EUROPEAN VACCINE INITIATIVE

ANNUAL REPORT 2012

For Donors

Version 0.3

European Vaccine Initiative

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List of Abbreviations

ADCI	Antibody-dependent Cellular Inhibition
ADVAC	Advanced Training in Vaccinology
AEFI	Adverse Effects Following Immunisation
AIDS	Acquired Immune Deficiency Syndrome
AMA1	Apical membrane antigen 1
ASH	Albert Schweitzer Hospital
ASTMH	American Society of Tropical Medicine and Hygiene
BMBF	Federal Ministry of Education and Research Germany
BPRC	Biomedical Primate Research Centre
cGMP	current Good Manufacturing Practice
CDC	Centres for Disease Control
ChAd	Chimpanzee adenovirus
CHMI	Controlled Human Malaria Infection
CHUV	Centre Hosptalier Universitaire Vaudois
CIC	Clinical Investiganional Centre
CMI	Cell-Mediated Immunity
CMO	Contract Manufacturing Organisation
CMP	Centre for Medical Parasitology
CNRFP	Centre National de Recherche et de Formation sur le Paludisme
CoA	Certificate of Analysis
CSA	Chondroitin Sulphate A
CSP	Circumsporozoite Protein
CT	Clinical Trial
DBL	Duffy-Binding-Like
DC	Developing Countries
DCVMN	Developing Countries Vaccine Manufacturer Network
DG	Directorate General
DGIS	Dutch Developmental Aid funding
DiCo	Diversity Covering
DP	Drug Product
DoP	Disease of Poverty
DS	Drug Substance
DSMB	Data Safety Monitoring Board
EATRIS	European Advanced Translational Research InfraStructure in Medicine
EC	European Commission
EDCTP	European and Developing Countries' Clinical Trials Partnership
EEIG	European Economic Interest Grouping
ELISA	Enzyme Linked ImmunoSorbent assay
ELISpot	Enzyme Linked Immuno Spot Assay
EMVDA	European Malaria Vaccine Development Association
EMVI	European Malaria Vaccine Initiative

ESAC	External Scientific Advisory Committee
ESOF	Euroscience Open Forum
EU	European Union
EVI	European Vaccine Initiative
FDA	Food and Drug Administration
FP7	Framework Program Seven
GADI	Global Adjuvant Development Initiative
GCLP	Good Clinical Laboratory Practice
GIA	Growth Inhibition Assay
GPI	Glycosyl Phosphatidyl Inositol
GSK	GlaxoSmithKline
HIV	Human Immunosuppressive Virus
IB	Investigator's Brochure
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICH	International Committee on Harmonization
ICS	Intracellular Staining
IDRI	Infectious Disease Research Institute
IFA	Immuno Fluorescence Assay
IFN	Interferon
IHI	Ifakara Health Institute
IMB	Irish Medicines Board
IMPD	Investigational Medicinal Product Dossier
Inserm	Institut National de la Sante et de la Recherche Medicale
INTS	Institut National de Transfusion Sanguine
IRB	Institutional Review Board
IVR	Initiative for Vaccine Research
KEMRI	Kenya Medical Research Institute
KHRC	Kintampo Health Research Centre
MCB	Master Cell Banks
ME-TRAP	multiple epitope-thrombospondin-related adhesion protein
MPIIB	Max Planck Institute for Infection Biology
MRC	Medical Research Council
MSP	Merozoite Surface Protein
MVA	Modified Vaccinia Virus Ankara
MVDAS	Modern Vaccines, Adjuvants & Delivery Systems
MVI	Malaria Vaccine Initiative
MVVC	Malaria Vectored Vaccines Consortium
MVW	Malaria Vaccine for the World
NHP	Non-Human Primates
NHRC	Navrongo Health Research Centre
NID	Neglected Infectious Disease
PAM	Pregnancy Associated Malaria
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PDP	Product Development Partnership

PE	*P. falciparum* infected Erythrocytes
PPD	Purified Protein Derivative
PRD	Poverty Related Diseases
QC	Quality Control
QP	Qualified Person
RCSI	Royal College of Surgeons Ireland
RIVM	National Institute for Public Health and the Environment
SAC	Scientific Advisory Committee
Sida	Swedish Development Agency
SME	Small and Medium-sized Enterprise
SOP	Standard Operating Procedures
SWE	Stable Water Emulsion
TB	Tuberculosis
TBVI	TuBerculosis Vaccine Initiative
TNA	TransNational Access
UCAD	Universite Cheikh Anta Diop
UCPH	University of Copenhagen
UHEI	University of Heidelberg
UNIL	University of Lausanne
UOXF	University of Oxford
USP	User Selection Panel
VFL	Vaccine Formulation Laboratory
VSCR	Vienna School of Clinical Research
WHO	World Health Organisation
WP	Work Package

FOREWORD BY MARITA TROYE-BLOMBERG, VICE-CHAIR OF THE EVI BOARD.

We work in challenging times: while the need for innovative healthcare solutions for those most at need is greater than ever, governments are restructuring their development aid programmes, and other traditional funders of health research are more and more focusing their programmes on local and national issues rather than global health issues. For organisations as EVI which work on a global scale and strive to have a global impact, creativity and tenacity is becoming ever more important.

The Board of EVI is confident that the EVI is playing an important and effective role as a Product Development Partnership (PDP) in the development of vaccines. This confidence is justified by the increasing recognition of the EVI platform by global organisations such as the World Health Organization (WHO), the European and Developing Countries' Clinical Trials Partnership (EDCTP), the European Commission (EC) and national research councils, and confirmed by the steady successful fundraising activities that have been completed in 2012.

The EVI governance bodies, together with the Secretariat, remain committed to provide the best possible support and services to scientists in Europe and beyond to fund their innovative research. In addition to its role as a PDP, EVI also demonstrates its support through its leadership and participation in different consortia such as the EC FP7-funded research infrastructure TRANSVAC which is aimed at providing a broad platform to the vaccine R&D community at large.

We hope you will enjoy reading this annual report.

Marita Troye-Blomberg

Vice-chair of the EVI Board

EXECUTIVE SUMMARY

2012 was again a highly successful year for EVI in which our base was reinforced and at the same time our disease scope broadened and our network grew.

Most importantly, in 2012, EVI has become de-factor the world's largest funder and developer of vaccines against Pregnancy Associated Malaria (PAM). In September the EC accepted the PlacMalVac consortium into negotiations. PlacMalVac is coordinated by University of Copenhagen and EVI is a partner. Combined with the BMBF-funded PRIMALVAC and PAMCPH projects, makes EVI partner in the main global efforts to make an effective vaccine against this often forgotten part of the malaria problem.

The second EVI Rendez-Vous was held on 5th December. It bought together more than 50 EVI stakeholders, grantees, partners, and external participants from a wide range of universities and international institutions covering research, public health, industry and finance.

Through its annual call for vaccine development EVI funded the SPOROVAC project led by Dr. Stephen Hoffman (USA). This consortium will perform a clinical trial at the Ifakara Health Institute (IHI) in Tanzania which will bring for the first time to a malaria-endemic country the concept of vaccination with a life-attenuated, GMP-graded, whole *Plasmodium falciparum* Sporozoite under a chemo-prophylaxis regime. This clinical trial is planned to start in Q3 of 2013.

CSVAC, P27A and AMA1-DiCo EVI-funded vaccine candidates moved from product to clinical development, which constitutes EVI's core activity. The product development work for the phase I clinical batches on AMA1-DiCo was finalised this year, and a phase I clinical trial will commence in 2013. CSVAC has already entered into a phase I clinical trial. The P27A project successfully applied for an EDCTP primer grant and will allow the execution of a phase Ib arm of the first clinical trial at IHI in Tanzania in Q4 of 2013. The phase Ia arm of the first-in-man clinical trial at CHUV in Switzerland which needs to precede the phase Ib arm will start in Q2 2013.

The phase I clinical trial of JAIVAC-1 was concluded with no safety issues reported. The project will be officially closed in 2013.

The projects funded by the EC and the EDCTP are developing according to the plan, and the most notable achievements were as follows:

MultiMalVax: together with the University of Oxford / Jenner Institute, EVI successfully applied to EC for the funding of the MultiMalVax consortium. This consortium will bring a combination malaria vaccine candidate to the clinic which will include vaccine components directed to elicit immune responses against proteins in the three different stages of the malaria parasite lifecycle.

EMVDA: The project was successfully ended in May. The final scientific and financial reporting was approved by the EC in December.

IDEA: The assessment of the impact of helminth infections on the immune response to the GMZ2 malaria vaccine candidate is performed in clinical trials at the Albert Schweitzer Hospital, Lambaréné, Gabon.

INYVAX: The INYVAX project ended in January 2012. A final successful annual meeting was held in Les Diablerets (CH), back to back to the TBVAC annual meeting.

MVVC: The clinical development of the two vaccine candidates is on-going with several clinical trial finishing, ongoing and starting in The Gambia, Kenya, Senegal and Burkina Faso. Several workshops and training were performed during the year. The MVVC consortium successfully applied for an EDCTP primer grant which will allow for continued clinical development after 2013 (MVVC2).

TRANSVAC: The project continued to have its rolling call for (free-) services to European groups in vaccine development. Furthermore, five new groups were integrated into the consortium as interested parties. The annual meeting was held in Hamburg in March and in June a second TRANSVAC stakeholder meeting was organised in Brussels**.**

For those who need more than the good news of science but also figures, EVI is proud to highlight some of the excellent result and ratios of its work that proves the sense of responsibility and conviction of the Secretariat. The return on investments of core donations is 2955% or in other words we raise another 29½ times funds for earmarked purposes for every Euro core donation we receive - thus it more than pays off to support EVI and regardless of the size of the donation it truly makes a difference.

Additionally we are often compared to other businesses as a result of the financial challenge in the European Union (EU) and we are more than happy to share our solvency/equity flag of 4.61 which in the qualification of the EC ranks as Good (the highest) – which indicates that the EVI finances remain strong!

Finally we are proud to announce our excellent management percentage of only 2.21% which is well below our own threshold of 7% - thus EVI are efficient in using the funds for the benefit of combating poverty related diseases.

Pleasant reading.

Odile Leroy, Executive Director

THE YEAR IN GENERAL

General

EVI signed a Memoranda of Understanding with the Sclavo Association. The Sclavo association is the coordinator of the EC FP7-funded ADITEC consortium. This research programme aims to accelerate the development of novel and powerful immunisation technologies and includes scientists from 13 countries and 42 research partners.

Fundraising

EVI is proud to announce successful fundraising at more than €14 Million raised with its partners in 2012 with around €2.2 Million for EVI. Furthermore, through the German Ministry of Research, as partner of the Network of Excellence on Infectious Diseases, EVI will have the opportunity to test its malaria vaccine candidates in phase I/II clinical trials in Germany and Gabon (estimated support ~€2.4M).

Innovation Call

In July, after recommendation by the EVI SAC the Secretariat has launched a first open call for Innovation and Discovery grants (maximum €500k financial support) for vaccines for all DoP and vaccine related technology. This call yielded many first time applicants to EVI from Asia, South America, Europe and USA. The development of a much needed human challenge model for Paratyphoid Infection will be funded and a study on the optimisation of the production and selection of antigen for a vaccine candidate against blood-stage *P. falciparum* malaria based on one of the most promising antigen recently discovered. Prof A. Craig, vice-chair of EVI SAC, highlighted to EVI Board that the results of this call are "a definite breakthrough of EVI strategy, demonstrating that EVI is now reaching a much larger community of excellent scientists".

EVI Vaccine Projects

Two new projects on PAM have started in 2012 through funding of the German Federal Ministry of Education and Research (BMBF), Institut National de la Santé et de la Recherche Médicale (Inserm), Institut National de la Transfusion Sanguine (INTS), EC, and Danish National Advanced Technology with further co-funding from Irish Aid.

EVI has also awarded a contract to Dr. Stephen Hoffman, to further develop a unique and novel concept of vaccination under chemoprophylaxis with a safe and weakened whole malaria parasite (PfSPZ). This project, SPOROVAC, will perform one clinical trial at IHI in Tanzania in the target population and includes further capacity strengthening in clinical development.

In other EVI projects, the P27A project (Prof Giampietro Corradin, Switzerland), and AMA1 DiCo project (Dr. Clemens Kocken, The Netherlands) successfully finished the process development which is required before clinical batches of vaccines can be safely and sustainably produced. P27A is ready to enter in phase Ia/b clinical trial which will be undertaken in Switzerland, Tanzania and Gabon. AMA1 DiCo is ready to enter in phase Ia/b clinical trial in France, and Burkina Faso. These two vaccine candidates cover a wide variety of naturally occurring malaria strains and thus might be more effective vaccine candidates.

The phase I clinical trial of the CSVAC project (Prof Adrian Hill, United Kingdom) is currently being conducted in Ireland (principal investigator Prof Sam McConkey, Republic

of Ireland). This clinical trial which is co-funded by Irish Aid and University of Oxford is the first clinical trial of its kind to be conducted in Ireland and created significant media coverage. The aim of the clinical trial -the results of which are expected mid of 2013- is to determine whether the vaccine is safe and produces an immunological response to malaria.

The JAIVAC-1 project (funded by Irish Aid and DGIS; Chetan Chitnis, India) will be officially closed in 2013 and its preliminary results were presented at the EVI Rendez-Vous on 6th December.

Through EC funding-EMVDA project which ended in 2012 six vaccine candidates have been developed:

1) The first cGMP clinical batch of the MSP1 full length antigen has been produced. Its inventor (Prof Herman Bujard, Germany) has successfully secured follow-up funding, started a SME and will take this unique protein to safety testing in a phase I clinical trial.

2) The start of the phase I clinical trial of the PfPEBS antigen (Prof Pierre Druilhe, France) has been exceptionally successful. Never in our collective EVI history did a vaccine concept take so little time from production to immunisation of a subject. The results are expected mid 2013.

3) Four vaccine candidates, ChAd63 AMA1 and MVA AMA1, and ChAd63 MSP1 and MVA MSP1, from UOXF have gone up to human challenge. (phase IIa clinical trial)

The MVVC project –funded by EDCTP and co-funded by Irish Aid, Sida (Sweden), Medical Research Council (UK) and the Federal Ministry of Science and Research, (Austria), is a large European and African consortium with, next to a comprehensive clinical development program, contains a large training and capacity building component. MVVC is coordinated by EVI and supports the development of two vaccine candidates, ChAd63 ME-TRAP and MVA ME-TRAP, (Prof Adrian Hill, UK). The phase I clinical trials in adults are completed and published and the phase I clinical trials in children and infants are currently on-going in The Gambia, with the phase II clinical trials in adults on-going in Senegal and Kenya. A phase Ib lead-in/IIb CT in infants and children commenced in December at CNRFP.

Cross-cutting activities

In parallel to vaccine manufacturing and testing, EVI is addressing challenging issues hampering the efficiency of vaccine development. EVI coordinates four international consortia aiming at harmonisation, infrastructure building and training in vaccine development since the technical development of vaccines will be extremely difficult in a non-receptive and non-enabling environment. EMVDA, INYVAX, OPTIMALVAC and TRANSVAC - all funded under the EC FP7 - are the examples of this approach. EVI led the harmonisation of the safety assessment of malaria and tuberculosis vaccines in pre-licensure safety trials, in a 2-years effort, involving 67 scientists from regulatory agencies, vaccine industry, academic, regulators, worldwide.

TRANSVAC, the leading European vaccine research infrastructure coordinated by EVI which acts as a complementary vaccine development platform and innovation catalyst. Since 2011 the infrastructure has successfully given out proprietary services to 19 European projects (public and private) through open calls and now serves as a mechanism to vaccine development scientists. Examples of provided services are complete animal experiments, genomic analysis (sequencing) of clinical trial samples and adjuvant testing panels. In 2012 TRANSVAC has integrated five additional groups which provide their complimentary new services to users on a paid basis. On a European level, EVI organises

a series of vaccine development stakeholders workshops committed to formulate and design a roadmap aimed at securing sustainable vaccine development infrastructures in Europe with representatives of vaccine manufacturers, biotech companies, academic research, regulatory authorities, product development partnerships and funding agencies.

EVI Rendez-Vous

On 6th December EVI held its second Rendez-Vous in which all EVI's governing bodies (EVI EEIG-Board, Board of Stakeholders, Scientific Advisory Committee and Secretariat) participated, plus more than 50 external participants from industry and a wide range of universities and international institutions covering among other fields, research, public health, finance

Secretariat

During the year the Heidelberg office was strengthen with new staff members: Stefan Jungbluth was hired as the Business Development Manager in June. Two new project managers were recruited: Céline Dutruel and Ines Petersen. Roland Kleine was hired as an administrative assistant. The total number of staff, including consultants, as at 31 December is 14.

INTRODUCTION

Vaccines preventing mortality and morbidity: blood-stage vaccines

Malaria disease results from blood-stage infection, and animal and humans immunological studies have demonstrated that the immune response induced by blood-stage antigens can protect against the diseases. The currently developed antigens are mainly merozoite antigens. EVI has developed several blood stage antigens, with the clear strategy of combining them in the final vaccine. The recent eradication push has questioned the role of blood-stage malaria vaccines because they are not solely targeting the blocking of transmission. However data from animal and human studies have shown that controlling the parasite density will reduce the generation of gametocytes in the blood stream, and then will also reduces the transmission.

Another challenge for the development of the blood-stage antigens is the antigenic diversity. Thus the selection of the antigens has to be based on the less polymorphic or the conserved domains of the antigens. Several approaches are under development, recombinant antigens (AMA1-DiCo, MSP1, EBA175), synthetic peptides (P27A), viral vectors expressed antigens (Me-TRAP, AMA1).

AMA1-DiCo

Partners

Biomedical Primate Research Centre, NL

Confarma, FR

European Vaccine Initiative, DE

Fraunhofer IME, DE

Gregory Fryer Associates Ltd, UK

Henogen Novasep, BE

Infectious Diseases Research Institute, USA

NNE Pharmaplan GmbH, DE

Nova Laboratories, Ltd, UK

Output Pharma, DE

Apical Membrane Antigen 1 (AMA1) is a leading candidate for a vaccine against *P. falciparum*. Recombinant proteins representing the whole ectodomain (Domains I – III) of *P. falciparum* AMA1 can induce antibodies that recognise native parasites and inhibit merozoite invasion of erythrocytes in vitro.

To investigate the role of human antibodies in naturally acquired immunity, children in three separate endemic populations were analysed for reactivities prior to a malaria transmission season and whether or not they suffered an episode of malaria throughout the subsequent transmission season. Recombinant proteins representing the different domains of AMA1 were used to dissect the antibody reactivities in detail. In two different communities in Kenya, antibodies against domain I were significantly associated with protection from subsequent malaria infections, in both univariate analyses and after adjusting for age. One of the Kenyan cohorts and a separate Gambian cohort antibodies to domain II were also associated with protection. However, for the Kenyan cohorts the protective associations of antibodies were only seen among the subjects that were parasite slide positive at the time of pre-season serum sampling, a phenomenon noted in previous studies from this area on antibodies to the infected erythrocyte surface. Antibodies to domain III were very rare in all populations. Results support the development of AMA1 as a vaccine candidate and particularly the inclusion of

domains I and II to induce antibody responses. They also highlight the importance of conducting prospective cohort studies in different endemic areas.

In an earlier phase of this project, a single allele PfAMA1 FVO [25-545] was produced under cGMP (See Faber et al. Vaccine 2008.08.55). The product was subsequently clinically evaluated in a phase I with three different adjuvants: alhydrogel, GSK's AS02A and Montanide ISA720. The results obtained were very promising, with average growth inhibition levels of up to 50% in the higher dosages AS02A and Montanide ISA720 (See Roestenberg, Plos One 2008).

One of the conclusions of this clinical trial was that the polymorphism in the PfAMA1 protein is a feature that should be addressed for the vaccine to be highly efficacious in the field.

The limited polymorphism (bi/trimorphism) of PfAMA1 enabled the design of three artificial PfAMA1 sequences with a very high coverage of naturally occurring alleles (on average > 97%). This Diversity Covering (DiCo) approach recommended by the SAC and approved by the Board in October 2008 is expected to overcome the polymorphism found in nature and to allow a broad response to all naturally occurring AMA1 alleles. The total budget of AMA1-DiCo will be up to € 5,206,111. Both in rhesus and rabbit immunogenicity studies this expectation has been met.

The main achievements of the project in 2012 were the preparation of the clinical batch of the AMA1-DiCo vaccine, the successful completion of the toxicology study indicating a good safety profile for the vaccine and the sponsor (Inserm)and the investigational phase Ia/Ib clinical trial sites selection (Hopital Cochin and CNRFP).

