EUROPEAN VACCINE INITIATIVE

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For Donors

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European Vaccine Initiative
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List of Abbreviations

3D7	*P. falciparum* clone 3D7
ADCI	Antibody-Dependent Cellular Inhibition
AIDS	Acquired Immunodeficiency Syndrome
AMA1	Apical Membrane Antigen 1
AS01B	GSK Biologicals' Adjuvant System AS01B
AS02A	GSK Biologicals' Adjuvant System AS02A
ASTMH	American Society for Tropical Medicine and Hygiene
AT	Austria
BCG	Bacillus Calmette-Guérin
BCTU	Bagamoyo Clinical Trial Unit
BE	Belgium
BELLEROPHON	Combining Cellular and Humoral Immune Responses as a Vaccine Strategy against *Staphylococcus aureus* Pathogen
BF	Burkina Faso
BK-SE36	*P. falciparum* serine repeat antigen-5 N-terminal domain formulated with aluminium hydroxyl gel
BMBF	German Federal Ministry of Education and Research
BMGF	Bill & Melinda Gates Foundation
BN	Benin
BoS	Board of Stakeholders
BPRC	Biomedical Primate Research Centre
BSI	British Society for Immunology
CBF	Clinical Biomanufacturing Facility
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
CD	Cluster of Differentiation
CERMEL	Centre de recherches médicale de Lambaréné
CERPAGE	Centre d'étude et de recherche sur le paludisme associé à la grossesse et l'enfance
CH	Switzerland
ChAd	Chimpanzee Adenovirus
ChAd63	Chimpanzee Adenovirus 63
CHMI	Controlled Human Malaria Infection
CHUV	Centre hosptalier universitaire Vaudois
CIC	Centre d'investigation clinique
CMO	Contract Manufacturing Organisation
CMP	Centre for Medical Parasitology
CNRFP	Centre national de recherche et de formation sur le paludisme
CommHERE	Communicating European Health Research Network
CRO	Contract Research Organisation
CS	Circumsporozoite
CSA	Chondroitin Sulphate A
CSP	Circumsporozoite Protein
CSVAC	A Circumsporozoite Protein Vaccine against malaria using the Adenovirus ChAd63 vector
C-tag	C-terminal four-amino-acid tag
D.C.	District of Columbia
DBL	Duffy-Binding-Like
DCVMN	Developing Countries' Vaccine Manufacturers Network

DE	Germany
DG	Directorate General
DiCo	Diversity Covering
DK	Denmark
DNA	Deoxyribonucleic acid
DNDi	Drugs for Neglected Diseases initiative
DSW	Deutsche Stiftung Weltbevölkerung
E. coli	*Escherichia coli*
EC	European Commission
ECRIN-ERIC	European Clinical Research Infrastructure Network - European Research Infrastructure Consortium
EDCTP	European and Developing Countries' Clinical Trials Partnership
EDUFLUVAC	Educate Influenza Vaccine
EEIG	European Economic Interest Grouping
EIB	European Investment Bank
eICT	An evaluation of the impact of malaria clinical trials on the delivery of health care, particularly for women and children, in sub-Saharan Africa
EIT	European Institute of Innovation and Technology
EKUT	Eberhard Karls Universität Tübingen
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immuno Spot Assay
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
ESAC	European Statistical Advisory Committee
ESWI	European Scientific Working Group on Influenza
EU	European Union
EVI	European Vaccine Initiative
FDA	Food and Drug Administration
FP7	Framework Programme Seven
FR	France
Fraunhofer IME	Fraunhofer Institute for Molecular Biology and Applied Ecology
FRMC	Financial Risk Management Committee
GAAP	German General Accepted Accounting Principles
GB	Gabon
GH	Ghana
GHB	German commercial code - Handelsgesetzbuch
GHIT	Global Health Innovation Technology
GIA	Growth Inhibition Assay
GLA-SE	Glucopyranosyl Lipid Adjuvant-Stable Emulsion
GM	The Gambia
GMP	Good Manufacturing Practice
GMZ2	Recombinant *Lactococcus lactis* Hybrid GLUtamate Rich Protein and Merozoite Surface Protein 3
GPI	Glycosylphosphatidylinositol
GSK	GlaxoSmithKline
GVIRF	Global Vaccine and Immunization Research Forum
HA	Haemagglutinin
His	Histidine

HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HTF	Danish National Advanced Technology Foundation
IABS	International Alliance for Biological Standardization
IAoCR	International Academy of Clinical Research
iBET	Instituto de Biologia Experimental e Tecnológica
ICGEB	International Centre for Genetic Engineering and Biotechnology
IDEA	Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth Infections: An African-European Research Initiative
IDMS	Isotope Dilution Mass Spectrometry
IDRI	Infectious Disease Research Institute
IDT	IDT Biologika GmbH
IE	Republic of Ireland
IFRS	International Financial Reporting Standard
IHI	Ifakara Health Institute
ILRI	International Livestock Research Institute
IMPD	Investigational Medicinal Product Dossier
IMT	Institute of Tropical Medicine
IMX	Tag developed by IMAXIO
IMX313	IMAXIO tag IMX313
IN	India
InnoMalVac	Optimising antigen production and selection for a vaccine against blood-stage Pf malaria based on PfRH5
Inserm	Institut national de la santé et de la recherche médicale
Intravacc	Institute for Translational Vaccinology
INTS	Institut national de transfusion sanguine
INYVAX	Optimisation of the Development of Poverty-Related Diseases Vaccines by a transversal approach, addressing common gaps and challenges
IPROVE	Innovation Partnership for a Roadmap on Vaccines in Europe
IRB	Institutional Review Board
IRD	Institut de recherche pour le développement
ISO	International Organisation for Standardisation
ISSSI	International Symposium on Staphylococci and Staphylococcal Infections
IT	Italy
JAIVAC-1	Malaria Recombinant Vaccine Candidate - PfMSP-119 and PfF2
JI	Jenner Institute
JP	Japan
kDa	Kilodalton
KE	Kenya
KEMRI	Kenya Medical Research Institute
KfW	Kreditanstalt für Wiederaufbau
KHRC	Kintampo Health Research Centre
LSHTM	London School of Hygiene & Tropical Medicine
LSTM	Liverpool School of Tropical Medicine
Matrix M	Adjuvant by Novavax, in which matrix complexes are formed by a specific mixture of Quillaja saponin, cholesterol and phospholipids

MCB	Master Cell Bank
ME-TRAP	Multiple Epitope-Thrombospondin-Related Adhesion Protein
MHRA	Medicine and Healthcare products Regulatory Agency
MP	Member of Parliament
MPA	Medical Product Agency
MPL	Monophosphoryl Lipid A
MRC	Medical Research Council
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSc	Master of Science
MUII	Makerere-UVRI research training programme in Infection & Immunity
MultiMalVax	Multi-stage Malaria Vaccine
MVA	Modified Vaccinia Virus Ankara
MVFG	Malaria Vaccine Funders Group
MVI-PATH	Malaria Vaccine Initiative PATH
MVTR	Malaria Vaccine Technology Roadmap
MVVC	Malaria Vectored Vaccines Consortium
MVVC2	Malaria Vectored Vaccines Consortium 2
NA	Neuraminidase
NDA	National Drug Authority
NHS	National Health Service
NI	Nigeria
NIBSC	National Institute for Biological Standards and Controls
NID	Neglected Infectious Disease
NIH-NIAID	National Institutes of Health - National Institute of Allergy and Infectious Diseases
NIHR	National Institute for Health Research
NL	The Netherlands
NTD	Neglected Tropical Diseases
OPEX	Operating expenses
OPTIMALVAC	Initiative on Optimising Malaria Vaccine Lab Assays Evaluation
P27A	Fragment P27A of the novel malaria protein PFF0165c
P27A-CTB	Safety and immunogenicity of P27A, a novel candidate blood-stage malaria vaccine, in malaria-exposed African adults
PAMCPH	Recombinant var2CSA protein as a vaccine candidate for pregnancy-associated malaria
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PDP	Product Development Partnership
PE	*Plasmodium falciparum*-infected Erythrocytes
PEGS	Protein Engineering Summit
PEI	Paul-Ehrlich-Institute
Pf	*Plasmodium falciparum*
PfAMA1	*Plasmodium falciparum* Apical Membrane Antigen 1
PfEBA-175	*Plasmodium falciparum* Erythrocyte-Binding Antigen-175
PfEMP1	*Plasmodium falciparum* Erythrocyte Membrane Protein-1
PfMSP	*Plasmodium falciparum* Merozoite Surface Protein
PfRH5	*Plasmodium falciparum* Reticulocyte-binding protein Homologue 5
PhD	Doctor of Philosophy

