4 Potential impact and use

1.4.1 Impact on design/revision of new/existing prevention interventions

Currently, 30 million women living in malaria-endemic areas of sub-Saharan Africa become pregnant each year. For these women, malaria is a threat both to themselves and to their

babies, with up to 200,000 newborn deaths each year as a direct result of malaria in pregnancy. In this context, relieving the burden of malaria can have consequences beyond prevention of malaria-related morbidity and mortality. The substantial burden represented by malaria must also be seen in the light of public health services in general and primary health care programmes in particular that are currently suffering from chronically low and severely over-stretched resources in the majority of the countries where P. falciparum is endemic. In many cases these resources are actually shrinking for a variety of reasons that include regional conflicts, economic hardships and the special requirements imposed on them by the AIDS pandemic. The availability of new or revision of existing prevention tools for PAM is thus recognised to be of utmost importance, given the reduced armamentarium available and the burden that it represents.

The STOPPAM project had two primary overall objectives, both of which are expected to have impacts on the implementation of public health policies related to reducing PAM-related morbidity and mortality. The first of these objectives was to define the period of pregnancy during which infection with *P. falciparum* is predominantly associated with poor outcome. The inflammatory studies results show that P. falciparum infection during pregnancy affects the plasma levels of various inflammatory markers, characterized in particular by transient but significant increases in IL-10 and IP10 regardless of gestational age. The preliminary results of the CMI analyses suggest that significant cellular changes were observed in P. falciparum-infected women. The analyses are still in progress in order to have significant statistical results, but is is clear that this information could be very important with respect to a revision of the current administration regimen of IPTp, to date the most effective and most widely adopted strategy for combatting PAM, to allow better targeting of the preventive effects of SP or its chosen replacement against PAM. Preliminary findings related to this, have already been disseminated. Additional data will be released in the near future.

The second objective is the design of PAM vaccine components, through elucidation of the critical var2csa and accompanying non-PfEMP1 conserved motifs mediating iE binding in the placenta. A first-generation PAM vaccine construct, the expected end-product of these efforts, will enter the pipeline of vaccine development, the ultimate aim being implementation of a much-needed new tool for the control of malaria in pregnancy. The timelines for vaccine development are notoriously difficult to define. This project allowed to identify the regions of the VAR2CSA protein that induce blocking antibodies**.** The expectation is that a first candidate anti-PAM vaccine - appropriately validated for safety [toxicology] and immunogenicity - should be available for first-in-man Phase I clinical trials 1 year from now.

1.4.2 Impact on maternal and foetal health

In the context of the thematic issue of malaria and pregnancy that is prioritized in the FP7 HEALTH-2007-2.3.2-4 Cooperation Call, the proposed specific targeted research project described here focuses on the mechanisms and timing of immunopathogenesis of malaria in pregnancy, and how these have impact on maternal and foetal health.

Reproductive health has been defined as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity, in all matters related to the reproductive system and its functions and processes. The concept is centred on human needs and development throughout the life cycle. These WHO/AFRO definitions of reproductive health include the **concept** that: Women should go through pregnancy and childbirth without danger to themselves or their children.

The integration of a modified IPTp regimen and, eventually, a vaccine against PAM, either separately or jointly into antenatal care programmes across malaria-endemic countries, will make a significant contribution to reducing maternal morbidity and mortality, and to improving health outcomes in infants, while also having a positive impact on poverty reduction. Such a reduction will accrue through relief of the burden at the individual and societal levels both of the debilitating effects of PAM on mothers themselves and of early-childhood illnesses and deaths of infants that occur at a higher incidence as a direct result of the impact of low birth weight associated with PAM. These beneficial health-related outcomes will thus have the potential to generate additional economic benefits by, for example, contributing to reductions in the level of demand on public health systems in the affected countries through improving their use. Improving women's health in this context may also lead to indirect economic benefits by reducing the time during which they are unable to work or to be involved in family care.

1.4.3 Impact for endemic countries

The African Summit on Roll Back Malaria held in April 2000 adopted the Abuja Declaration in which regional leaders committed their countries to achieving 60% coverage of pregnant women at risk for malaria with available control tools by the year 2005. Although this commitment was not reached, it was built on the observation that, in the majority of areas with stable malaria transmission in sub-Saharan Africa, more than 70% of women attend an antenatal health clinic at least once during their pregnancy. This level of attendance makes a clinic-based approach to prevention theoretically feasible.

This project produced two types of data, those related to the pathological mechanisms of PAM, and those related to vaccine design. The elucidation of the pathological mechanisms of PAM and their relation with the timing of infection, along with the putative revision of IPTp regimen, will mainly benefit, beyond any immediate benefit accruing directly to the study participants themselves, the governments of countries where malaria is endemic, in the form of their Ministries of Health and associated regional, national and local malaria control initiatives and antenatal care programmes.

The principal benefactors of the outcome of this project as regards vaccine design are the populations of malaria endemic countries themselves. However, this is a long-term benefit, and the immediate direct benefactors of these data will be industrial beneficiaries involved in vaccine development and international organisations which will be the likely stakeholders for large-scale use of this vaccine. Vaccine candidates have been intellectually protected prior to dissemination of knowledge concerning their content. Afterwards, the consortium proposes to disseminate these project results through a variety of channels.

The project in itself, regardless of scientific terms, served to enhance the research capacity of all beneficiaries. The project contributed to the strategic objectives of FP7 in several ways. A particularly important feature of the partnership concerns the core of concentrated expertise in the design and execution of field-based clinical trials that it has bring together. In this sense the partnership also promoted European scientific and technological culture through the participation of four Community-based research groups with only limited previous direct collaborative experience but which had broadly overlapping research interests. Finally, by means of both North-South and South-South exchanges of personnel and visits by scientists, the research capacity of the DC beneficiaries has been significantly enhanced. In the context of epidemiological studies and their conduct, the experience gained at the operational level will be invaluable for all the beneficiaries concerned, but especially so for the DC beneficiary groups. Such experience will be in increasing demand in the coming decade and beyond as the pipeline of development of drugs and vaccines for

malaria and the other major diseases of poverty generates new candidates that require field-testing.

1.4.4 Impact for EU Development Co-operation Policies

In terms of the main Programme objectives, this project aimed to promote and reinforce both Community and DC scientific capacities within the context of research on appropriate interventions for malaria control. Malaria remains one of the major health problems for Developing Countries in sub-Saharan Africa, but is also an increasing health risk for EU residents, with both direct and indirect economic costs.

The composition of the consortium exemplifies the broad aims of the 7th framework programme through the establishment of networks of research institutions pursuing common research goals in specific areas of interest. The four Community-based Beneficiaries involved in STOPPAM are all strong in their respective fields of research and the interactions facilitated by the project were guaranteed to have a positive impact on the European contribution to improvements in research capacity and public health in developing countries.

In general terms, outcome of this project contributed effectively to the Community's development policies in the following ways:

- Provide Developing Countries with cost-effective tools for improved maternal & infant health
- Strengthen Institutional development & linkages in Developing Countries
- Strengthen European-Developing Country co-operation
- Enhance European-Developing Country policy dialogue
- Enhance European Institutional collaboration

1.4.5 Contact details of the project

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