GMZ2

Partners

African Malaria Network Trust, TZ

Albert Schweitzer Hospital, GA

Centre National de Recherche et de Formation sur le Paludisme, BF

European Vaccine Initiative, DE

Henogen (now novasep), BE

Makerere University, UG

Medical Research Council, GM

Navrongo Health Reseach Centre, GH

Statens Serum Institut, DK

University of Tübingen, DE

The discovery of GLURP and MSP3 was based on the *in vitro* analysis of the passive transfer of clinical immunity by purified African Immunoglobulin G (Druihle et al. 1997, Sabchareon et al. 1991). These investigations have led to the elucidation of a putative effector mechanism in the defense against *P. falciparum* malaria, and the subsequent identification of the involved parasite molecules. The studies lead to the identification of the N-terminal region of GLURP (GLURP27-489) and the C-terminal region of MSP3, (MSP3210-380) (Oeuvray et al. 1994) as targets of biologically active antibodies.

Immuno-epidemiological investigations have confirmed the relevance of anti-GLURP and anti-MSP3 IgG antibodies to acquired protection: For GLURP, several independent studies performed in geographically different locations in Africa and Asia have demonstrated a statistically significant correlation between levels of GLURP-specific IgG3 and/or IgG1 antibodies and clinical protection against malaria. This association is highly significant and the significance is confirmed after controlling for the confounding effect of age-related increase in exposure to *P. falciparum*. These results

confirmed previous studies, which found that naturally occurring IgG antibodies to GLURP are associated with protection against disease in Gambian children and against high levels of parasitemia in children from Liberia and Burkina Faso. For MSP3, a high ratio (> 2) of cytophilic to non-cytophilic antibodies (IgG1 + IgG3 / IgG2+IgG4+IgM) allows distinguishing individuals without recorded malaria attacks from individuals with recorded malaria attacks. This difference is found in every age group among approximately 200 villagers from Dielmo who have been under daily clinical surveillance for more then eight years. Sequence analyses of the $GLURP_{27-489}$ and $MSP3_{210-380}$ regions from 44 field isolates and laboratory lines of *P. falciparum* show that defined epitopes in GLURP (P1, P3, and P4) (42) and MSP3 (b peptide) (30)which are targeted by Antibody Dependent Cellular Inhibition (ADCI)-effective human antibodies are almost completely conserved, suggesting that they are functionally constrained and not subject to selection for variation at the amino acid level. Of the different epitopes in the $GLURP_{27-489}$ region, P3 might be the most important, since affinity-purified human antibodies against the P3 peptide mediate the strongest ADCI-effect *in vitro*.

Two phase I clinical trials have been performed with the individual GLURP and MSP3 antigens as long synthetic peptides EMVI. Both vaccines induced strong humoral and cellular responses in the subjects, and the antisera could act synergistically with human blood monocytes to inhibit *P. falciparum* growth *in* vitro) (Hermsen et al. 2007). Further, a GLURP-MSP3 hybrid protein (GMZ2) malaria vaccine has been evaluated in phase I clinical trials in Europe and African adults (EMVI), as well as in phase I clinical trial in Gabonese children (EDCTP).

JAIVAC-1

Partners

Bharat Biotech, IN

DiagnoSearch Life Sciences Pvt. Ltd., IN

European Vaccine Initiative, DE

International *Centre for Genetic Engineering and Biotechnology, IN*

Intox Pvt. Ltd, IN

Lotus Labs. Pvt. Ltd., IN

Malaria Vaccine Development Program, IN

This project was selected for funding by the SAC and approved by the Board in 2003. The overall aim of this project was to develop and produce under cGMP conditions a bivalent malaria blood stage vaccine candidate, and to assess safety and immunogenicity in phase I clinical trial.

An effective vaccine is likely to require the combination of multiple *P. falciparum* antigens. The leading candidates for development of blood-stage malaria vaccines include merozoite surface proteins such as PfMSP-1, PfMSP-2, PfMSP-4 and PfMSP-5, rhoptry proteins such as PfAMA-1, PfRAP-1 and PfRAP-2, and microneme proteins such as PfEBA-175. These proteins play important functional roles in red cell invasion by *P. falciparum* merozoites. Therefore the International Centre for Genetic Engineering and Biotechnology (ICGEB) in New Delhi has developed a recombinant combination vaccine candidate, JAIVAC-1, based on two blood-stage *P. falciparum* antigens produced in *E. coli.* JAIVAC-1 is composed of a physical mixture of two recombinant proteins, namely, $PfMSP\text{-}1_{19}$, the 19 kD conserved, C-terminal region of PfMSP-1, and PfF2, the conserved, DBL receptor-binding domain of PfEBA-175. Both $PfMSP\text{-}1_{19}$ and PfEBA- 175 play distinct yet significant functional roles in red cell invasion by *P. falciparum* merozoites. It is therefore inferred that antibodies directed against their functional regions may have a synergistic

effect and block invasion efficiently thus providing significant protection against *P. falciparum* malaria.

This €1,573,313 project is co-funded by EVI and the Indian Government. The main achievement of the year 2012 is the analysis of the data collected during the phase I clinical trial.

EMVDA: European Malaria Vaccine Development Association

Partners

African Malaria Network Trust, TZ

Biomedical Primate Research Centre, NL

Centre Hospitalier Universitaire Vaudois, CH

European Vaccine Initiative, DE

Eberhard-Karls Universität Tübingen, DE

Etna Biotech, IT

National Institute for Medical Research, UK

Pevion Biotech, CH

Radboud University Nijmegen Medical Centre, NL

Ruprecht-Karls-Universität Heidelberg, DE

Statens Serum Institut, DK

Stockholm University, SE

Swiss Tropical Institute, CH

University of Edinburgh, UK

University of Oxford, UK

The European Malaria Vaccine Development Association (EMVDA) is an Integrated Project funded under the EC's Sixth Framework Programme (FP6), and coordinated by the EVI. The project duration is five and a half year, and was initiated in December 2006 with an overall budget of €13,500,000. The overall objective of EMVDA is to support the development of vaccines that protect against *P. falciparum* malaria in endemic areas.

EMVDA seeks to deliver progress in one specific area of the EC's policy initiative: that of developing a malaria vaccine to reduce the global burden of malaria. EMVDA provides the resources of its membership of leading European research laboratories to bring innovative elements into the structure and exploit new facilities to develop compare and test vaccine candidates for proof of concept. It joins this effort to African efforts to obtain and deploy a malaria vaccine. As an integral part of the malaria vaccine research and development process, EMVDA offers research partnerships and training to African scientists.

The main achievements of the year 2012

- EMVDA ended in May 2012 and the EC expressed that they were pleased with the EMVDA achievements during the lifetime of the project. It was decided to continue the annual meetings in order to share knowledge and network as well as publishing a paper on the EMVDA achievements.
- The implementation of the phase Ia clinical trial of PfPEBS vaccine candidate in only eight months. Never in our collective EVI history did a vaccine concept take so little time from production to immunisation of the first subject.

P27A

Partners

ALMAC Sciences, UK

CiToxLAB, FR

European Vaccine Initiative, DE

Gregory Fryer Associates Ltd, UK

Infectious Diseases Research Institute, USA

Nova Laboratories, Ltd, UK

Output Pharma, DE

University of Lausanne, CH

Preclinical validation of the vaccine potential of P27A, an intrinsically unstructured, 104-amino acid long hydrophilic fragment of the *P. falciparum* malaria protein PFF0165c (Olugbile S. et al., Infection and Immunity), submitted in 2007 by Professor Giampietro Corradin of the University of Lausanne (UNIL), was not originally recommended for funding by the SAC. However, in accordance with a Board decision to help improve certain proposals, a six month contract was signed with UNIL in September 2008 for the evaluation of the malaria vaccine potential of P27A with various adjuvants, and a successful proposal was submitted in response to the call in December 2008. The total budget of P27A is € 1,385,450

In the search for novel vaccine candidates through genome mining, both inhibition of merozoite invasion and monocyte triggering by antibodies in ADCI were investigated, using first, naturally occurring antibodies in individuals with acquired protection through exposure to the malaria parasite, and later on, antibodies induced by immunisation with the various constructs studied. From a series of 95 polypeptides corresponding to 95 novel unexplored *P. falciparum* alpha helical coiled coil segments of malaria blood stage proteins, the screening process focused on 18 such novel antigenic genes, i.e. recognised by antibodies in exposed populations. Affinity purified antibodies studied in both Growth Inhibition Assay (GIA) and ADCI assays revealed that antibodies specific to 11 peptides totally or partially interrupted the intra-erythrocytic development of *P. falciparum* solely in cooperation with blood monocytes. No direct effect was observed (Villard et al., 2007).

These results are in agreement with passive transfer experiments that showed that total immunoglobulin from protected individuals passively transferred in naïve recipients were effective mainly through a monocyte-dependent, antibody-mediated effect. Selection of the vaccine candidate proposed here resulted from a series of successive screens that highlighted P27A as target of an immune response with satisfactory characteristics for vaccine development (Olugbile et al., 2009).

In 2012, the Ifakara Health Institute in Tanzania, University of Lausanne and EVI have applied to EDCTP strategic primer grant call for the funding for the phase Ib part of the P27A clinical trial (CT). The outcome was positive and the grant agreement for the P27A CTb has been signed in December 2012. The main achievements of the project in 2012 were the preparation of the clinical batch of the P27A vaccine, the successful completion of the toxicology study indicating a good safety profile for the vaccine and the sponsor and the investigational phase Ia/Ib clinical trial sites selection (CHUV and IHI).

MVVC: Malaria Vectored Vaccines Consortium

Partners
Centre National de Recherche et de Formation sur le Paludisme, BF
European Vaccine Initiative, DE
Kenya Medical Research Institute, KE
Medical Research Council Laboratories, GM
Okairòs srl, IT
Université Cheikh Anta Diop, SN
University of Oxford, UK
Vienna School of Clinical Research, AT

MVVC is funded by EDCTP in response to a Call made in 2008: Malaria Vaccines Integrated Project – Clinical Trials/Capacity Building/Networking. The total funding provided by EDCTP is € 6,500,000. This is completed by co-funding from the Irish Aid Department of Foreign Affairs, the Swedish International Development Agency (Sida), the Medical Research Council (MRC), UK and the Federal Ministry of Science and Research, Austria and third-party contributions from all the partners of the project, the total budget being € 9,500,000. The project is scheduled to last for 4 years (2009 -2013).

The MVVC consortium includes four African and four European partners with EVI as coordinator. The collaborators and partner institutions were selected based on the proposed objectives of the consortium and what expertise they and their institutions will bring collectively to the mutual benefit of all partners. UOXF is sponsor of the clinical trials and has developed and manufactured the vaccines being tested. Okairos is specialised in development and production of adenoviral vectored vaccines. VSCR provides training and coordinates courses for members of the MVVC consortium. The three of the African centres (CNRFP, KEMRI, and MRC) are experienced in the conduct of clinical trials, the fourth centre, the Université Cheikh Anta Diop (UCAD) will set up the structure to conduct clinical trial and provide the facilities for the conduct of the malaria vaccine clinical trials. The projects main objective is the demonstration of the safety, immunogenicity and efficacy of the malaria vaccine candidates, ChAd63 ME-TRAP + MVA ME-TRAP in adults, young children and infants in sub-Saharan Africa, by integrating capacity-building and networking in the design and conduct of phase I and II clinical trials of viral vectored malaria vaccine candidates in East and West African adults, children, and infants.

Its specific objectives are as follows:

- To demonstrate the safety and immunogenicity of a ChAd63 and MVA prime-boost regime encoding the ME-TRAP malaria antigens, in adults and young children in sub-Saharan Africa.
- To assess the efficacy, safety, and immunogenicity of this new prime-boost regime in protection against clinical malaria in adults and children at multiple sites in East and West Africa.
- To ensure continued maintenance and further consolidation of the well-established sites at level 4 and to assist in the upgrading of the less-established sites from levels 1, 2 or 3 to level 3 or 4 clinical trial sites by the end of MVVC.
- To develop clinical trial capabilities, infrastructure and human resources that ensure the sustainability of the clinical trial sites after the end of the project.

- To develop the partners in the consortium into a well-established network using the already existing collaboration as a baseline for further development.
- To establish relationships with existing like-minded networks external to MVVC by using the partners' numerous existing networks, specifically encouraging South-South and North-South partnerships.

In 2012, the MVVC partners, together with Kintampo Health Research Centre (KHRC) and Novartis, successfully applied for an EDCTP strategic primer grant to continue and expand the work started in MVVC for two years (Field Trials of a New Combination Malaria Vaccine in West African Adults and Children (MVVC 2), 2012-2014). The main achievement of the year 2012 is the conduct of the phase IIb clinical trials in KEMRI and UCAD.

Pregnancy Associated Malaria (PAM) Vaccines

PAM is caused by *P. falciparum* infected Erythrocytes (PEs) that bind to the placental receptor Chondroitin Sulphate A (CSA) and sequester in the placenta, where they cause disease and death for the mother and her off-spring. Pregnant women are particularly vulnerable to this type of malaria because their immunity is reduced during pregnancy. Every year, more than 100 million pregnant women are threatened by PAM which causes the death of 80,000 - 200,000 children every year[1]. This problem has long been neglected, and no vaccine preventing PAM is available. Two new projects on **PAM** have started in 2012.

EVI has been able to raise funds from the German Federal Ministry of Education and Research (BMBF), Institut National de la Santé et de la Recherche Médicale (Inserm), European Commission (EC), and Danish National Advanced Technology with further co-funding from Irish Aid, and has set up collaboration with US-NIH. Thus the three most advanced groups dealing with this target will be collaborating. The two new projects started offer hope for reducing the burden of malaria in pregnant women and improving the health of mothers and new-borns.

The target product profile of PAM vaccines notably differs from the currently developed malaria vaccine. Those vaccines target young adolescent girls before childbearing age, and the vaccination should be associated to other vaccines targeting either prevention of rubella or prevention of uterine cervical cancer by Human papilloma virus vaccine. Depending of the other malaria vaccine available on the market, PAM vaccine could potentially be associated with booster dose of regular malaria vaccine in adolescent girls.

The projects focus on the distinct form of the parasite that infects the placenta, causing disease and death in mothers and infants. Evidence strongly supports var2CSA, a member of the PfEMP1 adhesins encoded by the *var* gene family, as the leading candidate for a pregnancy malaria vaccine[2]. Women acquire antibodies against var2CSA expressed by placental parasites over successive pregnancies, as they become resistant to pregnancy

[1] The impact of maternal malaria on newborns, T.K. Hartman et al., Annals of Tropical Paediatrics (2010) 30, 271–282

[2] Baruch et al., 1995; Su el al., 1995; Smith et al., 1995

malaria[3]. These data provide a rational basis for accelerating vaccine development aimed at blocking the adhesion of CSA-binding parasites to the placenta.

Var2CSA is a 350 kDa transmembrane protein with a 300 kDa extracellular region composed of six Duffy Binding-Like (DBL) domains and a cysteine-rich interdomain region module, as well as short inter-domain regions. It has been found that DBL3X is the principal target of the inhibitory antibodies, which efficiently abrogate parasite adhesion to CSA[4]. Naturally acquired antibodies and those induced by vaccination against the domain between the N-terminal sequence and the DBL2X segment target overlapping strain-transcendent anti-adhesion epitopes[5]. These results indicate that strategies aimed at blocking PE adhesion to CSA should focus on the N-terminal region of var2CSA.

PRIMALVAC

Partners

BIOTEM, FR

European Vaccine Initiative, DE

GTP Technology, FR

Infectious Diseases Research Institute, USA

Institut National de la Santé et de la Recherche Médicale, FR

ISCONOVA, SE

Pfenex Inc., USA

Voisin Consulting Life Sciences, FR

PRIMALVAC aims at developing a vaccine to prevent PAM and improve pregnancy outcomes. The main objective is to obtain proof of concept that a var2CSA based vaccine inducing long lasting or rapidly boosted cross reactive and inhibitory antibodies can be designed for human use. Recombinant forms of var2CSA will thus be generated, and their activity as immunogens that elicit functional and cross-reactive antibodies against placental parasite forms will be assessed. The candidate antigens that best meet strict immunogenicity criteria will be transitioned to preclinical and clinical development.

PRIMALVAC has a total budget of €6,864,000 and it is funded by the BMBF through KfW, EVI, the Inserm and the INTS. The project started in December 2011 and will have a duration of four years. The highlight of 2012 was the expression screening to down-select the vaccine candidates and expression systems that can be transferred to further preclinical and clinical development.

[3] Fried et al., 1998

[4] Avril et al., 2011; Dahlback et al., 2011

[5] Bordbar et al., 2011; Bigey et al., 2011

PAMCPH

Partners
University of Copenhagen, (DK)
European Vaccine Initiative, DE
ExpreS2ion Bio (DK)
CMC Biologics A/S (DK)

The overall objective of the project is to enable the manufacture of a vaccine which protects foetus and mother against the adverse effects of malaria during pregnancy. Within this project the success criterion is to define the optimal antigen and adjuvant formulation, show that it can be produced in a scalable manor and that it proves safe to use in animals. Centre for Medical Parasitology (CMP) one of the world leading institution in this research area has identified a main vaccine target. The vaccine candidate is a complex protein, not compatible with traditional vaccine production platforms. The technology at ExpreS2ion Bio is ideal for cost-effective expression of complex antigens and CMC Biologics A/S (CMC) has the technology and knowhow to scale up production and ensure its compliance with clinical Good Manufacturing Practice (cGMP) enabling to take major step towards solving a huge health problem. The overall aim of this project is to support the production of a recombinant var2CSA vaccine under cGMP that can be used in the clinical trials supported by the PlacMalVac project (European Commission Framework Program 7 funded project to start in 2013).

PAMCPH has a total budget of €2 Million and it is funded by the BMBF through KfW, with co-funding from University of Copenhagen (UCPH). The project started in September 2012 and will have a duration of four years. The main achievement in 2012 is the selection of the candidate antigen by the CMP team.

Vaccines preventing infection: liver-stage vaccines

The liver-stage or pre-erythrocytic vaccine strategies are designed to induce a immune response neutralizing the sporozoites, then preventing their invasion of the hepatocytes. This is typically a vaccine for travelers because it would prevent the advent of clinical disease if completely efficacious. A partially efficacious pre-erythrocytic vaccine would be expected to reduce the incidence of new blood stage infections.

CSVAC

Partners
European Vaccine Initiative, DE
Jenner Institute, University of Oxford, UK
Royal College of Surgeons in Ireland, IE

This project was selected for funding by the SAC and approved by the Board in 2008. The project main objectives were to generate a recombinant Chimpanzee adenovirus serotype 63 (ChAd63) with a gene encoding most of the circumsporozoite protein (CSP) (full length minus Glycosyl phosphatidyl inositol anchor sequence) and a recombinant Modified Vaccinia Ankara Virus (MVA) encoding the same insert, perform cGMP production of these vaccine candidates and conduct a dose escalating phase Ia clinical trial to assess the safety and immunogenicity of ChAd63 CSP and MVA CSP in humans. Process development and GMP production are supervised by UOXF and the phase I clinical trial was conducted at RCSI. UOXF acts as sponsor of the phase Ia clinical trial. The total budget of CSVAC is € 1,161,000.

The CSP is an attractive antigen because four efficacy trials in humans have demonstrated that two vaccines, RTS,S/AS02A and RTS,S/AS02D, which use this antigen alone can partially and temporarily prevent *P. falciparum* infection and clinical malaria.

The same antigen (CSP) has been used, but with an alternative delivery system, which uses the non-replicating ChAd63 as a vector along with a heterologous MVA boost. This new vaccine could also, in later clinical trials, be combined in a sequence with the current RTS,S/AS02D, which might produce stronger or more lasting immunity. Alternatively, and more readily, it could be combined with other ChAd63 and MVA vectors encoding Multiple Epitopes - Thrombospondin-Related Adhesion Protein (ME-TRAP), Merozoite Surface Protein (MSP1) and AMA1 being developed with support from the EC funded European Malaria Vaccine Development Association (EMVDA), the Medical Research Council (MRC), the Wellcome Trust and other funders.

The use of viral vectors rather than or in addition to a protein adjuvant vaccine has several well recognised advantages. In pre-clinical and clinical studies the T cell immunogenicity of viral vectors consistently exceeds that of protein/adjuvant vaccines, both for induction of effector T cell and memory T cell responses. In pre-clinical models of malaria there is extensive evidence that T cells against the liver- stage parasite induce protective immunity. However, it is also clear that high level antibodies against the central repeat of the CSP are protective in small animal models. Moreover, analysis of the immunological correlates of immunity induced by the RTS,S/AS02 vaccine in both phase IIa sporozoite challenge studies and in a recent clinical trial in Mozambique provide evidence that very high levels of antibodies correlate with protection in humans. However, this correlation is relatively weak and there may be a component of T cell mediated protection induced by the vaccine, even though the magnitude of the T cell response measured after vaccination is modest, a level of about 150 SFU / million Peripheral Blood Mononuclear Cells (PBMCs) on

Enzyme Linked Immuno Spot Assay (ELISpot). The main achievement of the year 2012 was the completion of the phase Ia clinical trial in 10 months.