PIM	Paratyphoid Infection Model
PlacMalVac	Clinical development of a var2CSA-based Placental Malaria Vaccine candidate
PNL	Profit and Loss
PRIMALVAC	Recombinant var2CSA protein as vaccine candidate for placental malaria
PSC	Project Steering Committee
PT	Portugal
qPCR	Quantitative Polymerase Chain Reaction
R	Programming language and software environment for statistical computing and graphics
R&D	Research and Development
R&I	Research and Innovation
R21	Circumsporozoite protein particle
RBM	Roll Back Malaria
RCSI	Royal College of Surgeons Ireland
RIMD	Research Institute for Microbial Diseases
RTS,S	The RTS,S vaccine was engineered using genes from the repeat and T-cell epitope of Pf malaria CSP, a hepatitis B virus envelope protein (HBsAg) and a chemical adjuvant to boost the immune response
S. aureus	*Staphylococcus aureus*
S. paratyphi A	*Salmonella enterica* serovar *paratyphi A*
S2	Schneider 2
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SC	Steering Committee
SE	Stable Emulsion
SE	Sweden
SE36	SERA5 N-terminal domain
SEmalvac	Serine repeat antigen-5 malaria vaccine
SERA5	Serine Repeat Antigen-5
Sida	Swedish Development Agency
SII	Serum Institute of India
SMEs	Small and Medium Enterprises
SN	Senegal
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
SRID	Single Radial Immunodiffusion
Swiss TPH	Swiss Tropical and Public Health Institute
TB	Tuberculosis
TRANSVAC	European Network of Vaccine Research and Development
TZ	Tanzania
UCAD	Université Cheikh Anta Diop
UCPH	University of Copenhagen
UG	Uganda
UHEI	University of Heidelberg
UK	United Kingdom
UNCST	The Uganda National Council for Science and Technology
UNIL	University of Lausanne

UOXF	University of Oxford
USA	United States of America
UVRI	Uganda Vaccine Research Institute
Var	Genes encoding the PfEMP-1 proteins
VAR2CSA	Variant surface antigen that mediates adhesion of the infected erythrocyte to CSA
VLP	Virus-Like Particle
VSCR	Vienna School of Clinical Research
WHO	World Health Organization
WP	Work Package

FOREWORD

Clemens Kocken, Chairman of EVI-EEIG

Another demanding year has passed, and it is pleasing to note that all EVI's activities are progressing well.

To focus on the more important activities, EVI has strengthened its blood-stage malaria portfolio, and I would like to highlight the encouraging results concerning the candidates P27A and AMA1-DiCo, as well as the significant efforts to harmonise the clinical development of placental malaria vaccine candidates between the French (PRIMALVAC) and Danish (PlacMalVac) teams, with the support of Patrick Duffy (NIH-NIAID, USA). The EDCTP-funded projects assessing the prime-boost approach of combination malaria vaccines at Oxford University (MVVC and MVVC2) are now harvesting the results of clinical trials, capacity building and networking. Numerous articles relating to EVI projects have been published in peer-reviewed journals during the year, including the roadmap for the establishment of a European vaccine R&D infrastructure.

It is especially pleasing to see EVI attracting new donors such as the Japanese GHIT, whose contribution will be used, together with the RIMD at Osaka University, for the clinical evaluation of a novel malaria vaccine candidate in Burkina Faso.

This year also saw the expansion of the EVI EEIG with the welcome addition of Institut Pasteur, Paris, which hosted the annual EVI Rendez-Vous event. Representing as I do the EEIG, it is encouraging to witness the increasing popularity of this event, which can be seen as a benchmark for EVI's success. Another important gathering of key players in the global malaria community was the EVI workshop "Malaria Vaccine Development in Europe – preparing for the future", to coordinate the further implementation of the Malaria Vaccine Technology Roadmap in Europe.

EVI is on the threshold of an exciting and challenging period, and it is my firm belief that the strong and dedicated team will continue to produce the first class results to which we have become accustomed.

EXECUTIVE SUMMARY

In 2014, EVI pursued its ongoing projects and also mobilised resources from the GHIT Fund, Japan, which allowed the new malaria vaccine development project SEmalvac to be launched, together with partners from Japan and Burkina Faso.

The EVI portfolio of vaccine candidates in 2014 included the following highlights:

The AMA1-DiCo vaccine candidate moved into active clinical development with the start of a two-centre clinical trial. Phases Ia and Ib were initiated in France and Burkina Faso, respectively. The vaccination phase will be completed in early 2015.