SPOROVAC

Partners

European Vaccine Initiative, DE

Ikafara Health Institute, TZ

Radboud University Nijmegen Medical Centre, NL

Sanaria Inc, US

Swiss Tropical and Public Health Institute, CH

University of Maryland, US

University of Oxford, UK/TH

This project was selected for funding by the EVI SAC and approved by the EVI Board in 2012. It aims to push forward the development of a liver stage vaccine, which will protect a vaccinated individual from developing malaria symptoms and also prevent transmission of the disease. The general approach that will be utilised is a Controlled Human Malaria Infection (CHMI) with infectious sporozoites from a chloroquine-sensitive *P. falciparum* strain in combination with chloroquine prophylaxis, which targets only the blood stages. SPOROVAC is based on the translation of a successful method of immunising against malaria, which consisted of three exposures to 12-15 infected mosquitoes, into three subsequent IV inoculations. The used vaccine candidate is supposed to yield a viable easily-administered vaccine against malaria and will be first tested in endemic Tanzania.

The two vaccination approaches with highest demonstrable efficacy (>90% efficacy) in human malaria (lasting for 10 – 28 months) both use whole sporozoites as the immunogen administered by mosquito bites. The first approach initiated in the 1970s and 1990s used radiation-attenuated sporozoites, and is now a gold standard in malaria vaccinology and the basis of Sanaria's first malaria vaccine candidate.

The second approach, based on consistent findings in murine malaria models, used fully infectious sporozoites administered by mosquito bite in conjunction with chloroquine chemoprophylaxis, and sterilely protected 100% of subjects at eight weeks, and 67% of subjects at 28 months after last immunisation. It also significantly delayed the onset of parasitemia in the two subjects who were not completely protected at 28 months (Roestenberg et al, 2009, 2011). This method of immunisation induces the highest level of efficacy and the longest duration of protection demonstrated for any malaria immunogen, and requires 20 to 40 times fewer infected mosquitoes (three exposures to 12-15 infected mosquitoes) than are required for inducing high-level protective immunity by irradiated sporozoites (greater than 1,000 sporozoites-infected mosquitoes, minimum of five exposures).

The project has a total budget of €1,500,000 and the main achievement of the year 2012 is the selection of the project and the production of clinical batch.

Vaccines preventing infection and morbidity/mortality: combination vaccines

A highly effective malaria vaccine is a major goal of global health research and will likely require a multi-stage product.

MultiMalVax

Partners

University of Oxford, UK

European Vaccine Initiative, DE

Novartis Vaccines and Diagnostics s.r.l., IT

Okairos s.r.l., IT

Université Pierre et Marie Curie, FR

A highly effective malaria vaccine is a major goal of global health research and one way to develop such a vaccine would be to combine vaccine candidates targeting several stages of the malaria life cycle.

The aim of the MultiMalVax an EC FP7 funded project started in October is to test such a multi-stage malaria vaccine to the point of proof-of-concept phase II testing in Europe, prior to clinical trials in malaria-endemic areas. Remarkable recent advances in vaccine design for all four stages of the *P. falciparum* parasite's life-cycle allow the testing of such a multi-stage multi-component vaccine for the first time, with strong chances of success.

These advances are:

i) The availability of a new vectored prime-boost vaccination regime based on the Okairos chimpanzee adenovirus technology that has been found to induce exceptionally potent $CD8^+$ T cell responses and high titre antibodies against multiple malaria antigens;

ii) The development of an improved version of the leading partially protective RTS,S sporozoite vaccine candidate, termed R21, that lacks the excess of carrier Hepatitis B antigen in RTS,S;

iii) The identification, using a vector technology screen, of the blood-stage antigen Rh5 as the first antigen to induce potent strain-transcending neutralisation of blood-stage parasites in in vitro growth inhibition assays; and

iv) The demonstration that vector-induced antibodies against two mosquito-stage antigens can induce 100% transmission blocking against field isolates of *P. falciparum* in Africa.

The project will undertake four phase I/II clinical trials to assess the pre-erythrocytic, blood-stage and mosquito-stage components individually, and then together, using state-of-the art immunomonitoring, key functional assays of vaccine-induced immunogenicity, and sporozoite and blood-stage parasite challenges to measure efficacy prior to field testing.

This SME-led collaboration of a leading SME, two universities, a global pharmaceutical company and EVI will provide complementary abilities to accelerate development of this promising product. The main achievement of the year 2012 is the start of the project with a successful kick-off meeting in Oxford (UK).

Harmonisation and Services

IDEA: Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth infections: An African-European Research Initiative

Partners

Academisch Medisch Centrum bij de Universiteit van Amsterdam, NLAcademisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, NL

Agence Nationale de Recherches Sur Le Sida et les Hépatites Virales, FRThe Chancellor, Masters and Scholars of the University of Oxford, UK

Swiss Tropical Institute,CH

Eberhard Karls Universitaet Tübingen, DE

European Vaccine Initiative, DE

Eurovacc Foundation, NL

Ecole Polytechnique Federale de Lausanne, CH

Fondation international de l'Hopital de Dr. Albert Schweitzer de Lambarene, GB

Kenya Medical Research Institute,KE

London School of Hygiene and Tropical Medicine, UK

Ludwig-Maximilians-Universitaet München, DE

Malaria Consortium LBG, UK

Medical Research Council on behalf of its MRC/UVRI Uganda Research Unit on AIDS, UK

Institut National de la Sante et de la Recherche Medicale, FR

Istituto Nazionale Malattie Infettive L.Spallanzani – IRCCS, IT

Ifakara Health Institute, TZ

National Institute for Medical Research - Mbeya

Only recently it has become widely appreciated that other infectious diseases, the so called Neglected Infectious Disease (NID), represent a major public health burden with a particularly great impact related to their widespread distribution across most low-income countries. NID are caused by a large variety of infectious agents and predominantly by different types of worms. Worms are highly prevalent in tropical regions. Although most infections are asymptomatic, heavy infections result in significant morbidity. Despite limited evidence for the intervention, recent years have seen significant scale-up of population-based national programmes for integrated control of worms, following concerted advocacy and major philanthropic donations. These programmes raise important research questions about the public health implications of co-infection and treatment for other diseases such as malaria, HIV and TB (Eziefula 2008). Indeed there is growing epidemiological evidence for interactions between worms and these diseases. The most recent estimates indicate that about two billion people are infected with worms corresponding to a large proportion of the world's population. Three hundred million people are severely affected and about 50% of cases are children. The worm infections include schistosomiasis and several species of intestinal worms also known as soil-transmitted helminths. WHO estimates that about 200,000 deaths every year are caused by schistosomiasis alone (http://www.who.int/en/).

Given the wide geographic overlap in occurrence, co-infections between worms and Human Immunosuppressive Virus (HIV), Tuberculosis (TB) and malaria occur in tens of millions of people and in both children and adults. In this regard, preliminary epidemiological data generated from a small number of studies indicated that about 25% of individuals affected by HIV, malaria or helminth infections were co-infected. Although worm infections and HIV, TB and malaria have been extensively investigated, only recently there has been increased attention to the potential impact of co-infections between worms and HIV, TB and malaria. Firstly, the interaction between these diseases has potential major public health implications by increasing the diseases burden since effective vaccines

are not yet available for these infections. Secondly, although the worm, HIV, TB and malaria-specific immune responses have been the target of extensive investigation, the precise immune correlates of protection remain unknown for all these diseases. Thirdly, there is no information on whether worm-induced immunity modulates HIV-, TB- and malaria-specific immune responses. Fourthly, there is limited knowledge of the influence of underlying worm infections on the clinical course of HIV, TB and malaria. Finally, the impact of worm infections on vaccination requires further investigation as very limited data suggest reduced effectiveness of vaccines in subjects with worm infections. IDEA is a five year EC-funded project with twenty consortium members coordinated by CHUV, UNIL and has a total budget of €10,300,000. The main achievement of the year 2012 is approval by the EC of the add-on worm studies to the GMZ2 multi-centre phase IIb CT on 29 June 2012.

OPTIMALVAC: Initiative on Optimizing Malaria Vaccine Lab Assays Evaluation

Partners
Barcelona Center for International Health Research, ES
Biomedical Primate Research Center, NL
Centers for Disease Control and Prevention, USA
European Vaccine Initiative, DE
Health Protection Agency/ National Institute for Biological Standards and Control, UK
ImmunoVacc Consulting, BE
Institut Pasteur, FR
PATH Malaria Vaccine Initiative, USA
Radboud University Nijmegen, NL
University of Stockholm, SE
University of Edinburgh, UK
University of Oxford, UK
World Health Organization, CH

The Initiative on Optimising Malaria Vaccine Lab Assays Evaluation (OPTIMALVAC) is a three year project funded under EC' FP7 with thirteen consortium members coordinated by EVI with a budget of €1,000,000 including complementary contributions from the PATH-Malaria Vaccine Initiative (MVI) (€561,395) and the Centres for Disease Control and Prevention (CDC) (€30,000). The Grant Agreement was signed by the EC on 7 September 2009.

A broad range of malaria vaccine candidates, derived from a diverse set of technologies, has been created from the multiple approaches being taken by different groups in developing malaria vaccines. The majority of vaccine candidates are recombinant proteins based on complex native antigens found on the surface of the parasite. The vaccine potential of these parasite surface antigens is often supported by epidemiological data, and by the ability to induce measurable antigen-specific antibodies or potential protective responses in animals, and later in humans. *In vivo* assays such as protection models in mice or non-human primates, as well as human sporozoite challenge, provide additional data for some relevant antigens (e.g. pre-erythrocytic antigens).

Individual groups have developed assays within the context of their vaccine discovery efforts, with identification of measurable processes for parasite growth and virulence to test specific antigens. In-house assays are strain-, stage- and even process-specific, and the ability to compare results between different candidates is further limited by diverse methodologies and assay components such as parasites, cells and reagents. The lack of harmonisation of malaria vaccine assays leads to scepticism about the comparability of assay results that in turn generate controversy and uncertainty about the efficacy of the vaccines.

The main goal was to harmonise the assays ImmunoFluorescence Assay (IFA), ADCI, Intracellular Cytokine Staining (ICS), ELISpot in order to facilitate comparison of results and improve decision making on vaccine construct development, product characterisation, down selection of vaccine candidates and/or formulations, and clinical development plans. The project was successfully completed in 2012.

INYVAX: Optimisation of the development of Poverty-Related-Diseases (PRD) vaccines by a transversal approach, addressing common gaps and challenges

Partners

Biomedical Primate Research Center, NL

Brighton Collaboration Foundation, CH

European Vaccine Initiative, DE

Fondation Mérieux, FR

PATH Malaria Vaccine Initiative, USA

TuBerculosis Vaccine Initiative, NL

Université de Genève, CH

World Health Organization, CH

A number of new vaccines are being developed against poverty-related infectious diseases of major global public health importance.

The development of these vaccines is facing the same kinds of challenges and gaps, which still prevent the following:

1. Establishment of readily accessible formulation and scale-up process development capacity for neglected disease vaccines;
2. Establishment of a systematic approach for prioritising formulation of vaccine candidates using accepted preclinical criteria;
3. Development of information-sharing tools to strengthen connections between scientists, developers and clinical investigators.

These challenges include difficulties in accessing know-how and technology platforms in vaccine development, formulation and delivery, difficulties in harmonising safety data collection, and an insufficient number of trained scientists able to undertake leadership roles in vaccine development.

INYVAX is a €932,335, three year project funded under EC's FP7 coordinated by EVI. The project started in 2009 and ended in successfully in February 2012.

TRANSVAC: European Network of Vaccine Research and Development

Partners

Biomedical Primate Research Centre, NL

Central Veterinary Institute, NL

European Vaccine Initiative, DE

Helmholtz Zentrum für Infektionsforschung GmbH, DE

Health Protection Agency, UK

LIONEX GmbH, DE

London School of Hygiene and Tropical Medicine, UK

Max Planck Institute for Infection Biology, DE

Tuberculosis Vaccine Initiative, NL

University of Oxford, UK

University of Lausanne (WHO reference centre), CH

Vakzine Projekt Management GmbH, DE

Although expertise already exists within Europe spanning different diseases types, there is currently very limited coordination between vaccine Research and Development (R&D) groups, assay developers, and vaccine producers. Unarguably, fragmentation of expertise and facilities has slowed and in some instances distinctly impeded the development and validation of promising vaccines. To address these challenges the European vaccine development community needs to establish a collaborative vaccine development infrastructure based on shared visions and goals.

Despite Europe's significant vaccine R&D expertise, there is currently a strong need to improve cooperative efforts between R&D groups and vaccine producers across Europe. At present, any R&D group wishing to develop a new experimental vaccine needs to individually locate and approach a fragmented and non-harmonised group of vaccine development service providers.

TRANSVAC is a collaborative infrastructure project funded under the EC FP7. The program runs from October 2009 till October 2014 and has a total budget of €9,899,999. The project is the joint effort of leading European groups in the field of vaccine development, and is coordinated by the EVI. TRANSVAC was designed in order to enhance European research and training and foster the seamless implementation of a permanent research infrastructure for early vaccine development in Europe.

TRANSVAC aims to accelerate the development of promising vaccine candidates by bridging the gap between bench research and clinical trials through the provision of expertise on e.g. antigen discovery, formulation, in vivo models and antigen production. The project will be the European driving force for vaccine development by establishing an efficient sustainable collaborative infrastructure based on a shared visions and goal.

The main achievement of the year 2012 are:

- In addition to the initial panel of nine services, the TRANSVAC transnational access platform has integrated five Interested Parties which provide their services to users on a paid basis.
- TRANSVAC has liaised with other vaccine related projects in Europe such as ADITEC and EATRIS.
- Through an initiative of TRANSVAC a proposal was submitted with EATRIS, ADITEC under coordination of European Vaccine Manufacturers to the EC call FP7-HEALTH-2013-INNOVATION-1. This proposal (VIPER) is for a coordination action which will be a continuation of the stakeholder series.
- TRANSVAC and EATRIS are co-signatories on a reply to an EC consultation (DG Research Innovation: Unit B3) on possible topics for future activities for integrating and opening national research infrastructures consultation.

PRECLINICAL, PROCESS, PRODUCTION, INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

AMA1-DiCo

The AMA1-DiCo 1, 2 and 3 Drug Substance (DS) batches were released by the end of year 2011 at Fraunhofer-IME. At Nova Laboratories, AMA1-DiCo 1, 2 and 3 DS were blended in a 1:1:1 ratio, formulated and lyophilised. In March, two thousand tree hundred (2300) GMP Drug Product (DP) (batch EVIy003-2012) vials have been manufactured at Nova Laboratories and CoAs are available for all release assays. Long term stability studies have started in April. An accelerated stability (seven days at +30°C) has been conducted and no degradation was reported.

The repeated doses toxicological study in rabbits using the maximal intended human dosage of AMA1-DiCo and GLA-SE or Alhydrogel® indicated no safety issue (WIL-Research).

The Investigational Medicinal Product Dossier (IMPD) was in its finalisation status by the end of year (Gregory Fryer Associates).

The AMA1-DiCo DP batch release by Nova Laboratories Qualified Person (QP) is scheduled in Q1 2013.

CSVAC

No activity in 2012.

GMZ2

No activity in 2012.

EMVDA

Comparative evaluation and concept development

The selection process for vaccine candidates to enter into GMP production and phase I clinical trial was reviewed and approved by the External Scientific Advisory Committee (ESAC) and amended during the EURHAVAC workshop in February 2008. The first selected EMVDA vaccine candidate was ChAd63 and MVA vectored vaccine candidates using MSP-1 and AMA1 (UOXF). The full size MSP-1 vaccine candidate (UHEI) and the *P. falciparum* pre-erythrocytic and blood stage pfPEBS (formerly known as SR11.1) vaccine candidate (CHUV) were thereafter selected to be funded.

EMVDA ChAd63 and MVA vaccine candidate (UOXF)

No activity in 2012.

EMVDA MSP1 full length vaccine candidate (UHEI)

In 2012, clinical grade MSP-1D, sufficient for some 20,000 human vaccine doses has been released by BIOMEVA (Germany). Aluminium hydroxide (Rehydragel LV) and IDRI GLA-SE were selected as adjuvants for the preclinical studies. Potency and toxicology studies have been completed at Confarma (France) and showed that MSP-1 is immunogenic and well tolerated. DP long term stability studies have been initiated in 2012.

The IMPD has been prepared and provided that approval by Regulatory Authorities is obtained, a first-in-man study with the most complex malaria antigen studied up to date will be feasible in 2013.

EMVDA pfPEBS vaccine candidate (CHUV)

The clinical batches of pfPEBS peptide (formerly known as SR11.1; Inventor Dr. P. Druilhe, Vac4All, Paris) have been released in April. The regulatory dossier was successfully accepted by the Swissmedic, Swiss Regulatory authorities.

JAIVAC-1

No activity in 2012

MultiMalVax

At the University of Oxford, the final stages of research in which the transmission blocking antigens are to be selected were started. Furthermore, process development for GMP production runs at Okairos for viral vectors encoding the blood-stage antigen Rh5 were initiated.

P27A

The GMP P27A DS batch was released in September 2011 at ALMAC Sciences. In February 2012 at Nova Laboratories, following formulation and filling development, 2,450 GMP DP vials have been filled with the liquid form of P27A; Certficate of Analysis (CoAs) are available for all release assays.

Long term, real time stability (DP stored at -20°C) studies have started in June.

A repeated doses toxicological study in rabbits using the maximal intended human dosage of P27A and GLA-SE or Alhydrogel® has been completed and no safety issue was reported CiToxLAB.

The IMPD has been prepared and was in its finalisation status by the end of year (Gregory Fryer Associates).

The P27A DP batch release by Nova Laboratories QP is scheduled in Q1 2013.

PAMCPH

The antigen selection part has commenced and UPCH has down selected one antigen and two back-up, which are fragments of the var2CSA protein, expressed in the S2 cell line. In parallel with antigen selection, a tender has been launched for the selection of the CMO. The technology transfer will be initiated at the beginning of 2013 and all the manufacturing should follow.

PRIMALVAC

Within the first year of the project, a screening was performed to determine the best expression system and best protein variant. A total of five protein variants were tested, covering the following domains of var2CSA: DBL1X-2X, DBL1X-3X, DBL2X-3X, DBL3X-4ε, and the full-length extracellular domain DBL1X-6ε.

Expression screening of different protein variants in *Pseudomonas fluorescens* was performed by the USA company Pfenex and in *E. coli*, *L. lactis*, *P. pastoris* and CHO cells by GTP Technology (France). According to the pre-defined Go/No-Go criteria, expression screening in *P. fluorescens*, *P. pastoris* and *L. lactis* did not lead to promising results and was stopped. Larger analytical scale production of the two best expressed constructs in CHO

cells and in the *E. coli* shuffle strain was finished in December. Immunogenicity testing of the four proteins will start in January 2013 in small animal models by a company called BIOTEM (France). Results are expected in Q1/2013.

As cGMP production of the final selected protein is envisaged without His-tag, GTP started the development of the constructs without His-tag in December.

SPOROVAC

Sanaria's vaccine is a live whole organism vaccine comprised of sporozoites. The manufacturing process begins with a cell bank initiated in vitro culture of *P. falciparum* blood stage parasites. These parasites are fed to aseptic mosquitoes. The sporozoites that develop in the salivary glands of the fed mosquitoes are harvested, purified, formulated, vialed and cryopreserved in liquid nitrogen vapour phase. The manufacture and release of Sanaria's sporozoite challenge product is performed under cGMP. For the SPOROVAC project the first clinical batches were produced in October / November.

TRANSVAC

Preclinical, Process and Production

The research component of TRANSVAC targets the improvement of the use of (molecular) assays and standardised reagents, global analyses, adjuvants, animal models and vaccine and cell bank production specific to the development of experimental vaccines. Seven of the 15 project Work Packages (WPs) in TRANSVAC are dedicated to research into these aspects of vaccine development. In 2012 the following main results were obtained:

Production of recombinant vaccine candidate

Four recombinant vaccine candidates from *Mycobacterium tuberculosis* (Antigen 85A-B (Rv3804c, Rv1886c, Rv0129c), PstS1 (38kDa; Rv0934)) were selected. All selected candidates are highly immunogenic proteins. From *P. falciparum*, three different peptides were identified after epitope mapping from different *P. falciparum* proteins (MSP2 and a conserved *Plasmodium* protein of unknown function). An expression plasmid expressing all three epitopes was constructed (MSP-FusN). All four proteins from *M. tuberculosis* and MSP-FusN were produced as recombinant proteins in *E. coli* and purified to > 99% homogeneity. Expression of the target proteins was achieved in animal source free full medium. The antigens 85A, PstS1 and MSP-FusN were transferred to cGMP production.

In total twelve important antigens, such as diagnostic markers as ESAT6, CFP10, and PstS1 were distributed in 17 countries. These important diagnostic markers are used for research projects on novel TB diagnostics and drug and vaccine development in several countries, especially in high burden regions such as Brazil. Seven antigens have been used as modified antigens on immobilised on coated surfaces for the establishment of novel Point of Care TB diagnostics. Quality Control (QC) of vaccine candidates is constantly validated by HZI-PROQC (ESI-QqTOF-MS, MALDI-TOF/TOF-MS, NMR, Edman degradation).

Evaluation of influenza vaccine candidates in different animal models

New data on mouse models (HIS mouse, immunological analysis), guinea pig models (development of tools), pigs (comparison of neonatal, young and adult pigs), and non-human primates (species comparison, molecular analysis of immune responses) have been generated.

Definition of biomarkers of protective immunity through global analyses of host responses after vaccination

A first stand-alone data analysis based on Agilent microarrays and a phase Ia clinical trial with *M. bovis* BCG vaccination, using two different tuberculin skin test groups (purified protein derivative (PPD)+ and PPD-) was completed by MPIIB. The results indicate that, although there are only a low number of regulated genes in common between both PPD+ and PPD- groups, the group specific results were clearly higher and readily measureable, while the PPD+ group had a significant higher number of regulated genes than the PPD- group.

Transnational Access Services

The TRANSVAC SAC and User Selection Panel (USP) have completed evaluation of applications received in response to the TRANSVAC transnational access services call during 2012. A total of 14 user projects have been selected in 2012 and have been given access to the following services:

Users selected for the TransNational Access (TNA) calls for applications in 2012 (calls 1201-5 to 1210-8)

Applicant / User	***Access granted to***	***Disease***
Animal Health and Veterinary Laboratory Agency, New Haw, UK Dr. Bernardo Villarreal-Ramos	ILLUMINA Deep Sequencing	Tuberculosis
University of Zaragoza, Zaragoza, Spain Prof Carlos Martin	AGILENT Microarrays	Tuberculosis
Scientific Institute of Public Health, Brussels, Belgium Dr. Kris Huygen	Large Animal studies	Tuberculosis
Inserm, Lille, France Dr. Jean-Claude Sirard	Vaccine formulation laboratory	Influenza
Inserm, Lille, France Dr. Jean-Claude Sirard	Large Animal studies	Influenza
Inserm, Lille, France Dr. Jean-Claude Sirard	AGILENT Microarrays	Influenza
Medical Research Council Clinical Trials Unit, London, UK Dr. Sarah Joseph	ILLUMINA Deep Sequencing	HIV/AIDS
Barcelona Centre for International Health Research, Barcelona, Spain Dr. Carlota Dobano Lázaro	AFFYMETRIX Microarrays	Malaria
Inserm, Lille, France Dr. Camille Locht	AGILENT Microarrays	Pertussis
Statens Serum Institut, Copenhagen, Denmark Dr. Peter Andersen	Stable Reference Reagents	Tuberculosis
Institute of Pharmacology and Structural Biology/CNRS, Toulouse, France	Vaccine formulation laboratory	Tuberculosis

Applicant / User	***Access granted to***	***Disease***
Mrs Martine Gilleron		
Poznan University School of Medical Science, Poznan, Poland Pro. Andrzej MACKIEWICZ	AFFYMETRIX Microarrays	Melanoma
Statens Serum Institut, Copenhagen, Denmark Dr. Dennis Christensen	AFFYMETRIX Microarrays	Tuberculosis
Centro Nacional de Biotecnología, Madrid, Spain Prof Mariano Esteban Rodríguez	Rhesus Macaque Models	HIV/AIDS

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DELIVERY PLATFORMS, ADJUVANTS AND VIRAL VECTORS

EVI has purchased, under a material transfer agreement, cGMP -grade Glucopyranosyl Lipid Adjuvant Stable Emulsion and Stable Emulsion from IDRI for toxicology studies and is currently negotiating the transfer agreement to use the adjuvant in clinical studies.

EVI has also filled 5,000 vials of 0.6ml of Aluminium Hydroxyde under cGMP conditions at Serum Institute of India to be used in all its preclinical and clinical trials.

AMA1-DiCo

GLA-SE and aluminium hydroxyde as a comparator, will be used as adjuvants in the phase Ia/Ib clinical trial.

CSVAC

The malaria antigen, Circumsporozoite Protein (CSP) is delivered in a prime boost strategy by two different vectors, Adenovirus (ChAd63) and Modified Vaccinia Ankra (MVA).

EMVDA

Preclinical development of new virosomally formulated vaccine components

The immunogenicity of virosomally formulated *P. falciparum* vaccine components incorporating the synthetic peptides from large scale GMP production was assessed. The pre-clinical profiling of the candidate antigens (AMA-1, MSP-1, MSP-3, D13) has been performed. In particular cross-reactivity with the target proteins expressed by *in vitro* cultivated *P. falciparum* parasites was analysed. Work focused on the in depth characterisation of immune responses elicited by the virosomally formulated peptide, polypeptide, protein fragment or fusion protein antigens, respectively, by profiling sets of monoclonal antibodies generated against them.

Generation of live attenuated recombinant measles virus based vaccine candidates

A recombinant measles viral vector (MV) technology has been used to produce a anti-malaria multivalent vaccine candidate inducing protection against severe malaria infection. Different surface antigens from *P. falciparum* have been selected as vaccine targets, in particular MSP-1 full length, CSP and AMA-1 DiCo. These antigens have been inserted at different loci on the viral genome. Twenty-six different MV-malaria recombinant plasmids have been designed and constructed by classical cloning techniques.

GMZ2

Aluminium hydroxide is the reference adjuvant currently being used in all the proposed clinical trials of GMZ2. GMZ2 is expressed in *Lactococcus lactis*.

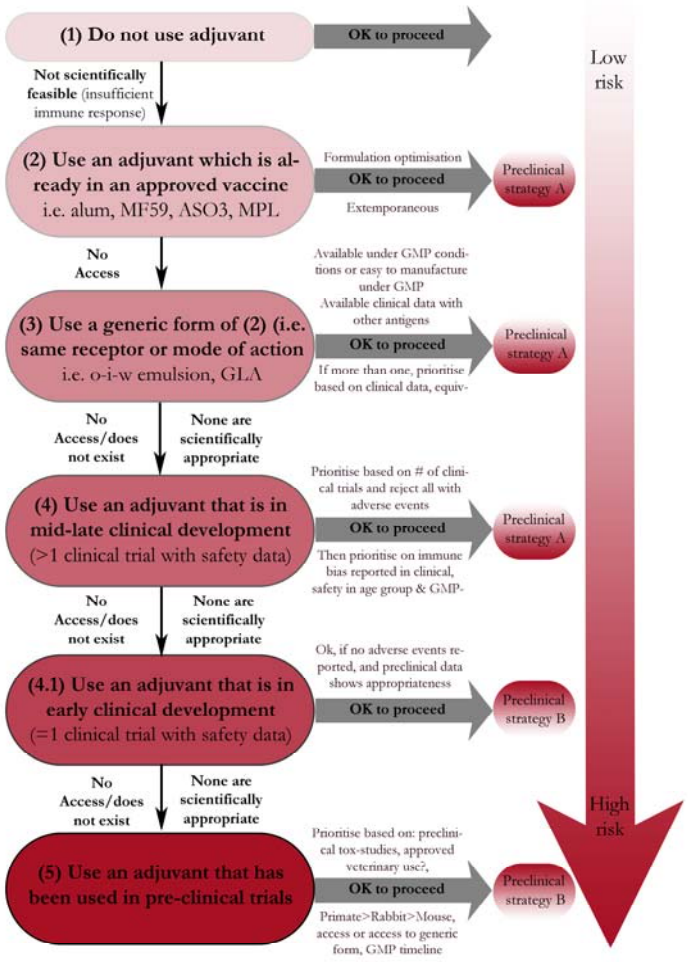
INYVAX

Most research on new vaccines such as malaria, HIV and TB, has not been performed using appropriate adjuvants or formulations. This is particularly true where research and

development has been undertaken in the public or small biotech sector. There is therefore a need to ensure the availability of potent adjuvants to the public research sector to facilitate the development of effective vaccines against diseases for which we do not yet have vaccines and also to improve vaccines such as influenza, TB, etc. With INYVAX support, the Initiative for Vaccine Research (IVR) at WHO has strengthened the Global Adjuvant Development Initiative (GADI), and WHO has also extended the Adjunet network to Europe.

The INYVAX rules for decision making in formulating the vaccines with adjuvant are extremely useful to advice scientists on how they should approached the challenge of optimising immunogenicity of their antigens; (see fig 1).

Figure 1: INYVAX decision making tree for formulating vaccines with adjuvant



JAIVAC

The adjuvant selection involved Aluminium hydroxyde, AS02A, Montanide ISA 51 and Montanide ISA 720. Based on the immunogenicity as assessed by ELISA, IFA and parasite growth inhibition data, it was recommended that Montanide ISA 720 be considered for further clinical development. JAIVAC-1 is expressed in *E. coli*.

P27A

Two adjuvants will be used in the clinical trials: aluminium hydroxyde as a reference adjuvant and also because it has shown good results in preclinical studies and GLA-SE from IDRI.

PRIMALVAC

The following adjuvants will be tested in preclinical studies: no adjuvant, aluminium hydroxide, GLA-SE (IDRI) and Matrix Abisco 100 (ISCONOVA).

TRANSVAC

Coherent development of novel and improved vaccine formulations

Two antigens (AMA1 and Ag85A) and three adjuvants (aluminium hydroxide, a Stable Water Emulsion (SWE) and a Liposome-QS21 formulation) were selected and combined to obtain six formulations. Standard Operating Procedures (SOPs) for the future validation assays for the vaccine formulations were produced. The vaccine formulations were subsequently tested in mice. A study was initiated to assess the magnitude of the T and B cell responses elicited by the six vaccine formulations outlined above. In addition, the correlation between T and B cell responses and the functionality of the B cell responses was assessed. The Liposome-QS21 adjuvanted formulations yielded the highest IgG titres, with an IgG2 dominated response. The magnitude of the T cell responses (IFNγ and IL-5 ELISpot) was found to be correlated as well as the magnitude of B cell responses and T cell responses. The functionality of the immune response to the AMA1 antigen was assessed using growth inhibition assays. As the amounts of serum available from mice were not sufficient for extensive functional analyses, a rabbit experiment was performed. Potency assays were developed for three AMA1 vaccine formulations and the set-up of these potency assays can directly be extrapolated to other antigens.

Development of cell line substrates for the production of viral vaccines

A cell bank of VERO (ex. WHO) cells suitable for partners to use for making pre GMP starting materials for vaccines has been manufactured by the UOXF. It has been externally tested for mycoplasma and is clean. It is not a fully certified cGMP bank (this was not covered by this collaboration agreement).

CLINICAL DEVELOPMENT

Selection of sponsors and clinical trial centres for phase I clinical trials

EVI has conducted the selection of a clinical trial sponsor for several core projects. The selection process included multiple potential sponsor sites. After a first selection based on capacities and costs, an audit was performed at three sites by an external auditor and a member of EVI. The selection of a sponsor was based on the audit results and was further recommended by the EVI SAC and approved by the EVI Board.

AMA1-DiCo

The AMA1-DiCo phase Ia/Ib clinical trial will be staggered, randomised, single-blind, multi-centre and will involve healthy malaria non-exposed European adults and malaria exposed African adults.

The primary objective of the clinical trial will be to evaluate the safety of 50 μg AMA-1 DiCo malaria vaccine candidate with GLA-SE and aluminium hydroxide as adjuvant, in healthy European adults not previously exposed to the parasite *P. falciparum* and in healthy African adults exposed to the parasite.

The secondary objectives will be the assessment of the humoral and cellular immune responses. Exploratory objectives will include the assessment of the quality of the humoral response.

The safety will be evaluated by an independent Data Safety Monitoring Board (DSMB).

As per its statutes, EVI shall not act as a clinical sponsor and will only act as funding agency. EVI has therefore conducted the selection of a clinical trial sponsor. Inserm (France, Prof Odile Launay) was approached in February, audited in April and the AMA1-DiCo project was presented to the Cossec (Scientific Advisory Committee of Inserm) in May. The sponsor Inserm-EVI contract was signed in December. Of note, the contract requires that the sponsor follows the Brighton Collaboration guidelines on safety and reactogenicity assessment as developed by the INYVAX consortium. Moreover, all relevant documents related to the immunogenicity assessment must follow the recommendations of the OPTIMALVAC/EMVDA collaborative projects.

The CNRFP (Dr Sodiomon Sirima, Burkina Faso) has been selected as the African clinical trial site.

The phase Ia/Ib AMA1-DiCo clinical trial is scheduled to 2013.

CSVAC

The clinical trial commenced at RCSI with vaccination of first subject on 04 January. It was a non-randomised clinical trial in 24 healthy, malaria-naïve adults of the ChAd63 and MVA replication-deficient viral vectored vaccines both encoding the CSP of *P. falciparum*. ChAd63-MVA CS was administered in a heterologous prime-boost regime eight weeks apart. Two different doses of ChAd63 CS were assessed $5x10^9$ Viral Particles (vp) and $5x10^{10}$ vp following satisfactory DSMB safety review. Serial assessments of immune response were performed using ELISpot. The vaccine combination was safe and well tolerated at both doses of ChAd63 CS. The reported AE's were of the nature and severity described in the Investigator's Brochure (IB). No SAE's were observed.

A report of the Irish Medicines Board (IMB) inspection of the RCSI clinical trial conducted in July was received in August. There were no critical findings observed by the assessors. Responses to the queries were submitted to the IMB in September.

The last two clinical visits took place on 30 October, both day 90 visits for the last group of subjects. There are further 180 day telephone calls to be made according to IMB requirements. The last three subjects should have their final telephone follow-up call in February 2013. Final results of the clinical trial are expected in Q1 2013.

The project was granted a no-cost extension which expires on 31 July 2013. This resulted from earlier issues with the process development of ChAd63 CS. This will enable the analysis of samples and report writing to be completed.

PRIMALVAC

Within four years, it is expected to finalise the first phase Ia/Ib clinical trial in healthy adult subjects non-exposed to malaria and in malaria-endemic regions in sub-Saharan Africa. This clinical trial will be designed to assess the safety and the immunogenicity of different dosages of the selected var2CSA vaccine candidate.

EMVDA

EMVDA ChAd63 and MVA vaccine candidate (UOXF)

During the EMVDA project, UOXF has designed, generated and tested four new blood-stage malaria vaccine candidates. ChAd63 and MVA vaccine candidates expressing bi-valent *P. falciparum* MSP-1 and AMA1 transgenes have been shown to be safe and highly immunogenic in mice, rabbits, rhesus macaques and humans. UOXF took all vectors through successful GMP manufacture and into a series of three phase I/IIa clinical trials in healthy adult subjects following the receipt of regulatory and ethical approvals. Efficacy of these T cell- and antibody-inducing vaccines was tested in healthy malaria-naive adults against CHMI delivered by mosquitoes infected with 3D7-strain *P. falciparum* sporozoites in an initial small pilot safety phase IIa clinical trial (VAC037) and a subsequent larger phase IIa clinical trial (VAC039). The blood-stage malaria vaccines were administered alone (MSP1 versus AMA1), coadministered together (MSP1+AMA1) or coadministered with a pre-erythrocytic malaria vaccine candidate (MSP1+ME-TRAP). It was shown that the induction of strong cellular immunity by viral-vectored vaccines encoding MSP1 and AMA1 does not impact on parasite growth rates in the blood of malaria-naive adults following mosquito bite CHMI. In a subset of vaccinated volunteers, sterilizing immunity or a delay in time to diagnosis without an altered parasite multiplication rate (PMR) was observed; effects consistent with vaccine-induced pre-erythrocytic, rather than blood-stage, immunity (Sheehy et al, Mol Ther. 2012).

EMVDA pfPEBS vaccine candidate (CHUV)

The phase I clinical trial started in second quarter of 2012 at CHUV after the successful completion of recruitment of 36 subjects. This study intended to test the hypothesis that the malaria antigen PfPEBS, manufactured as a synthetic protein and adjuvanted with aluminium hydroxide will be well-tolerated and immunogenic. The study enrolled 36 healthy adult subjects (18-45 years) and randomized them in a double-blind manner into three arms of 12 subjects each; two of the arms will receive either 5µg or 30µg, both adjuvanted with aluminium hydroxide, given as a 2-dose schedule with a 28 day interval. The third arm of 12 subjects will act as controls, and they will receive aluminium hydroxide

only injections. The sponsor for the two phases is Vac4all and the results are expected in the summer of 2013.

P27A

The P27A phase Ia/Ib clinical trial will be staggered, randomised, multi-centre and will involve healthy malaria non-exposed European adults and malaria exposed African adults.

The primary objective of the clinical trial will be to evaluate the safety of maximal dosage of 50 μg P27A malaria vaccine candidate with a lower and higher dose of GLA-SE and Alhydrogel® as adjuvant, in healthy European adults not previously exposed to the parasite *P. falciparum* and in healthy African adults exposed to the parasite.

The secondary objectives will be the assessment of the humoral and cellular immune responses.

Exploratory objectives will assess the quality of the humoral and cellular immune responses.

The safety will be evaluated by an independent DSMB.

As per its statutes, EVI shall not act as a clinical sponsor and will act as funding agency. Several potential sponsors for the P27A clinical trial have been approached. Contract negotiation are ongoing with CHUV, finalisation is scheduled for Q1 2013. Of note, the contract requires that the sponsor follows the Brighton Collaboration guidelines on safety and reactogenicity assessment as developed by the INYVAX consortium. Moreover, all relevant documents related to the immunogenicity assessment must follow the recommendations of the OPTIMALVAC/EMVDA collaborative projects.

The coordinating and principal investigator of the European site is Prof François Spertini, (CHUV), Prof Blaise Genton (CHUV) will act a co-investigator. The principal investigator of the African site is Dr Seif Shekalaghe (IHI)) and Dr Salim Abdulla (IHI) will act as co-investigator.

The regulatory submission of the Clinical Trial Application (CTA) and the start of the phase Ia/Ib P27A clinical trial are scheduled in 2013.

PAMCPH

The clinical development of this vaccine candidate will be part of the EC FP7 funded project, PlacMalVac to be started in April 2013.

GMZ2

The EDCTP funded multi-centric phase IIb clinical trial of the GMZ2 malaria vaccine candidate continued into 2012 with the vaccine candidate develop and manufactured through EVI funding. The investigational sites which continued to follow up children recruited in 2011 included the Iganga site, Makerere University, Uganda, Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso and Navrongo Health Research Centre (NHRC), Ghana. In 2012, follow-up of subjects continued at Albert Schweitzer Hospital (ASH) Lambaréné, Gabon and at the three investigational sites mentioned above. Results of the multi-centre phase IIb clinical trial are expected in Q2 2013.

JAIVAC-1

A total of 45 young adults received two doses of vaccine, and where followed for safety and immunogenicity one year after the first dose, except for one subject who had to

withdraw his consent as he moved away from the Bengaluru. No Serious Adverse Events were reported. The independent DSMB did not raised any safety concerns. Analysis of safety and immunogenicity has been completed in 2012.

ELISA results indicate that PfF2 was immunogenic with significantly higher antibody titres at the higher doses (25 and 50 compared to 10 micrograms). However, immune responses generated by *Pf*MSP1-19 were not supporting the continuation of the project. An integrated clinical study report has been compiled, and it will be finalised in 2013. Manuscripts for publication in a peer-review journal will be submitted during 2013.

SPOROVAC

This project aims to utilise and foster the malaria trial capabilities and infrastructure in Tanzania created by a unique Tanzanian initiative in collaboration with EU and USA partners at the Swiss Tropical and Public Health Institute and Sanaria Inc., respectively, to establish first-in-humans clinical trial capabilities for malaria vaccines in Tanzania. In SPOROVAC subjects will be challenged for the first time using CHMI in a vaccine trial in Africa; thereby eliminating the inconsistency and lack of reliability of natural exposure to mosquito bites in field trials, thus significantly cutting costs and time to completion. This will also provide the foundation for a future trial comparing efficacy of the SPOROVAC concept in protecting subjects challenged by CHMI and by natural exposure.

The SPOROVAC clinical trial will be performed in unison with a comparable clinical trial at the University of Tübingen. In 2012 the SPOROVAC team started deliberations with the US Food and Drug Administration (FDA) and Tanzanian Regulatory Authorities to prepare for the submission of the regulatory dossier for the clinical trial.

IDEA

The IDEA WP on the assessment of the intestinal helminth infections on the immune response of TB, Malaria, and HIV vaccine is co-lead by UOXF and EVI, and the activities commenced in April 2011.

The add-on studies for malaria vaccine trials (GMZ2) in Lambaréné, Gabon are on-going. The clinical trial has been completed and samples collected for analysis. Laboratory activities are expected to be completed by the end of the year 2013. The difficulties with adding on worm studies to on-going clinical trials for TB and HIV still persist. At the annual meeting in Paris in September, it was decided to try to conduct two small stand-alone phase I clinical trials at two of the partner sites in order to meet the deliverables for this WP. Discussions are currently on-going and final decisions will be made in Q1 2013. In addition, options for additional intervention trials involving cholera, meningitis and influenza vaccines are being discussed as a back-up plan.

MVVC

The MVVC project intends to conduct a series of clinical trials to answer the question whether the prime-boost vaccine combination using ChAd63 ME-TRAP and MVA ME-TRAP is safe and immunogenic and will lead to efficacy in the target population.