The P27A candidate also commenced active clinical development with the launch of a two-centre clinical trial. Phases Ia and Ib were initiated in Switzerland and Tanzania, respectively. The vaccination phase will be complete in early 2015.

A major milestone was achieved in the MVVC project with the last subject last visit of the phase IIb clinical trial that aims to assess the efficacy of the ChAd63/MVA ME-TRAP vaccine candidates in Burkinabe children aged 5–17 months.

As stated above, the SEmalavac project was awarded in 2014 and kicked off in August. The planned phase Ib clinical trial has already received ethical clearance in Burkina Faso, and immunisation of the subjects is scheduled to begin in early 2015.

The InnoMalVac project progressed according to plan with protein expression, purification and characterisation. The crystal structure of PfRH5 with its receptor was published in Nature.

The highlight of the placental malaria projects PRIMALVAC and PAMCPH/PlacMalVac in 2014 was the conclusion of process development for both vaccine candidates and the initiation of GMP manufacturing. The two clinical trial protocols are now being designed. EVI committed significant efforts to ensure the harmonisation of the clinical trial activities in both projects. Two workshops were organised by EVI, aiming to harmonise the clinical development and the functional immunoassays for a placental malaria vaccine.

The human challenge study foreseen in the PIM project received ethical and regulatory approval and the challenge of the first volunteers began in May.

The main achievements of the IDEA project in 2014 involving EVI were the ethical and regulatory approval of two small standalone phase I clinical trials to study the influence of helminth infection on TB and HIV vaccine-induced immunity. Both clinical trials were initiated successfully.

The main achievements of the EDUFLUVAC project in 2014 included the generation of baculovirus vectors expressing the selected antigens, and the preparation of baculovirus-derived VLPs and their use for mouse immunisation studies.

The EVI workshop "Malaria vaccine development in Europe – preparing for the future" was held on 20–21 November 2014 in Brussels, Belgium. The aim of the workshop was to bring together key players in the European malaria vaccine development community to define and prioritise key future activities, and to outline Europe's contribution to the implementation of the updated malaria vaccine technology roadmap in a global context with the major stakeholders.

The fourth EVI Rendez-Vous was hosted for the first time by the Institut Pasteur in Paris. Approximately 80 participants attended the presentation of the current EVI project portfolio.

The current year will see major decisions taken and objectives set for the sustainable development of our planet. By supporting the development of products that aim to improve global health, EVI will continue to make small but important contributions to this process in the future.

Odile Leroy, Executive Director

THE YEAR IN GENERAL

Fundraising

In 2014, EVI together with other partner organisations received funds that allowed the continuation of current projects and successfully mobilised new funds sufficient to start one new vaccine development project, SEmalvac. A total of €684,619 was raised in 2014.

EVI Vaccine Projects

Malaria vaccine projects

The new project SEmalvac, supported by the GHIT Fund, kicked off in 2014. This project will include a phase Ib clinical trial that has already received ethical clearance in Burkina Faso.

Several projects initiated or continued the clinical development of vaccine candidates. The assessment of the AMA1-DiCo and P27A vaccine candidates was initiated in two-centre phase Ia/Ib clinical trials, AMA1-DiCo in France and Burkina Faso, and P27A in Switzerland and Tanzania. A major milestone was achieved in the MVVC project with the last subject last visit of the phase IIb clinical trial. Furthermore, the MVVC2 consortium began clinical testing at MRC, The Gambia, with the first vaccinations in May, and is preparing for the clinical trial at CNRFP, Burkina Faso. In the MultiMalVax project, the GMP manufacture of several antigens, and the clinical assessment of the PfRH5-vectored vaccines, has already begun.

The InnoMalVac project established cell lines expressing different variants of the PfRH5 antigen. The purified proteins were characterised and tested for functional antibody induction, and were also used to determine the crystal structure of PfRH5 in a complex with its receptor and neutralising antibodies.

The three projects concerning the development of placental malaria vaccines progressed as anticipated during 2014. The PRIMALVAC consortium completed process development for its vaccine candidate and GMP manufacturing has started. The PAMCPH consortium generated and analysed the MCB, followed by the transfer and validation of the analytical methods, upstream and downstream process transfer, and the GMP engineering run. The PlacMalVac consortium prepared and submitted the draft clinical trial protocol to the EC.

Other projects

Other pathogens and diseases currently targeted by EVI include influenza and *Salmonella paratyphi*. The EDUFLUVAC project advanced this year, achieving the generation of baculovirus vectors expressing selected HA and NA antigens, the preparation of VLPs and their use for mouse immunisation studies. In the PIM project, the clinical trial application received ethical and regulatory approval and the human challenge study was initiated.