The phase Ib adult clinical trials of these vaccine candidates ChAd63 ME-TRAP and MVA ME-TRAP at KEMRI and MRC Gambia and in children aged 2-6 years at MRC Gambia have been completed. A phase Ib clinical trial in infants aged 5-12 months and 10 weeks commenced at MRC Gambia in January 2012. The follow-up is on-going. The vaccine candidates have shown a good safety profile at both sites and good immunogenicity data were obtained. No Serious Adverse Event (SAE) related to the vaccine candidates have been reported. The results of the phase Ib adult clinical trials are published in PLoS One.

Manuscripts are in preparation for the adult phase Ib clinical trial immunology data and the phase Ib clinical trial in children aged 2-6 years (MRC).

A phase IIb adult efficacy clinical trial has been completed at KEMRI. Data analysis is on-going and first results are expected in early 2013. A second phase IIb adult efficacy clinical trial is currently underway at UCAD invetsigational site in Guediawaye. The UCAD efficacy study is scheduled to be completed in Q1 2013. A phase Ib lead-in/IIb clinical trial in the target age group (5-17 month old infants and children) commenced in Q4 2012 at CNRFP.

Recruitment and follow-up of subjects enrolled in the baseline epidemiological studies at UCAD and CNRFP in Q4 2011 continued during the year and follow-up will be completed in 2013. All recruitment targets have been met at both sites.

CAPACITY BUILDING, WORKSHOPS, TRAINING

Capacity Building

EMVDA

The objective of the capacity building was to improve the current IFA, ELISA as well as to standardise T-Cell assays and GIA. These assays have been used in assessing immune responses to potential malaria vaccine candidate antigens in relation to protection from clinical malaria in cohort studies conducted in different epidemiological settings. The harmonised and validated SOPs developed have so far been adopted with several on-going malaria vaccine field studies in Africa.

JAIVAC

Odile Leroy, Executive Director of EVI and Nathalie Imbault Quality Assurance Director did visit the new facilities of the Malaria group at ICGEB. The tremendous efforts and investment were acknowledged and the team of Dr Chetan Chitnis, was encouraged to further develop the Good Clinical Laboratory Practice (GCLP) laboratory.

MVVC

The site infrastructure and laboratory equipment upgrade has been completed at CNRFP at the site in Banfora and at UCAD at the research site in Keur Socé. Both sites are now functioning effectively.

Several exchange visits took place during this reporting period to reinforce collaboration especially between the African project partners.

Training

AMA1-DiCo

Kwadwo Asamoah Kusi presented his PhD entitled: "Towards a blood stage malaria vaccine; dealing with allelic polymorphism in the vaccine" at the Leiden University, the Netherlands in January. The work is described in this thesis was co-funded by EVI and was carried at the BPRC.

EMVDA

PhD programme

The objective of the PhD programme was conducting a specific EMVDA PhD programme to generate well-trained malaria scientists with expertise in basic and applied science relating to malaria vaccine development. Eight EMVDA PhD students were selected and during the lifetime of the project, each student has presented their research including their results and work plans at the EMVDA annual research conferences in order for the EMVDA consortium to review the progress of the students. The ESAC has been impressed about the scientific work conducted by the PhD students.

Industrial training

The aim of the industrial training programme between AMANET, ETNA and Zydus Cadila Health Care, was to support the training of four African scientists as an integral part of the malaria vaccine research and development process. The four African scientists have been involved in cellular biology and virology, basic techniques in Zydus Cadila (India) and Etna Biotech (Italy).

IDEA

The seven PhD student fellowships at four African institutions continued their work into 2012.

INYVAX

INYVAX has been involved in supporting and also developing several training programs for both European and low income vaccine developers. A general training program on vaccine formulation with adjuvants has been prepared. The first course took place January 2012 and was provided by the TRANSVAC consortium. INYVAX has also continued its support of students attending the Advanced Training in Vaccinology (ADVAC) course at Fondation Mérieux. The annual ADVAC course for scientists in relation to PRD vaccines took place in May at the Fondation Mérieux conference centre. The 2012 course was conducted in May for two weeks, five participants have been registered as 2012 INYVAX students.

MMVC

Dr Jean-Baptiste Yaro (CNRFP) successfully completed his studies in Clinical Research at the VSCR and graduated with a Master's degree in Clinical Research in July 2012. Training of the other six post-graduates is on-going: Three PhD students, two Master students and one post-doc at the African sites. Immunological studies performed by the postdoc Francis Ndungu (KEMRI) and collaborators were published in several international journals (see publications sections).

P27A

During the year, the PhD student Maxmillian Mpina was selected. His work will focus on the immunoassay development and harmonisation required for the P27A clinical trial at IHI and CHUV. Part of the PhD fellowship will be supported by the EDCTP P27A CTb grant

TRANSVAC

In September 2012, the first four-day training course "Practical approaches to vaccine development" was organised and held at the Vaccine Formulation Laboratory (VFL), UNIL. 15 participants working in vaccine development were selected through a competitive process to attend the training course. Participants' course registration fees and hotel accommodation costs were covered by the TRANSVAC project; however participants were responsible for their travelling to Lausanne. Overall, 26 experts from industry, academia, government institutions, public bodies, and consultants presented numerous aspects of vaccine development providing a thorough overview of the full vaccine development process. A second training course will be organised at the VFL in March 2013.

Workshops

OPTIMALVAC

A workshop was held in Paris, France on 21-22 March for consortium partners and invited collaborators. SOPs, protocols and guidance documents as well as analytical and scoring methodologies were discussed.

The workshop was divided into three parts:

-Recognition of parasite proteins by antibodies – Review of protocols, harmonisation results and statistical analysis (IFA and Western Blot)

-Definition of overall plans for testing and assessment of options (ICS and ELISpot)

-Cell-mediated immunity (CMI) responses - Review of protocols, reference reagents, technical specifications

MMVC

Five workshops were successfully conducted under the MVVC project:

- One-day Protocol Development Workshop (VSCR), The Gambia, 18 January
- CMI Training, Senegal, 16-20 July organised by Prof T. Dieyé and Dr Badara Cissé (UCAD) and collaborators
- Full Protocol Development Workshop (VSCR), Austria, 6-10 August
- Data Management Workshop (VSCR), Burkina Faso, 3-7 September
- Applying Good Clinical Practice (GCP) (VSCR), Senegal, 10-12 September

TRANSVAC

Vaccine Development Stakeholders Meeting and Workshops

On a European level, the TRANSVAC consortium organises a series of vaccine development stakeholders workshops committed to formulate and design a roadmap aimed at securing sustainable vaccine development infrastructures in Europe. This series of meetings brings together an unprecedented mix of representatives of vaccine manufacturers, biotech companies, academic research, regulatory authorities, product development partnerships and funding agencies. Through the participant selection the consortium strives to have representatives at national and European level to be included in the discussion and to have a real contribution to vaccine policy development and the future of vaccine development infrastructures in Europe. The consortium is compiling a Vaccine R&D Infrastructure roadmap as a legacy and policy guidance document.

The second TRANSVAC stakeholder workshop (56 participants) was held at Vertretungdes Landes Baden-Württemberg bei der EU in Brussels in June, focusing on two main topics:

- What are regulatory challenges in vaccine development and how can we solve them together?
- How can the 'One Health' concept help us during the quest for new and better vaccines?

The meeting was a success with lively discussions and formulation of shared recommendations.

Furthermore, TRANSVAC has liaised with other vaccine related projects in Europe such as ADITEC and EATRIS. In September TRANSVAC and ADITEC signed a memorandum of understanding. Both are funded by the EC and have parts of their program dedicated to the delivery of vaccine R&D services. Progressive interaction between these programs is under discussion and will be continued to avoid duplication and to share information. Through an initiative of TRANSVAC, EATRIS and ADITEC were co-signatories on a reply to an EC consultation (DG Research Innovation: Unit B3) on possible topics for future activities for integrating and opening national research infrastructures consultation

The roadmap will be circulated in Q1 2013 for validation amongst European stakeholders and a final workshop will be held in Brussels in June 2013 and bring together all top level stakeholders in vaccine R&D.

HARMONISATION

EMVDA

Comparative pre-clinical and clinical ELISA, IFA and GIA

Efforts were undertaken to further harmonise GIA and IFA assays and a GIA standard was produced to aid further harmonisation. GIA protocols with reduced assay volumes were further developed and implemented. Assays to determine the inhibition of antigen processing have also been developed and harmonised. The harmonised GIA was used in comparative immunogenicity studies. Three comparative immunogenicity studies (including ELISA) were done and analysed.

Optimisation and standardisation of an ADCI assay

A standardised ADCI assay has proven to be a very difficult to establish. Several partner laboratories have had some limited success in setting up a reproducible assay. Three workshops were organised to discuss and organise the assay. Several issues remain yet unsolved, these include unavailability of a reference standard and limited access to a reliable source of monocytes (either cell lines or through blood bank supplies). Next to the ADCI assay attempts were made at a novel assay, which measures antibody dependant respiratory burst (ADRB) triggered by antibody-opsonised merozoites. This assay may be an easier to harmonise assay that measures antibody dependent cell mediated immunity.

Comparison of human challenge models for protective efficacy for blood stage vaccines

CHMI conducted in a small number of international centres, is a powerful tool for evaluation of malaria vaccine efficacy and immunological studies. RUNMC and UOXF compared and optimised protocols for quantitative Polymerase Chain Reaction (qPCR) detection of parasites and an international workshop was organised to harmonise CHMI protocols with international centres.

In addition a clinical trial was conducted to explore mechanism of protection in subjects protected by sporozoite immunisation delivered by mosquito bites whilst taking CPS protocol. By exposing CPS-immunised subjects to a challenge infection either by mosquito bites or by intravenous injection, it was clearly established that CPS induced immunity is pre-erythrocytic in nature.

IDEA

Significant effort has been made towards harmonisation of immunological assays and diagnostic methods across the sites. Workshops have been held on PCR Diagnosis of Helminth and Malaria and on Gene Profiling Analysis. Multiple North-South and South-South exchanges have taken place.

INYVAX

Development of the guidelines for the collection, analysis and presentation of Adverse Events Following Immunization (AEFI) in pre-licensure clinical vaccine trials in resource limited countries continued into the year with the Brighton collaboration leading the work package. A final draft document has been circulated. In addition, a template for AEFI reporting (case report form) and a template for the safety section of clinical trial protocols have been developed and are being finalised by the working group.

OPTIMALVAC

OPTIMALVAC was a success in bringing for the first time the main actors in malaria vaccine development to agree to participate in the harmonisation of very complex immunoassays, including assays that have lacked reproducibility between laboratories for the last decade. OPTIMALVAC partners have developed and exchanged reference reagents, guidance documents for ADCI, ICS and ELISpot, SOPs for IFA and software tools which have been made available at the www.malariaresearch.eu, www.optimalvac.eu and www.euvaccine.eu websites. Informed Consent form templates have been developed to accommodate regulatory and ethical considerations of the OPTIMALVAC project. OPTIMALVAC has facilitated links between HIV, TB, cancer and malaria assay harmonisation communities in much more robust ways than was the case previously. The establishment of service/reference centres for the above mentioned assays is envisaged. Malaria vaccine assay harmonisation can now be viewed as a jointly planned activity at the level of funding organisations.

The consortium continued their further collaboration in 2012 with to the external laboratories:

- National Institutes of Health (NIH), Bethesda, MD, USA
- Walter Reed Army Institute for Research (WRAIR), Silver Spring, MD, USA
- KEMRI, Kilifi, Kenya
- IDRI, Seattle, WA, USA
- Seattle Biomedical Research Institute, Seattle, WA, USA
- ICGEB, New Delhi, India
- Malaria Research and Training Centre (MRTC), Bamako, Mali
- MRC Gambia, Banjul, The Gambia
- CNRFP, Ouagadougou, Burkina Faso
- Albert Schweitzer Hospital, Lambaréné, Gabon
- Noguchi Memorial Institute for Medical Research, Ghana

OPTIMALVAC partners and various collaborators of the above mentioned institutions were invited and attended the workshop in Paris, France on 21-22 March. The OPTIMALVAC Steering Committee chaired by Odile Leroy, met in regular teleconferences, and in a face-to-face meeting in Paris in March.

TRANSVAC

Harmonisation of immuno-assays for clinical trials

Selected assay SOPs have been assessed and reviewed and consensus SOPs for core aspects of these assay platform has been established. Regulatory considerations have been taken into account during the qualification process. A final stage of collaborative study is scheduled to validate the agreed SOPs of these assays.

An ICS reference reagent has been characterised for additional cytokine profiling, such as TNFα, IL-2, IL-6, and IL-10 in addition to CD4+ and IFNγ+ expression. A development of a non-cell based ELISpot reference preparation in conjunction with Aston University

has demonstrated the proof-of-concept that liposomes encapsulating cytokine IFNγ can be freeze-dried and rehydrated to form spots on ELISpot wells. Further optimisation of formulation is required. The lyophilised formulation of mycobacterial antigen 85A has been optimised and stability study is in progress. A specific subset of malaria reactive serum samples had been pooled and lyophilised as candidate preparation for reference reagent. This preparation will be evaluated in an international collaborative study to be established as international standard.

Harmonisation of global analysis platform

The main results were agreements of networking and coordinating, issues of standardisation, harmonisation and profiling, the definition of sample requirements, sample quantity, sample quality for the different platforms, total number of samples for comparative analysis and most important SOPs for sample collection, preparation and isolation. These general recommendations and protocols were implemented where appropriate by the WP partners. Continuous and regular contact between the global analyses platform partners as well as to the other WP's has been successfully established and continued in the second reporting period by both regular face-to-face meetings and teleconferences that are held upon informal and formal requests

OUTREACH, COMMUNICATION

AMA1-DiCo

Dr Stephan Hellwig (Fraunhofer-IME, Aachen, Germany) presented the "GMP Production of pfAMA1 Diversity-Covering variants" at the World vaccine conference on 12 April, National Harbor, Maryland, USA.

Dr. Nicolas Havelange (EVI) presented the "Challenges in clinical batches production of malaria vaccines" at the Vaccine Technology IV conference on 21 May, Albufeira, Portugal.

Dr Pierre Loulergue (Groupe hospitalier Cochin Broca Hôtel Dieu (CIC BT505), Paris, France) presented the "Challenges of sponsoring a clinical trial of a product not developed in-house" at the EVI Rendez-Vous on 06 December in Heidelberg, Germany.

CSVAC

The CSVAC project team had a face to face meeting at RSCI in Dublin, in March were the clinical trial including study update, requirement, results to date and monitoring were discussed. The meeting was followed by a visit of the clinical trial site.

Dr. Eoghan de Barra, Investigator for the clinical trial at RCSI presented a CSVAC poster as a late breaker at the American Society of Tropical Medicine and Hygiene (ASTMH) Conference in Atlanta in November. This was well received. An abstract was submitted to the Malaria Vaccine for the World (MVW) Conference that will take place in Lausanne, Switzerland in April 2013.

Prof McConkey presented the CSVAC project at the Rendez-Vous meeting in Heidelberg in December.

P27A

Prof François Spertini (CHUV) presented the "P27A combined phase Ia/Ib clinical trial: a fast move to the field" at the EVI Rendez-Vous on 06 December in Heidelberg, Germany.

PRIMALVAC

PRIMALVAC kick-off meeting was held on the 5th January in Paris. A PRIMALVAC press release was published in August with the UniversitätsKlinikum Heidelberg press office and on different websites.

Benoit Gamain (Inserm) and Eric Devic (GTP Technology) presented the on-going PRIMALVAC work at the EVI Rendez-Vous on 06 December in Heidelberg, Germany.

EMVDA

Conferences

The fifth EMVDA Annual Research Conference (Berlin, Germany) has been attended by the Consortium, ESAC members and PhD students. Progress made in all work packages was presented as well as the work conducted by the PhD students. It has been recommended to continue the meetings after the project lifetime and therefore an EMVDA annual meeting is planned to be held in May 2013 in Heidelberg, Germany.

Simon Douglas (UOXF) gave a presentation entitled "PfRH5 is highly susceptible to vaccine-inducible cross-strain neutralizing antibody " at the Molecular Approaches to Malaria Conference (Melbourne, Australia). He also gave a presentation entitled "P falciparum merozoite neutralisation by anti-PfRH5 antibodies " at the British Society of Parasitology Conference (Glasgow, UK).

MultiMalVax

The Kick-off meeting was held in Oxford in the first week of November.

Prof A. Hill (Jenner Institute / UOXF) presented the on-going MultiMalVax work at the EVI Rendez-Vous on 06 December in Heidelberg, Germany.

IDEA

The IDEA annual meeting was held in Paris, France on 24-27 September. The meeting discussed project updates and future activities. The 2012 annual meeting also incorporated an EC symposium which brought together scientists who are interested in research on helminth diseases and co-infections with HIV, Malaria and TB. The symposium was attended by participants from four major research projects funded by the EC under the FP7 in the area of helminth diseases.

INYVAX

The final INYVAX consortium meeting was attached to the NEWTBVAC annual meeting and held on 30 January in Les Diablerets, Switzerland where the WP leaders presented the work progress in the final year.

One objective of INYVAX was to develop a comprehensive service provider database of European organisations, institutions, biotechnology companies and pharmaceutical industries developing vaccine technologies and to develop a strategy across PRD vaccine for selecting manufacturers and sub-contractors.

Collection and analysis of all PRD publications from the past five years resulted in a list of technologies activities and attributes for the database. The database was developed in collaboration with Forion Webprofessionals. European Service Providers were contacted since early 2012 to enter their data to the database. Data entry and service provider search is possible after subscription to the database available at: www.euvaccine.org. This publically accessible database links vaccine researchers with readily accessible formulation and scale-up process development capacity, regulatory support and clinical trial expertise. Everyone involved in the vaccine development chain is encouraged to join the database and upon doing so gains access to a comprehensive collection of vaccine development solutions.

OPTIMALVAC

The OPTIMALVAC Annual/Final Meeting was organised by EVI and held in Paris, France on 21st March 2012 for consortium partners and invited collaborators. The achievements of the consortium in harmonising malaria vaccine laboratory vaccine assays within the three year project duration were highlighted and strategies for further harmonisation efforts developed.

The OPTIMALVAC second periodic, final and financial reports were submitted on 30 May and approved by the EC in August.

MVVC

The EDCTP MVVC Second Annual Technical and Financial Report was submitted on 31 January and approved by EDCTP in April.

The Second MVVC Annual Meeting was co-organised by EVI and MRC Gambia in Banjul, The Gambia on 16 – 19 January. A poster and brochure describing MVVC partners and activities has been developed and distributed to the MVVC partners for further promotion of the MVVC project.

MVVC presentations at international conferences:

Nicola Viebig: "The Malaria Vectored Vaccines Consortium: Integrating capacity building and networking in the design and conduct of Phase I and II clinical trials of viral vectored malaria vaccines in East and West African children and infants", Meeting of the German Societies for Parasitology/Tropical Medicine and International Health, 14–17 March, Heidelberg, Germany

Francis Ndungu, Kenyan Society for Immunology Annual Conference, 23–24 May, Nairobi, Kenya

Muhammed Afolabi: "Heterologous prime-boost vaccination with ChAd63 ME-TRAP and MVA.ME-TRAP is safe and immunogenic in Gambian infants", 61st ASTMH Meeting, 11–15 November, Alanta, USA

Mansour Ndiath: "Keur Socé Health and Demographic Surveillance Site: Sites description, Base findings and policy implication", Poster presentation, 61st ASTMH Meeting, 11-15 November, Atlanta, USA

Francis Ndungu, Federation of African Immunological Societies Annual Conference, 2–5 December, Durban, South Africa

Caroline Ogwang: "Malaria Vectored Vaccines Consortium Clinical Trials: Adults to Infants in West and East Africa", EVI Rendez-Vous, 6 December, Heidelberg, Germany

TRANSVAC

Mark Geels gave a presentation entitled "TRANSVAC: European Network of Vaccine Research and Development", Meeting of the German Societies for Parasitology/Tropical Medicine and International Health, 14–17 March, Heidelberg, Germany

Regitze Thögersen gave a presentation entitled "TRANSVAC: European Network of Vaccine Research and Development" (poster), EVIMalLar meeting 14–16 May, Heidelberg, Germany

TRANSVAC Interested Parties

It was decided to launch a call in order to add Interested Parties to the TRANSVAC project. I.e. it was decided integrating Interested Parties that are offering paid services which are not covered under TRANSVAC in order to sustain vaccine research infrastructure in Europe

The call was launch in January and the Interested Parties were selected in April.

The services provided by the Interested Parties have been integrated in the advertising plan and the TNA call in order for them to extend their network and make their services

available on a paid basis to the scientific community. In addition to the initial panel of nine services, the TRANSVAC TNA platform has integrated in July five Interested Parties which provide their services to users on a paid basis. The five newly included services are:

- The GMP Pilot Production Plant from the Vaccinology Department of the National Institute for Public Health and the Environment (RIVM), The Netherlands.
- The Vaccine Development and Production Service from the Animal Cell Technology Unit of the Institute of Experimental and Technological Biology (IBET), Portugal.
- The MultiBac Platform Service from the European Molecular Biology Laboratory (EMBL), France.
- The Protein and Peptide Chemistry Facility Service from the Department of Biochemistry of the University of Lausanne (UNIL), Switzerland.
- The Reverse Transcription Multiplex Ligation-Dependent Probe Amplification (RT-MLPA) Assay Service from the Department of Infectious Diseases of the Leiden University Medical Centre (LUMC), The Netherlands.

Interested users can get more information on the paid services on the TRANSVAC website and can directly liaise with the service providers until new funding capacity is available within TRANSVAC. An "advisory scientific review process" is also offered to the applicants who want to get advice on their project, objectives, and the methodology used. This review process is organised in parallel to the review of the applications to the free-of-charge services.

International Fora and External Communications

EVI took part in a total of twenty five international meetings, seminars, congresses etc. mainly in Europe. Flyers were distributed at selected meetings, and presentations were made at strategic meetings either on the role of PDPs or research infrastructures for vaccine development. A full detailed list of meetings attended can be found on www.euvaccine.eu/news-events/events/events-attended-evi. The list below reflects the meetings at which EVI was invited to give a (poster) presentation.

Phacilitate Vaccine Forum 2012, Washington, 30 January - 1 February 2012 9th North American Vaccine Forum

The event once again provided a highly valuable meeting place for senior level industry and public sector figures driving the development of novel prophylactic and therapeutic vaccines.

Mark Geels gave a presentation entitled: How is the European Vaccine Initiative addressing the global need for new vaccines?

Annual meeting of NEWTBVAC, Les Diablerets, 31 January – 3 February

NEWTBVAC (2010-2014) is the successor of the successful TBVAC project (2004-2009) also with TBVI as coordinator

NEWTBVAC is a project for the discovery and preclinical testing of new tuberculosis vaccine candidates. Odile Leroy gave a presentation entitled: Future Collaborations.

WHO (IVR) Scientific Forum: Accelerating Development of Second Generation Malaria Vaccines and Malaria Vaccine Funders' Group Meeting, Geneva, 20 – 22 February

The purpose of the IVR Scientific Forum was to being to review progress of second generation malaria vaccines, review the lessons learned by malaria vaccine development over the last 5 to10 years, and discuss ways to maximize the possibility of achieving the 2025 roadmap goal.

The possible outcomes of the Scientific Forum included a consensus on ways to accelerate second generation malaria vaccine development. Following the Scientific Forum, a closed meeting of the Malaria Vaccine Funders' Group Meeting was held in the afternoon of 22 February 2012. Issues for discussion included updates on progress and challenges faced by each funder. The MALVAC Committee meeting took place on the morning of 22 February 2012. The purpose of the committee meeting was to review the recommendations from the Scientific Forum and make recommendations to WHO in relation to vaccine development in this area.

Odile Leroy gave an update on EVI activities at the Malaria Vaccine Funders Group Meeting on 22 February.

2nd Annual Global Vaccine Forum: Challenges in the World of Novel Vaccines, Vienna, 1 – 2 March

The forum focused on challenges that all vaccine industry stakeholders are facing with regard to the demand for novel vaccines.

The 2nd Annual Global Vaccine Forum represented a unique platform to review and understand unmet needs that the vaccine industry players have to confront.

Odile Leroy gave a presentation during the session on Novel Vaccines in the Developing World entitled: Vaccines for Diseases of Poverty – Where Are We?

Joint meeting of the German Society for Tropical Medicine and International Health (DTG) and German Society for Parasitology (DGP), Heidelberg, 14 – 17 March

Mark Geels gave a presentation entitled: TRANSVAC: European Network of Vaccine Research and Development; Nicola Viebig presented the work of The Malaria Vectored Vaccines Consortium: Integrating capacity building and networking in the design and conduct of phase I and II clinical trials of viral vectored malaria vaccines in East and West African children and infants, and Odile Leroy gave a presentation entitled: The contribution of product development partnerships and the example of the European Vaccine Initiative.

8th Annual BioMalPar Conference, Heidelberg, 14 – 16 May

The meeting was sponsored by the European Network of Excellence, EVIMalaR

The purpose of the BioMalPar annual conference was to bring together malaria researchers from Europe and overseas (including Africa, America, Asia and Australia) in order to present and share recent groundbreaking findings on fundamental malaria research. New insights were also featured through the use of poster sessions. This meeting also provided an enriched environment for researchers at all stages of their career to interact with international leaders in the field. The meeting offered an excellent opportunity for sharing ideas and for potential development of new worldwide collaborations.

Regitze Louise Thøgersen presented a poster on the TRANSVAC project.

Vaccine Technology IV, Albufeira, 20 – 25 May

The goal of Vaccine Technology IV was to gather together many of the key leaders in the field to discuss and review progress made in generating new vaccine targets, new technologies for vaccines and new adjuvants.

Key strategic issues were also discussed, such as how to generate a new vaccine very quickly, and also how to make vaccines more available to the developing world.

Nicolas Havelange gave a presentation entitled Challenges in clinical batches production of malaria vaccines.

Modern Vaccines, Adjuvants & Delivery Systems (MVDAS), Copenhagen, 4 – 6 July

The drive for the new generation of vaccine therapies has precipitated a concurrent need for new and improved adjuvantation/delivery systems for these new vaccines.

This new international MVDAS conference focused on updating the community on new adjuvant/delivery systems/technologies associated with developing modern vaccines strategies and vaccine research. There is now an urgent need for the development of these potent and safe adjuvants and delivery systems and MVADS 2012 offered researchers a fresh forum to discuss this important topic in detail.

A special EVI session was held on 6 July: European Vaccine Initiative: Vaccine Development in Europe

Euroscience Open Forum (ESOF) 2012, Dublin, 11 – 15 July

ESOF is an inter-disciplinary, pan-European meeting, held under the auspices of Euroscience.

The event brought together 6,000 scientists, business leaders, government officials and international media to discuss the best of European science and to address all of the major global challenges, including Energy, Climate Change, Food and Health.

EVI organised a successful and well-attended session, titled "Tomorrow's vaccines today", at ESOF on the 14th of July 2012.

The session focussed on why vaccine development serves as an ultimate example of the innovation needed in the fight against modern day global health problems. For vaccine development to succeed it is crucial that efforts in research, education and funding are well coordinated to foster an enabling environment in which out-of-the-box thinking is encouraged and innovation can deliver products.

Speakers from Academia included (David Klatzmann, Hôpital Pitié–Salpêtrière, France), Biotech (André Habel, Themis Bioscience, Austria), Industry (Danilo Casimiro, MSD, USA) and PDPs/Research Infrastructures (Odile Leroy, EVI, Germany).

Parlamentarischer Abend, Berlin, 11 September

The meeting was arranged by Deutschlands F&E-Finanzierung für armutsbedingte und vernachlässigte Krankheiten.

Stefan Jungbluth presented the PRIMALVAC project.

Actualités Pharo, Marseille, 13 – 14 September

Actualités Pharo is organised by the Institut de médecine tropicale du Service de santé des armées

Odile Leroy was invited to speak during the session Vers l'élimination du Paludisme (Title: Malaria vaccines: where are we and where are we going?)

World Health Summit, Berlin, 21 – 24 October

The World Health Summit is the annual conference of the M8 Alliance of Academic Health Centres and Medical Universities, organised by Charité Universitätsmedizin Berlin in collaboration with the National Academies of Sciences of more the 67 countries and their Interacademy Medical Panel (IAMP).

The World Health Summit's mission was to bring together researchers, physicians, leading government officials and representatives from industry as well as from Non-Governmental Organisations (NGOs) and health care systems worldwide to address the most pressing issues facing medicine and health care systems over the next decade and beyond.

During the session on "Do We Need a Global Convention for Research & Development?", Odile Leroy gave a talk on "Possible Implications of a Convention for R&D in the European Context".

ADITEC Annual Meeting, Nice, 29 – 31 October

ADITEC is a collaborative research programme that aims to accelerate the development of novel and powerful immunisation technologies for the next generation of human vaccines. Scientists from 13 countries and 42 research partners collaborate in the ADITEC project, which has existed since 2011. The first annual meeting was held in October 2012. All ADITEC partners were invited to present the results for the first year of research.

Odile Leroy participated in the round table.

13th Annual General Meeting of Developing Countries Vaccine Manufacturers' Network (DCVMN), Bali, 31 October – 3 November

DCVMN is a voluntary public health driven alliance of vaccine manufacturers from developing countries that aims to make a consistent supply of quality vaccines that are accessible to developing countries.

Nicolas Havelange gave a presentation entitled: European Vaccine Initiative partnerships.

GOVERNANCE & FUND RAISING

Governance

This year has been very active for the governing bodies of EVI.

The EVI SAC met three times: 1) for the review of applications to the call for vaccine development, and for a review of the portfolio in March, 2) for the review of applications to the call for Innovation and Discovery in September, and 3) for the annual review of the portfolio in December, a closed meeting before and after the EVI RdV. Three new members joined the eight existing members: Giuseppe Del Giudice for his expertise in immunology, infectious diseases, vaccines, vaccine adjuvants, David Goldblatt for his expertise in paediatrics, immunology and infectious diseases, and Shabir Madhi for his experience as investigator in paediatric vaccines development. Unfortunately Shabir had to resign after three months due to his increasing workload. Furthermore Roland Dobbelaer having decided to finally take full retirement also resigned after the meeting in December. EVI extends its thanks to Roland for his invaluable and wise support since September 2009. The EVI SAC is now faced with the challenge of finding two replacement experts in 2013.

The EVI Board also met three times: 1) for the first bi-annual meeting in March, 2) for the review of EVI governance in October, and 3) for the last bi-annual meeting in December. The EVI Board also held one teleconference for specific topics needing in depth discussions and exchanges. The EVI Board approved the project recommended by EVI SAC for the vaccine development grant: "Efficacy of *Plasmodium falciparum* Sporozoite Chemoprophylaxis Vaccine (PfSPZ-CVac) in Tanzania", a Steve Hoffman (Sanaria Inc.) project called SPOROVAC, as well as part of two projects for the innovation and discovery grants: 1) "Optimising Antigen Production and Selection for a Vaccine against Blood-Stage *Plasmodium falciparum* Malaria based on the Pf Reticulocyte Binding Protein Homologue 5 (PfRH5)" a Simon Draper (University of Oxford) project called InnoMalVac, and 2) "Development of a controlled human Paratyphoid Infection Model (PIM) to evaluate novel paratyphoid vaccines" a Andrew Pollard (University of Oxford) project called PIM. Furthermore, after the retirement of Sir Brian Greenwood end of 2011, Professor David Salisbury, Chair of the Vaccine Jenner Foundation, join the EVI EEIG-Board, and kindly agreed to chair the selection sub-committee of the Board.

The EVI Board of Stakeholders met only once separately, as the second meeting was a joint meeting with the EVI Board.

Together with an external consultant, Michael Kelly from Empeira, EVI Board and EVI Secretariat looked at how governance could be improved, especially with regard to maintaining links with the donors. During the October meeting, Michael Kelly gave a talk entitled: "Governance Best Practice applied to EVI-EEIG". He also reviewed the current governance of EVI and has made recommendations for further improvement. He strongly encouraged EVI to put in place risk management and internal audit functions. The first internal audit took place at the end of 2012, and risk management will be implemented in 2013.

The EVI EEIG signed one Memorandum of Understanding with the Sclavo Vaccine Association, the coordinator of ADITEC, a large European research consortium funded by the EC. This new MoU will allow EVI information sharing, and further strengthen cooperation with other important stakeholders in the vaccine development field.

Participants at EVI SAC, BoS and Board meetings

EVI-EEIG Board

20 March, face to face meeting, IWH, Heidelberg

Claire Boog, RIVM, The Netherlands

David Salisbury, Jenner Vaccine Foundation, UK

Clemens Kocken, BPRC, The Netherlands

Terry McWade (Vice Chair), RCSI, Ireland

Martin Trillsch substitute for Claus R. Bartram, Heidelberg University, Germany

Marita Troye-Blomberg (Chair), Stockholm University, Sweden

Roland Dobbelaer (SAC Chair, non-voting)

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault and Jill Iversen

8 October, teleconference

David Salisbury, Terry McWade, Marita Troye-Blomberg, Alister Craig (SAC Vice Chair)

From EVI: Odile Leroy, Sten Larsen, and Nathalie Imbault

26 October, face to face meeting, Institut Pasteur, Paris

Clemens Kocken, Terry McWade, Marita Troye-Blomberg, Michael Kelly, Consultant, Empeira, Republic of Ireland

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault and Jill Iversen

7 December, face to face, IWH Heidelberg, combined with a Board of Stakeholders Meeting

EEIG Board:

Clemens Kocken ,Terry McWade ,Martin Trillsch ,Marita Troye-Blomberg, Roland Dobbelaer (SAC, non-voting member) ,Michael Kelly, Consultant, Empeira, Republic of Ireland

Board of Stakeholders:

Diarmuid O'Donovan, Irish Health Service Executive, representing Irish Aid, Republic of Ireland

Sodiomon Bienvenu Sirima, CNRFP, Burkina Faso Charles de Taisne, Sanofi Pasteur, France

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault and Jill Iversen

Board of Stakeholders

20 March, face to face meeting, IWH Heidelberg

Suresh Jadhav, Serum Institute of India

Diarmuid O'Donovan, Sodiomon Bienvenue Sirima, Charles de Taisne

Terry McWade (Board Vice Chair, non-voting)

Marita Troye-Blomberg (Board Chair, non-voting)

Andrea Holzaepfel (observer), KfW for Bundesministerium für Bildung und Forschung (BMBF), Germany

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault and Jill Iversen

Scientific Advisory Committee

19 March, face to face meeting, IWH Heidelberg

Alister Craig (Vice Chair), Liverpool School of Tropical Medicine, UK

Roland Dobbelaer (Chair), Belgium

Ingileif Jonsdottir, Landspitali University Hospital, Iceland

Samuel McConkey, Royal College of Surgeons in Ireland, Republic of Ireland

Mahamadou Ali Thera, University of Bamako, Mali

Aissatou Touré, Institut Pasteur de Dakar, Senegal

EVI Secretariat

10 September, face to face meeting, Paris

Alister Craig (Vice Chair), Roland Dobbelaer (Chair),

Guiseppe Del Guidice, Novartis Vaccines and Diagnostics, Research Center, Italy

David Goldbaltt, Institute of Child Health, University College London, UK

Joachim Hombach, World Health Organization, Switzerland

Ingileif Jonsdottir, Samuel McConkey, Mahamadou Ali Thera, Aissatou Touré.

From EVI: Odile Leroy, Sten Larsen, Nathalie Imbault and Ines Petersen

5 – 6 December, face to face meeting, IWH Heidelberg

Alister Craig (Vice Chair), Guiseppe Del Guidice, Roland Dobbelaer (Chair), Joachim Hombach, Ingileif Jonsdottir, Samuel McConkey, Mahamadou Ali Thera, Aissatou Touré

EVI Secretariat

Fund Raising

2012 was another very successful year for EVI regarding fundraising. A total amount of slightly more than €14 Million was jointly raised between EVI and its partners, the funds corresponding to EVI alone amounting to approximately €2.2 Million. Two projects were granted by the EC. PlacMalVac has the objective to advance the development of a var2CSA-based vaccine against PAM, whereas in MultiMalVax will develop a multi-stage malaria vaccine to the point of proof-of concept phase II testing. Apart from these EC projects, two additional strategic primer grants were awarded in which EVI participates and in which the clinical development of different malaria vaccines will be advanced.

Furthermore, through the German Ministry of Research, as partner of the Network of Excellence on Infectious Diseases, EVI will have the opportunity to test its malaria vaccine candidates in phase I/II clinical trials in Germany and Gabon (estimated support ~€2.4M).

In addition to the grants awarded to EVI in 2012, EVI submitted several proposals to the final call for proposals in Health under the EC FP7. A total of six Stage 1 proposals were presented to different topics of which four proposals were selected for the submission of full Stage 2 proposals. Finals results of the evaluation process are expected for Spring 2013. Furthemore, EVI was contacted to integrate a consortium between stage 1 and 2, to strengthen the governance and management of the consortium.

In 2012, EVI also started developing and implementing a novel fundraising strategy with the aim to diversify the sources of future income and thereby reducing the risks of depending on a limited number of funding sources. The expanded scope of the novel strategy includes in particular targeting corporate donors and charities with interest in diseases of poverty.

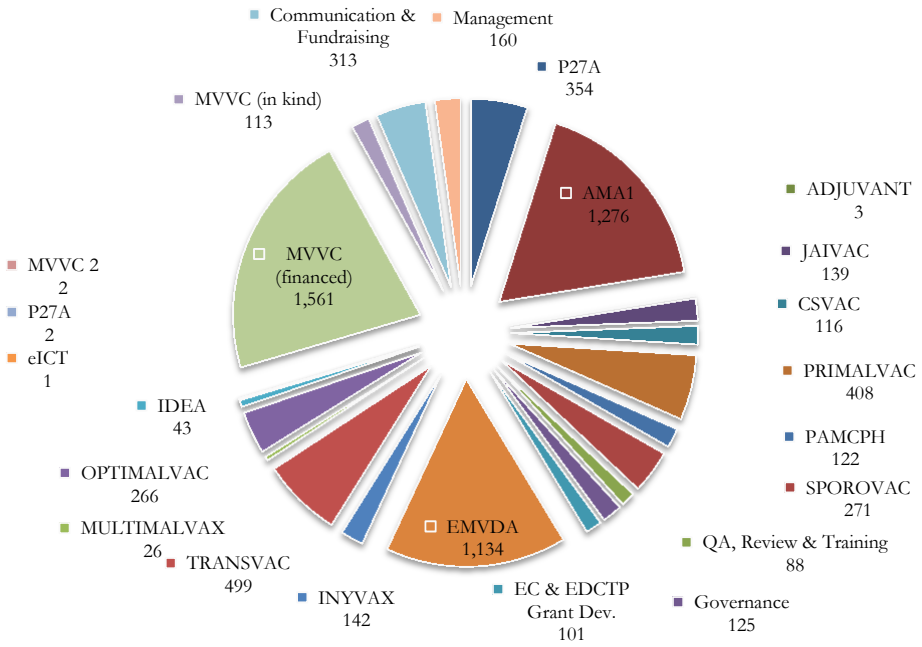
Donor	Title	Total Amount	Total EVI
EDCTP	P27A phase Ib clinical trial on malaria blood stage vaccine	€ 938,380	€ 225,451
EDCTP	Field Trials of a New Combination Malaria Vaccine in West African Adults and Children (MVVC 2)	€ 1,239,153	€ 108,640
EC	MultiMalVax- A Multi-Stage Malaria Vaccine	€ 6,000,000	€ 700,000
EC	PlacMalVac	€ 5,935,544	€ 1,163,164
TOTAL Raised BY EVI & partners:		***€ 14,113,077***	***€ 2,197,255***

FINANCIAL UPDATE 2012

The year 2012 was yet again an interesting year for EVI. We have seen encouraging developments in vaccine development, whereby projects progressing strongly in production and clinical development, and in our EC/EDCTP projects significant deliverables and milestones have been efficiently met, which are evident in the financial figures. EVI Secretariat has, in the current reporting period, once again shown conscientiousness and an extraordinary level of achievement in all areas of EVI activities. This year showed that progress can be made with an on full funds utilisation and good business acumen. EVI is, as always indebted to its granters for their strong support, and EVI Secretariat would like to extend our heartfelt thanks to Irish Aid, DGIS, BMBF, EDCTP, and the EC for their invaluable encouragement.

Figure 1 below shows the cost activity over the current reporting period, where expenditure in the broad portfolio of EVI, EDCTP and EC projects, has technically produced a high level of outcome in comparison with the level of funding. The financial conclusion of the current reporting period is that EVI performance is unceasingly strong and that funds are properly utilised to accelerate the development of vaccine against diseases of poverty.

Figure 2 -Total EVI Activity 2012 (€'000)



KEY RATIOS 2012

The following key ratios are the result of the EVI 2012 Operations

MANAGEMENT PERCENTAGE			
Year	Decided threshold	Result	Direct investment percentage of each EURO donated
2010	7.00%	2.14%	**98%**
2011	7.00%	4.02%	**96%**
2012	7.00%	2.20%	**98%**

For each EURO donated to EVI almost 98% are directly invested for vaccine development against diseases of poverty.

QUICK RATIOS

INDICATORS	RATIOS' RESULTS	
	FIGURE	QUALIFICATION
Quick ratio (liquidity)	4.13	Good
Gross Operating Profit Ratio (Financial Autonomy)	0.00	Good
Profitability	941.62	Good
Solvency	4.61	Acceptable
INDICATORS	**NOTEWORTHY VALUE'S RESULT**	
	FIGURE	QUALIFICATION
Equity Flag	4.61	Good

PURPOSE	INDICATORS	WEAK* 0	ACCEPTABLE* 1	GOOD* 2
Liquidity	Quick ratio	$i < 0.5$	$0.5 \leq i \leq 1$	$i > 1$
Financial autonomy	Gross Operating Profit Ratio	$i > 0.40$ or <0	$0.40 \geq i \geq 0.30$	$0 \leq i < 0.30$
Profitability	Profitability	$i < 0.05$	$0.05 \leq i \leq 0.15$	$i > 0.15$
Solvency	Solvency	$i > 6.00$ or < 0	$6.00 \geq i \geq 4.00$	$0 \leq i < 4.00$
PURPOSE	**INDICATORS**	**WEAK**		**GOOD**
Equity Flag	Solvency	$i > 10.00$ or < 0		$i \leq 10.00$ and ≥ 0

* Qualifications as decided by the EC

SUMMARY OF OTHER IMPORTANT RATIOS**

INDICATOR	FIGURE	EXPLANATION
RoA on EVI Grants signed***	**866%**	Grants effect (signed grants) on core donations to EVI
RoA on EVI investment core projects***	**418%**	Four times earmarked funds raised for EVI projects for each core euro donation
RoA on core donations for EVI Secretariat***	**2,955%**	29½ times more funds raised for all earmarked purposes for each core euro donation

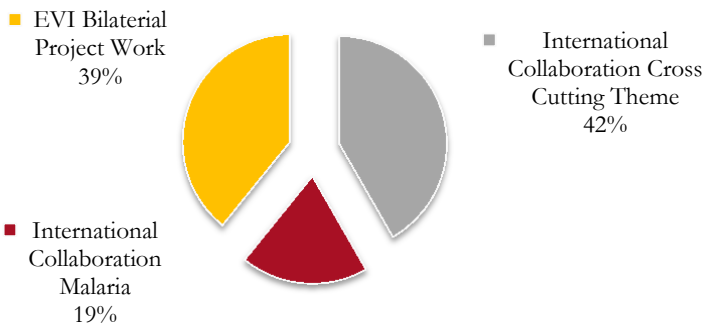
** The return on assets (RoA) percentage shows how efficient EVI uses its assets in generating new revenue

***Achieved in the period of 2006-2012

INTERNATIONAL COLLABORATION

EVI is more than anything an international organisation collaborating on malaria and other cross cutting vaccine themes through coordination and networking on a global level. In 2012 61% of EVI activities was direct international collaboration with partners and stakeholders from Europe, Africa, Asia and North America. 39% was bilateral work, which by its nature, also counts as international collaboration. See figure 2.

Figure 3 -International Collaborations (in %)



EVI PROJECT ACTIVITIES

Over the past 12 Months the EVI vaccine portfolio has seen increasing activity. cGMP manufacturing is on-going, and clinical trials are progressing surely and steadily especially concerning AMA1-DiCo.

Figure 4 -EVI Portfolio Investment (€'000 and in %)

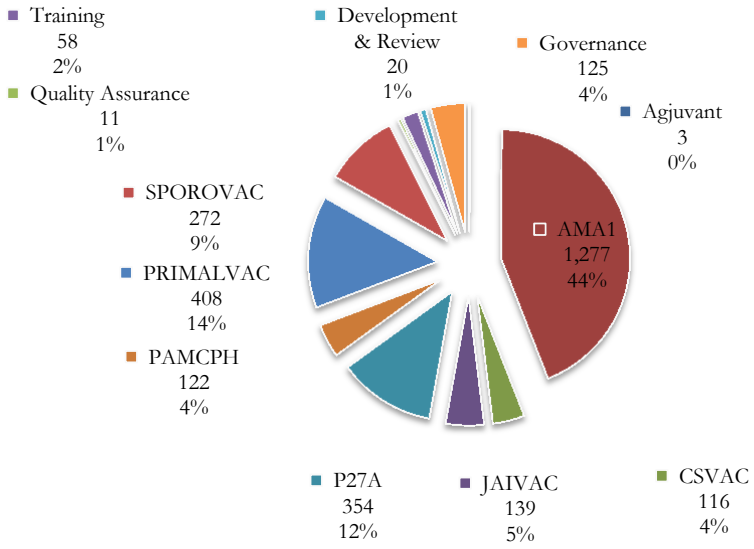
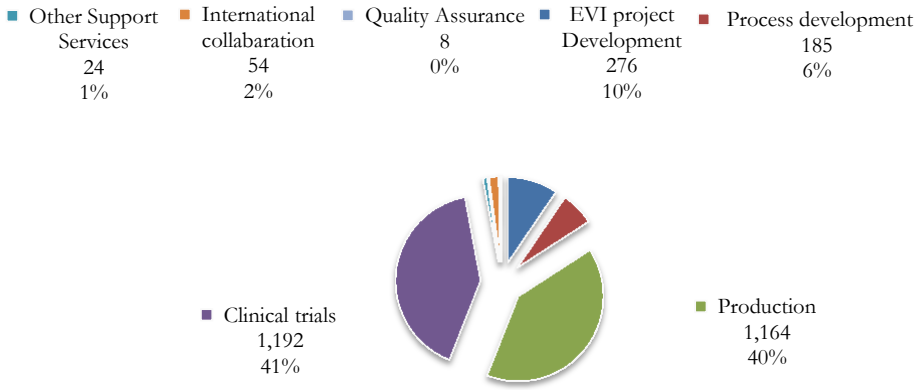


Figure 4 depicts investment over the past 12 months dominated by cGMP production and clinical trials up to 81%. Investment over the next 12 months will continue to be dominated by cGMP production and clinical trials, including investments in process development, especially for the PAM projects.

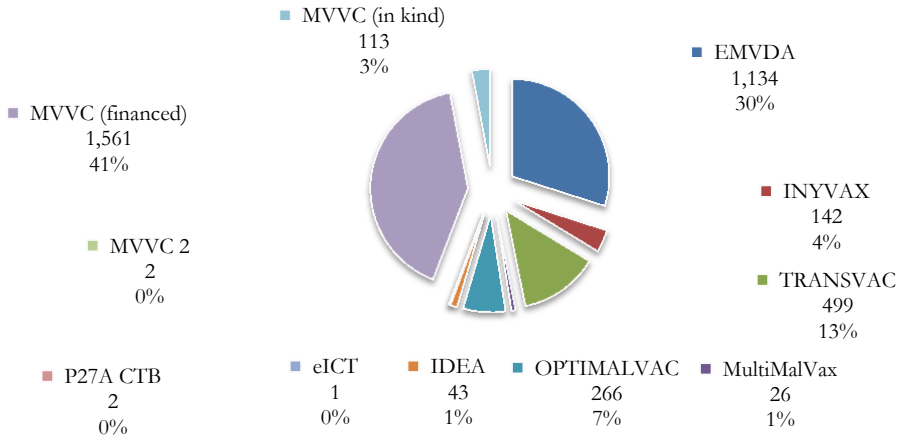
Figure 5 - Portfolio investment type (€'000 and in %)



EVI EC & EDCTP ACTIVITY

Besides the EVI portfolio of specific investment in various vaccine candidate projects, EVI is involved in several EC and EDCTP funded projects. Figure 5 shows expenditure on all the projects. Not surprisingly, the largest expenditure is attributed to the EDCTP project MVVC which is drawing closer to a conclusion. EMVDA has also seen increased activity up to May 2013 together with TRANSVAC which is due to end 2013.

Figure 6 - EC and EDCTP Activity (€'000 and in %)

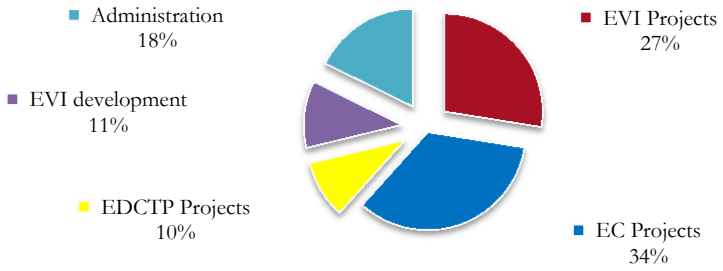


STAFF TIME (HOURS) IN THE CURRENT REPORTING PERIOD

In 2012 EVI managed to pick up speed on the EC and EDCTP projects as reflected in the figure below. Although staff spent 18% of their time on administration, then overall management expenditure only accounted for 2.21% of total global expenditure.

By the end of 2012 most staff where based at EVI Headquarters in Heidelberg, Germany and only five members of staff are placed outside of Germany, two of which are at the registered office in Denmark. The strategy of EVI to strengthen the executive office and continue to reduce expenditure on consultants was implemented in 2011-12 and will continue to be in effect for 2013.

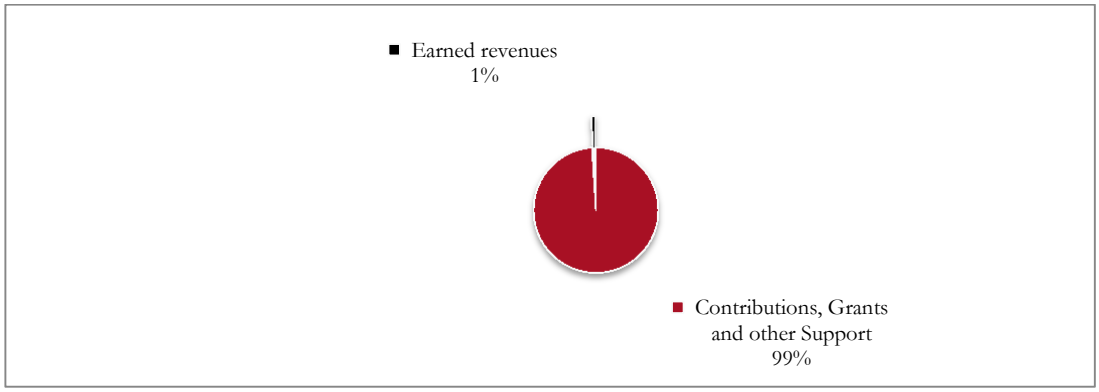
Figure 7 - Staff time - Hours (in %)



Income and expenditure composition

EVI's income consists entirely of public funding coming from the EC, national government grants and EDCTP. Only one percent is of other source in 2012.

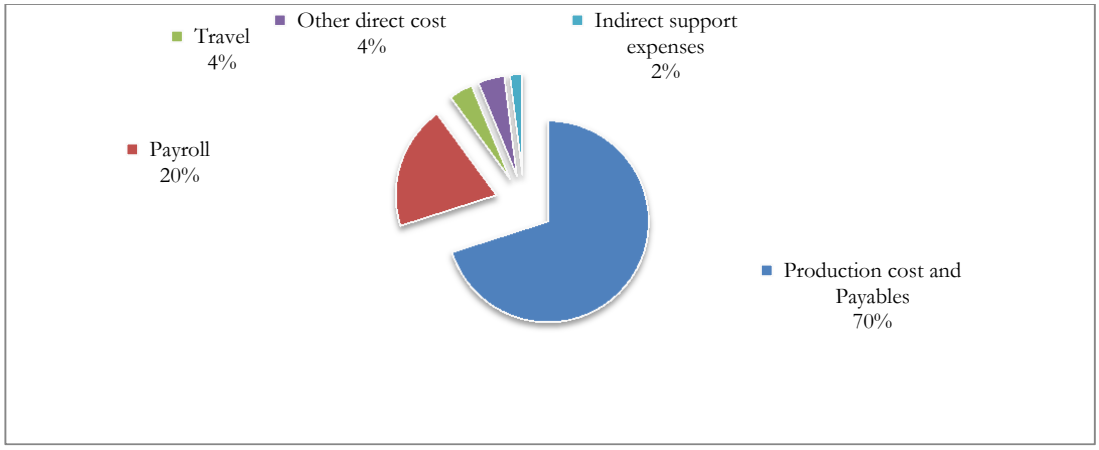
Figure 8 – Income composition (in %)



EVI's expenditures are primarily consisting of production and clinical trial outsourcing cost. Secondary it consists of payroll which is strongly linked to the EC and EDCTP projects and of course EVI core vaccine projects.

EVI has during 2012 made considerable cost savings on travel cost which only compromise of 4% of the total EVI cost. This is due to an economy due to travel policy and environment protection policy.

Figure 9 – Expenditure composition (in %)



FINANCIAL AUDITS 2012

The following financial audits where performed during the current reporting period:

COMPLETED BY FALK & CO	
EVI organisational financial audit 2011	Successful, No qualifications
DGIS grant financial audit 2011	Successful, No qualifications
BMBF grant financial audit 2011	Successful, No qualifications
EMVDA project financial audit 2010-12	Successful, No qualifications
TRANSVAC project financial audit 2011-2012	Successful, No qualifications
EVI organisational audit 2012	Successful, No qualifications

COMPLETED BY KPMG ON BEHALF OF THE EC	
FP7 projects TRANSVAC, INYVAX, OPTIMALVAC	Successful, No qualifications

CONTINUES INTERNAL CONTROL AUDIT BY PRENTIS & CO.	
Internal Control Audit	Successful, No qualifications

FINANCIAL NOTES 2012

Principal accounting policies

(a) General comment

EVI fully lives up to the demands of German General Accepted Accounting Principles (GAAP) and empowers its staff working on project to participate in budget controlling and controlling of spending continuously. Then taking into consideration it's seize, EVI do much more controlling than legally required for living up to the highest systemic standards. EVI operates an extensive continues internal control system for the financial management for the purpose of living up to the highest standards for public funds management. EVI operates a sharp diversification of financial task and, despite having a relative small secretariat; we ensure an extensive and detailed controlling of all transactions by the staff in the Financial Management team, the Executive Director and the empowered project leaders. EVI carefully monitors the liquidity and plan its fundraising to plan for its liquidity for years in advance as part of risk management. EVI has setup and developed AESIRAS accounting which now operates as the tool for accounting and financial management for EVI/non-profit business with an astonishing four dimensional accounting/analysis programme and matrix account analysis tool.

(b) Basis of accounting

The basis of accounting is in accordance with German GAAP. Other accounting policies are described in the EVI handbook, and Rules of Procedures together with relevant policies known and applied by EVI staff. EVI accounting method is accrual based, with consideration for projects governed by external guidelines.

(c) Funding parties

EVI is currently funded by Government agencies (Irish Aid, DGIS, BMBF) and the EC in addition to the EDCTP.

EVI is always open to new donors and other private funders who share our vision of a world free of the burden of diseases of poverty or who perhaps purely wants to support a good cause for the benefit of combating poverty.

(d) Realised Income policy

Public Grants/Donations received by EVI are posted on the balance sheet as deferred income. Grant related expenditures are posted on the Profit and Loss (PNL), and as such figure as income for EVI. Only income generated from sales or other economic activity is directly recognised as income on the PNL.

(e) Payables

All amounts payable by EVI are charged to the PNL in the cost relevant year on the basis of accrual accounting. Payables are identified, evaluated and approved by the relevant project leaders for proof of deliverables and milestones. The finance team then account them accordingly to the respective accounts and dimensions segmented by defined details.

(f) Investment income and interest receivable

Interests received on EVI funds are included in the PNL in the year for which it is receivable. It is posted on the EVI administrative cost centre, and can be utilised as core support.

(g) Primary and secondary commerce

EVI´s primary focus is to develop vaccines for the benefit of combatting the diseases of poverty. As a secondary commerce EVI may perform sales of services and product in shape of lecturing, workshops and debates where needed in addition to utilise to the full extent any surplus of product available.

(h) Funds accounting

Funds held by EVI are either:

• Core support funds – these are funds set aside for eligible EVI project relevant expenditures.

• Earmarked (Restricted) funds – these are funds related to specific earmarked projects including EC/EDCTP and other similar type projects

(i) Time recording

EVI operates, on daily basis, a comprehensive time management recording system that fully lives up to the demands of public management with emphasis on transparency, accountability and accuracy. The system identifies every productive hour by the staff, which again are segmented in defined dimensions in detail, and are accounted into the accounting system as such.

(j) Budget planning

Budget planning is performed by the Finance Director each year – with the support of the project leaders who are responsible for reporting and planning each there area of responsibility in detail. The Finance Director receives and compiles the overall budget and presents it to the Executive Director who in turn reports the budget to the EVI-EEIG Board through a work plan proposal.

(k) Equity

Funds held by EVI as equity:

Result of the year is transferred to equity to be utilised as strategic reserve for research and development for the organisation. EVI does not pay out any dividends or similar to its shareholder by statutes of the organisation.

(l) Foreign currencies

Transactions in foreign currencies are translated into Euro at rates prevailing on the date of the transaction using xe.com, with the one exception of Danish Kroner which is politically fixed at a rate of 7.45. EVI has for the year 2012 made use of the following currencies: EUR, DKK, INR, USD, GBP and XOF.

(m) Auditors

EVI is audited by FALK & Co, who forms part of the global alliance of independent firms called PRAXITY.

The auditor issues the audit report, which is made available in full to EVI-EEIG Board members and Board of Stakeholders, including all donors. The financial audit report contains analysis of EVI and relevant recommendations by the auditor.

In the current annual report the conclusion – the auditor's opinion - together with the audited PNL and balance sheet is shown and made public. The opinion is shown in German and an English translation prepared by the auditor.

In addition EVI has out-sourced its internally audit to Prentis & Co, Cambridge, UK .

(n) **External Audit**

In 2012 EVI had the pleasure to be financially audited by the European Commission for three EC projects; TRANSVAC, INYVAX and OPTIMALVAC. The audit where performed by the KPMG on behalf of the EC and EVI extends its appreciation for a productive cooperation.

(o) Final remarks and thanks

EVI would like to thank all of our donors, stakeholders, subcontractors and partners in vaccine development. We would, from a financial point of view, like to extend our appreciation to the BDO offices in Germany, France, Belgium, Denmark and United Kingdom for well organised payroll management and tax advice. EVI sends it's thanks to LETT law firm in Copenhagen for dealing efficiently and professionally with our rights in Denmark. EVI would like to thank our internal auditor from Prentis & Co and FALK & co for their role as financial auditors of EVI both for annual audit and by project for which we remain stronger.

Donations/Grants received

BMBF	€	672,433
EC IDEA	€	5,348
EC PHARVAT	€	20,152
EC EMVDA	€	799,109
EC INYVAX	€	134,415
EC OPTIMALVAC	€	150,000
EDCTP MVVC	€	1,572,569
EDCTP eICT	€	1,782

Interest earned

Interest Danish Account	€	63
Interest German Accounts	€	8,064
Interest UK Account	€	0
Total	€	8,124

EVI extends its thanks and appreciation to all its donors and grant providers

Staff

List of staff (as at 31 December 2012)

	First Name	Last Name	Title/Function in EVI	Placement
1	Odile	Leroy	Executive Director	Germany
2	Mark	Geels	Project Manager	Germany
3	Nathalie	Imbault	Quality Assurance, External Relations & Communication, Director	Germany
4	Roland	Kleine	Office Clerk	Germany
5	Thorsten	Kohaut	Finance Manager	Germany
6	Nicola	Viebig	Project Manager	Germany
7	Celine	Dutruel	Project Manager	Germany
8	Ines	Petersen	Project Manager	Germany
9	Stefan	Jungbluth	Business Manager	Germany
10	Nicolas	Havelange	Production, Director*	Belgium
11	Sophie	Houard	Vaccine Development Manager	Belgium
12	Egeruan Babatunde	Imoukhuede	Clinical & Regulatory Affairs, Director	UK
13	Joanna	Korejwo	Project Manager	France
14	Sten	Larsen	Finance & Human Resource, Director	Denmark
15	Jill	Iversen	Web Master*	Denmark
16	Regitze Louise	Thoegersen	Program Manager	Denmark
17	Harry	Van Schooten	Public Health and Business Development Advisor*	The Netherlands

*Consultant

Male	8
Female	9

Total Staff of EVI 31 December 2012 **17 (13.5 FTE)**

Income realised

Contributions, Grants and other Support		
Revenue from indirect contributions	€	266,621
National Government agency grants	€	4,062,677
EU Grants	€	2,109,883
EDCTP Grants	€	1,564,876
Total Contributions, Grants and other Support	**€**	**7,737,437**
Earned revenues		
Interest-savings/short-term investments	€	8,124
Non-inventory sales - gross	€	800
Total Earned Revenues	**€**	**8,924**
Total Income Realised	**€**	**8,012,981**

Direct & indirect project expenditures *

Grants, contracts, & direct assistance		
Contracts - program-related	€	2,446,727
Benefits paid to or for MVVC consortium members	€	1,465,880
Benefits paid to or for EU consortium members	€	1,178,818
Total Payables	**€**	**5,091,425**
Salaries & wage expenses		
Salaries & wages international staff	€	282,026
Salaries & wages German staff	€	423,475
Casual labour wages	€	50,000
Payroll taxes, etc.	€	318,750
In house consultancies.	€	137,591
Statutory social security expenses	€	228,041
Contributions to health and safety agency	€	1,983
Voluntary social benefits not subject to wafe tax	€	694
Employee benefit expenses	€	360
Holiday pay accrued	€	1,453
Total salary cost	**€**	**1,444,373**

Contract service expenses		
Accounting fees	€	51,872
Accounting Fees – SUB**	€	14,000
Legal fees	€	200
Professional fees - other	€	75,582
Consultancies - contract	€	5,600
Facility & equipment maintenance expenses		
Software Licenses	€	8,181
Software Licenses – SUB**	€	5,319
Repairs and maintenance	€	963
Publishing cost including copy and printing	€	7,979
Publishing cost including copy and printing – SUB**	€	5,203
Books, subscriptions, references	€	4,000
Equipment, hardware & software		
Minor hardware purchases	€	1,624
Minor software purchases	€	1,204
Depreciation & amortisation	€	14,11
Travel & meetings expenses		
Travel (Flights)	€	86,465
Travel (Train, Ferry, Taxi, other)	€	43,142
Travel (refund for own use of travel means)	€	2,436
Hotel and other accommodation costs	€	58,852
Conferences, conventions, meetings	€	26,954
EU Conferences, conventions, meetings	€	23,576
EDCTP Conferences, conventions, meetings	€	5,234
Travel allowances for employees	€	22,823
Restaurant, catering and other travel provisions	€	6,074
External Staff Training costs	€	1,163
Total travel cost	€	**276,719**
Other direct expenses		
Recruitment costs	€	9,528

Insurances	€	13,690
Membership dues - organisation	€	478
Staff development	€	32
Internal Staff Training costs	€	15,717
Internal Staff teambuilding costs	€	18,334
Advertising expenses	€	2,825
Contingency provisions	€	-16
Indirect business expenses		
Telephone & telecommunications	€	27,206
Broadband & other internet connections	€	1,247
Postage & shipping	€	12,590
Office Supplies	€	12,005
Printing & copying	€	456
Fees & Charges	€	15,105
Hosting agreement costs	€	65,000
Organisational (corporate) expenses	€	11,541
EVI Board, BoS & SAC expenses		
Board travel cost	€	1,517
BoS travel cost	€	3,793
SAC meetings	€	8,229
SAC travel cost	€	15,502
EC ESAC, SAC, SC expenses		
ESAC travel cost	€	9,159
SAC meetings	€	7,088
SAC travel cost	€	3,672
SAC travel cost – SUB*	€	2,618
Total expenses	**€**	**7,265,669**

Result of the year

2012 Result:

Transferred to Equity – Reserved for R&D	€	**747,312**

** SUB is subcontracted cost as according to EC guidelines*

*** Expenditures as per account – for identified by project relevance see - expenditures by project table.*

Major payables

EVI project payments	Project relevance	Period		Amount
EMBL	EMVDA	2012-01	€	55,095
Progressima	EMVDA	2012-01	€	3,640
Almac	P27A	2012-02	€	254,384
Diagnosearch	JAIVAC	2012-02	€	21,788
Nova Laboratories	AMA1-DiCo	2012-03	€	111,410
Pfenex	PRIMALVAC	2012-03	€	102,316
ICGEB	JAIVAC	2012-04	€	93,943
Rita Walt	PRIMALVAC	2012-05	€	3,653
Fraunhofer	AMA1-DiCo	2012-06	€	26,755
Inserm	PRIMALVAC	2012-06	€	234,574
Output	AMA1-DiCo	2012-06	€	32,573
Wil Research	AMA1 - DiCo	2012-06	€	288,586
Diagnosearch	MANAGEMENT	2012-07	€	11,637
Confarma	AMA1-DiCo	2012-08	€	64,247
GFA	AMA1-DiCo	2012-08	€	19,777
Universite de Lausanne	P27A	2012-09	€	15,700
Betty Dodet Bioscience	TRANSVAC	2012-10	€	16,000
Eltium	AMA1-DiCo	2012-10	€	4,060
Inserm	AMA1-DiCo	2012-10	€	656,589
RCSI	CSVAC	2012-10	€	80,000
Sanaria	SPOROVAC	2012-10	€	250,000
UCPH	PAMCPH	2012-12	€	100,000

MVVC project payments	Project relevance	Period		Amount
UOXF	MVVC	2012-05	€	427,946
KEMRI	MVVC	2012-05	€	264,983
CNRFP	MVVC	2012-05	€	303,528

MRC Gambia	MVVC	2012-05	€	141,217
Okairos	MVVC	2012-05	€	4,840
VSCR	MVVC	2012-05	€	47,817
UCAD	MVVC	2012-05	€	275,549

EC project payments	**Project relevance**	**Period**		**Amount**
BPRC-UNIL	TRANSVAC	2012-07	€	-43,368
BPRC-UNIL	TRANSVAC	2012-07	€	43,368
BPRC	OPTIMALVAC	2012-08	€	8,093
UEDIN	OPTIMALVAC	2012-08	€	19,714
UOXF	OPTIMALVAC	2012-08	€	5,868
RUNMC	OPTIMALVAC	2012-08	€	22,492
CRESIB	OPTIMALVAC	2012-08	€	7,280
WHO	OPTIMALVAC	2012-08	€	69,796
BPRC	INYVAX	2012-08	€	13,562
TBVI	INYVAX	2012-08	€	14,809

EC project payments	**Project relevance**	**Period**		**Amount**
WHO	INYVAX	2012-08	€	21,954
Univ. Basel	INYVAX	2012-08	€	19,895
UNIGE	INYVAX	2012-08	€	3,250
Fondation Merieux	INYVAX	2012-08	€	25,046
BPRC	EMVDA	2012-12	€	44,775
Stockholm University	EMVDA	2012-12	€	1,778
Etna	EMVDA	2012-12	€	21,554
Universitätsklinikum Tübingen	EMVDA	2012-12	€	234
CHUV	EMVDA	2012-12	€	412,979
UEDIN	EMVDA	2012-12	€	30,365
Swiss TPH	EMVDA	2012-12	€	404
UMCN	EMVDA	2012-12	€	118,977
UHEI	EMVDA	2012-12	€	315,992

Expenditures by project

PROJECT CODE	Amount spent (incl. partner pay)		In percentage
P27A	€	354,196.15	4.87%
AMA1-DiCo	€	1,276,875.65	17.57%
Adjuvant Platform	€	3,222.19	0.04%
JAIVAC	€	139,162.21	1.92%
CSVAC	€	115,530.99	1.59%
PRIMALVAC	€	407,742.98	5.61%
PAMCPH	€	122,252.74	1.68%
SPOROVAC	€	271,457.01	3.74%

Quality Assurance	€	10,414.58	0.14%
Development and Review	€	19,715.70	0.27%
Training internal/external	€	57,844.76	0.80%
Governance	€	125,067.22	1.72%

EU Grant development	€	67,877.56	0.93%
EMVDA	€	1,134,450.60	15.61%
INYVAX	€	141,554.10	1.95%
TRANSVAC	€	499,232.89	6.87%
MultiMalvax	€	26,348.79	0.36%
OPTIMALVAC	€	265,649.21	3.66%
IDEA	€	42,647.62	0.59%

EDCTP Grant dev.	€	33,286.46	0.46%
EDCTP eICT	€	553.77	0.01%
EDCTP P27A	€	1,943.89	0.03%
EDCTP MVVC 2	€	1,706.57	0.02%
EDCTP MVVC (financed)	€	1,560,671.95	21.48%
EDCTP MVVC (in kind)	€	113,346.60	1.56%

Communication	€	219,240.38	3.02%
Fund Raising	€	93,586.57	1.29%

Management	€	160,090.21	2.20%
TOTAL	**€**	**7,265,669.35**	100.00%

Balance overview of donor and EC/EDCTP funds (in €)

Donator/Grant	Type	Balance 31/12 2011	Received 2012	Cost 2012	Balance 31/12 2012
Irish Aid - IE	Core	**1,172,351**	0	2,030,738	**- 858,387**
Board Funds - EVI	Core	**3,263,032**	0	36,102	**3,226,930**
BMBF - DE	Restricted	**320,481**	672,433	566,895	**426,019**
DGIS - NL	Restricted	**833,023**	0	1,428,942	**- 595,919**
TRANSVAC - EC	Restricted	**6,293**	0	499,233	**- 492,940**
PHARVAT - EC	Restricted	**-30,732**	20,152	- 10,580	**0**
IDEA - EC	Restricted	**31,052**	5,348	42,648	**- 6,248**
INYVAX - EC	Restricted	**-25,605**	134,415	108,810	**0**
OPTIMALVAC - EC	Restricted	**73,075**	150,000	223,075	**0**
EMVDA - EC	Restricted	**316,189**	799,109	1,134,451	**- 19,153**
MultiMalVax - EC	Restricted	**0**	0	26,349	**- 26,349**
MVVC - EDCTP	Restricted	**22,123**	1,552,569	1,542,454	**32,238**
eICT – EDCTP	Restricted	**0**	1,782	554	**1,228**
MVVC2 – EDCTP	Restricted	**0**	0	1,707	**- 1,707**
P27A - EDCTP	Restricted	**0**	0	1,944	**- 1,944**
Admin EVI	Core	**1,113,530**	266,621	619,139	**761,012**
Equity Reserves	Core	**0**	747,312	0	**747,312**
Total core		**5,548,913**	**1,013,933**	**2,685,979**	**3,876,867**
Total restricted		**1,545,899**	**3,335,808**	**5,566,482**	**- 684,775**
Total EVI funds		**7,094,812**	**4,349,741**	**8,252,461**	**3,192,092**

EVI Inventory value estimated 31/12/2013

P27A	€	139,440.00
AMA1-DiCo	€	279,650.00
Adjuvants	€	39,312.00
TOTAL	**€**	**458,402.00**

The asset created are meant to be for free as part of clinical trials, however where surplus exist can be used for other purposes.

Value is based on lowest market rate estimated – the value does not appear as assets for the company since its primary use is for clinical trials – given for free.

EVI Finished Production Inventory 31/12/2013

INVENTORY ID	NAME	PRODUCT TYPE	DESCRIPTION	BATCH NUMBER	STOCK 01/01/12	CHANGES 2012	QUANTITY 31/12/12
NOVALABS	ALMy001	P27A Vaccine	P27A Line A	ALMy001	903	-18	885
NOVALABS	ALMy001	P27A Vaccine	P27A Line B	ALMY001	865	-43	822
NOVALABS	EVIy003	AMA1 - DiCo Vaccine	pfAMa1 DiCo 60µg Lyophilized	EVIy002	1147	-68	1079
NOVALABS	EVIy002	Adjuvant Alum	Alhydrogel Line A	EVIy003	1916	-188	1728
NOVALABS	EVIy002	Adjuvant Alum	Alhydrogel Line B	EVIy003	1916	-204	1712
OUTPUT GmbH	GLA-SE 20u/ml	Adjuvant-IDRI - Mixed	20u/ml. 4% Oil - 0.4ml/Vial	0054-10F002	250	-208	42
OUTPUT GmbH	GLA-SE 0.1mg/ml	Adjuvant-IDRI - Non Oil	0.1 mg/ml - 1 ml/Vial	QF547	30	-12	18
OUTPUT GmbH	EM060G 4% oil, 0.4 ml	Adjuvant-IDRI - OIL	4% oil, 0.4 ml - 0.4ml/Vial	0038-10F001	200	-15	185
OUTPUT GmbH	PfAma1-DiCo1	AMA1 - DiCo Vaccine	Bulk drug Substance	101108	12	-1	11
OUTPUT GmbH	PfAma1-DiCo2	AMA1 - DiCo Vaccine	Bulk drug Substance	101115	11	-1	10
OUTPUT GmbH	PfAma1-DiCo3	AMA1 - DiCo Vaccine	Bulk drug Substance	101122	8	-1	7
Serum Institute of India (SII)	Alhydrogel	Adjuvant Alum	0.5 ml/vial	EAlH1001	5320	0	5320

Financial statements as audited for the year ending 31st December 2012

PROFIT AND LOSS	EUR 2012	EUR 2011
1. Turnover	800.00	0.00
2. Other operating income from donors	8,004,057.29	11,256,044.20
3. Miscellaneous operating income	0.00	0.00
4. Subtotal I	**8,004,857.29**	**11,256,044.20**
5. Personal wages		
a. Wages and Salaries	-1,216,331.83	-1,225,185.74
b. Social security costs	-228,040.72	-188,774.25
c. Thereof for pensions: EUR 0.00	0.00	0.00
	-1,444,372.55	**-1,413,959.99**
6. Depreciation on Tangible fixed Assets	-14,111.40	-10,291.12
7. Other operating Expenses	-5,807,185.40	-10,113,420.00
8. Subtotal II	**739,187.94**	**-281,626.91**
9. Other Interest and similar income	8,124.11	281,626.91
10. Net Result	**747,312.05**	**0.00**
11. Tax	0.00	0.00
12. Result after tax	**747,312.05**	**0.00**

BALANCE SHEET / ASSETS		EUR 2012		EUR 2011
Assets				
A. Fixed Assets				
Tangible Assets				
Other Equipment, office and plant equipment		**44,948.98**		**27,706.96**
B. Current Assets				
I. Other Assets	14,820.30		6,294.50	
II. Cash in hand, Cash in Banks	4,106,846.20	**4,121,666.50**	9,309,921.73	**9,316,216.23**
C. Prepaid expenses				
I. Other Prepaid Expenses		**26,114.67**		**9,727.66**
		4,192,730.15		**9,353,650.85**

BALANCE SHEET / LIABILITIES AND EQUITY		EUR 2012		EUR 2011
A. **Equity**				
Result of the Year		**747,312.05**		**0,00**
B. **Accruals**				
Other Accruals		**280,615.05**		**688,872.10**
C. **Liabilities**				
1. Liabilities in relation to grants received				
a. National governments grants liabilities	2,444,781.34		7,094,812.83	
b. European Union and other restricted grant liabilities	315,991.72		1,196,344.47	
Thereof with a remaining term up to one year	2,760,773.06		8,291,157.30	
2. Creditors (Trade Liabilities)	340,796.01		338,448.80	
Thereof with a remaining term of up to one year	338,448.80		338,448.80	
3. Other Liabilities	63,233.98		35,172.65	
Thereof from taxes	25,912.54		17,549.14	
Thereof from social security	-6,777.88		157.75	
Thereof with a remaining term of up to one year	63,233.98	**3,164,803.05**	35,172.65	**8,664,778.75**
		4,192,730.15		**9,353,650.85**

Financial Audit statement for the year ending 31st December 2012

To European Vaccine Initiative-EWlV, Heidelberg:

We have audited the annual financial statements, comprising the balance sheet, the income statement and the notes to the financial statements, together with the bookkeeping system of European Vaccine Initiative EWlV, Heidelberg, for the business year from January 1 to December 31, 2012. The maintenance of the books and records and the preparation of the annual financial statements in accordance with German commercial law and supplementary provisions in the statutes are the responsibility of the entity's management. Our responsibility is to express an opinion on the annual financial statements, together with the bookkeeping system, based on our audit.

We conducted our audit of the annual financial statements in accordance with Section 317 of the German Commercial Code and the German generally accepted standards for the audit of financial statements promulgated by the Institut der Wirtschaftsprufer (Institute of Public Auditors in Germany). Those standards require that we plan and perform the audit such that misstatements materially affecting the presentation of the net assets, financial position and results of operations in the annual financial statements in accordance with German principles of proper accounting are detected with reasonable assurance. Knowledge of the business activities and the economic and legal environment of the entity and expectations as to possible misstatements are taken into account in the determination of audit procedures. The effectiveness of the accounting related internal control system and the evidence supporting the disclosures in the books and records and the annual financial statements are examined primarily on a test basis within the framework of the audit. The audit includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the annual financial statements. We believe that our audit provides a reasonable basis for our opinion.

Our audit has not led to any reservations.

In our opinion, based on the findings of our audit, the annual financial statements as of December 31, 2012 of European Vaccine Initiative-EWIV, Heidelberg, comply with the legal requirements and the supplementary provisions in the statutes and give a true and fair view of the net assets, financial position and results of operations of the entity in the accordance with principles of proper accounting.

Heidelberg, den 11. April 2013

FALK GmbH & CO KG WIRTSCHAFTS-PRÜFUNGS-GESELLSCHAFT SIEGEL HEIDELBERG

FALK GmbH & Co KG
Wirtschaftsprüfungsgesellschaft
Steuerberatungsgesellschaft

(Meyer)
Wirtschaftsprüfer

(Ahrens)
Wirtschaftsprüfer

Cash management (bank accounts) as at 31st December 2012

Cash in German Key Accounts (EUR)	€	260,715.51
Cash in Danish Bank (DKK)	€	73,966.64
Cash in UK Bank (DKK)	€	22,164.05
Cash in German Savings accounts (EUR)	€	3,750,000.00

Hosting costs

EVI is hosted by the Heidelberg University with the following costs:

Hosting costs – Legal support € 65,000

Total 2012 service charges € 65,000.00 (2011 = € 65,790.58)

Remuneration of governing bodies

Travel and subsistence costs are refunded to Board, BoS and SAC members in connection with meetings and conferences including an honorarium to SAC members.

We formally sign and approve the EVI Annual Financial Report for the year 2012 ending 31st December 2012 in accordance with EVI-EEIG Board decision.

The governing accounting principles and the overall presentation of the Annual Financial Report are deemed to give a true and fair illustration of EVI activities.

Date : / / 2013

Sten Larsen, EVI Finance Director

Date : / / 2013

Odile Leroy, EVI Executive Director

Date : / / 2013

Terry McWade, Chair of EVI-EEIG Board

Acknowledgements

Grateful thanks are extended to the following people, who have contributed significantly to the success of EVI: Especially all the participants in the clinical trials funded by EVI.

Our Board Members and Donors:

Andrea	Holzaepfel	Germany
Andreas	Holtel	Belgium
Annie	Vestjens	The Netherlands
Brian	Greenwood	United Kingdom
Charles	de Taisne	France
Charles	Mgone	Tanzania
Christos	Profilis	Greece
Claire	Boog	The Netherlands
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Diarmuid	O'Donovan	Republic of Ireland
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Marita	Troye-Blomberg	Sweden
Marja	Esveld	The Netherlands
Sodiomon	Sirima	Burkina Faso
Suresh	Jadhav	India
Terry	McWade	Republic of Ireland

Our Scientific Advisors:

Aissatou	Toure	Senegal
Alister	Craig	United Kingdom
Ingileif	Jonsdottir	Iceland

Juhani	Eskola	Finland
Mahamadou Aly	Thera	Mali
Marie-Paule	Kieny	Switzerland
Roland	Dobbelaer	Belgium
Giuseppe	Del Giudice	Italy
David	Goldblatt	United Kingdom
Joachim	Hombach	Switzerland
Samuel	McConkey	Republic of Ireland
Shabir	Madhi	South Africa

Our Partners

Academisch Medisch Centrum bij de Universiteit van Amsterdam	NL
Academisch Ziekenhuis Leiden – Leids Universitair Medisch Centrum	NL
African Malaria Network Trust	TZ
Agence Nationale de Recherches Sur Le Sida et les Hépatites Virales	FR
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Biomedical Primate Research Centre	NL
BIOTEM	FR
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Central Veterinary Institute	NL
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Centre National de Recherche et de Formation sur le Paludisme	BF
CiToxLAB	FR
Confarma	FR
DiagnoSearch Life Sciences Pvt. Ltd.	IN
Eberhard-Karls Universität Tübingen	DE
Ecole Polytechnique Federale de Lausanne	CH
Etna Biotech	IT

Eurovacc Foundation	NL
Fondation international de l'Hopital de Dr. Albert Schweitzer de Lambarene	GB
Fondation Mérieux	FR
Fraunhofer IME	DE
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GTP technology	FR
Health Protection Agency – CPER	UK
Health Protection Agency/ National Institute for Biological Standards and Control	UK
Helmholtz Zentrum für Infektionsforschung GmbH	DE
Henogen (now novasep)	BE
Ifakara Health Institute	TZ
ImmunoVacc Consulting	BE
Infectious Diseases Research Institute	USA
Institut National de la Sante et de la Recherche Medicale	FR
Institut Pasteur	FR
International Centre for Genetic Engineering and Biotechnology	IN
Intox Pvt. Ltd	IN
Istituto Nazionale Malattie Infettive L.Spallanzani – IRCCS	IT
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Kenya Medical Research Institute	KE
LIONEX GmbH	DE
London School of Hygiene and Tropical Medicine	UK
Lotus Labs. Pvt. Ltd.	IN
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Makerere University	UG
Malaria Consortium LBG	UK
Malaria Vaccine Development Program	IN
Max Planck Institute for Infection Biology	DE
Medical Research Council, Gambia	GM
Medical Research Council on behalf of its MRC/UVRI Uganda Research Unit on AIDS	UK

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Output Pharma	DE
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Swiss Tropical Institute	CH
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TuBerculosis Vaccine Initiative	NL
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University of Ibadan	NI
University of Lausanne	CH
University of Lausanne (WHO reference centre)	CH
University of Maryland	US
University of Oxford	UK
University of Stockholm	SE
Vakzine Projekt Management GmbH	DE
Vienna School of Clinical Research	AT
Voisin Consulting Life Sciences	FR

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AMA1-DiCo

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