In the IDEA project, which studies the interplay between poverty-related diseases and helminth infections, the main achievements in 2014 involving EVI were the ethical and regulatory approval of two small stand-alone phase I clinical trials and their successful initiation.

Finally, in the BELLEROPHON project exploring new vaccine technologies, the antigen composition of the vaccine candidate was selected in 2014.

Cross-cutting Activities

The IPROVE project aims to develop a vision of future priorities for funding and programming initiatives at the EU level in the field of vaccines and vaccination. During 2014, the first two stakeholder consultation meetings were organised, the first on vaccine SMEs and the second on training and communication in vaccines and vaccinology.

EVI Rendez-Vous

EVI's fourth Rendez-Vous took place at Institut Pasteur in Paris on 3 December. Approximately 80 participants attended this year's presentation of the EVI project portfolio.

Workshop "Malaria vaccine development in Europe – preparing for the future"

This workshop was organised by EVI and held on 20–21 November 2014 in Brussels. It brought together experts from the European, North American and African malaria vaccine communities, with the objective to set out key strategic activities for the coming years, and to integrate European vaccine development with global activities in the context of the updated Malaria Vaccine Technology Roadmap.

Governance

Institut Pasteur, France, became the seventh EVI Member by joining the EVI EEIG. Institut Pasteur is represented on the EVI Board by Claude Leclerc. The EVI SAC also underwent several changes: First, Mahamadou Thera, University of Bamako, Mali, was approved as the new Chair, following the departure of Alister Craig from the Liverpool School of Tropical Medicine, UK, who held the position for one year. Furthermore, David Goldblatt from the Institute of Child Health, University College London, resigned from the EVI SAC in 2014. Marcel Tanner from the Swiss Tropical and Public Health Institute was approved as a new member of the EVI BoS.

INTRODUCTION

Vaccines that prevent infection: liver-stage vaccines

Liver-stage or pre-erythrocytic vaccine strategies are designed to induce an immune response that neutralises the sporozoites and prevents their invasion of hepatocytes. This is typically a vaccine for travellers because it would prevent the advent of clinical disease if completely efficacious. A partially efficacious pre-erythrocytic vaccine would also be expected to reduce the incidence of new blood-stage infections.

Partners

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

CSVAC

The main objectives of EVI's project CSVAC were to produce a recombinant form of ChAd63 using a gene encoding most of the CSP (full length minus the GPI anchor sequence) and a recombinant MVA based on the same insert, followed by the GMP manufacturing of the vaccine candidates and a dose-escalation phase Ia clinical trial to assess the safety and immunogenicity of ChAd63 CSP and MVA CSP in humans. ChAd63-MVA CS administered in a heterologous prime-boost regime was shown to be safe and highly immunogenic, inducing high-level T-cell responses to CS. The study was published in PLOS One in 2014.

Partners

Centre national de recherche et de formation sur le paludisme, BF
European Vaccine Initiative, DE
Kenya Medical Research Institute, KE
Medical Research Council, GM
ReiThera s.r.l., IT (formerly Okairòs s.r.l., IT)
Université Cheikh Anta Diop, SN
University of Oxford, UK
Vienna School of Clinical Research, AT (until 31 Jan 2013)

MVVC

MVVC was funded by EDCTP in response to the 2008 call "Malaria Vaccines Integrated Project – Clinical Trials / Capacity Building / Networking". The total funding provided by EDCTP was €5,613,936, complemented by co-funding from the Irish Aid, Ireland, Sida, Sweden, MRC UK, the Federal Ministry of Science and Research, Austria, and third-party contributions from all the project partners, making a total budget of €9,514,711. The project lasted for five years (2009-2014).

The MVVC consortium included four African partners and initially four European partners, with EVI as the coordinator. The collaborators and partner institutions were selected according to the proposed objectives of the consortium and the collective expertise they offered for the mutual benefit of all partners. UOXF sponsored the clinical trials and developed and manufactured the vaccine candidates. ReiThera s.r.l. (formerly Okairos s.r.l.), remains a separate entity after the acquisition of Okairos AG by GSK in May 2013. VSCR provided and coordinated training courses for the MVVC consortium. Three of the African partners (CNRFP, KEMRI and MRC) are experienced in clinical trials, and the fourth (UCAD) has set up clinical trials infrastructure and conducted its first malaria vaccine phase IIb clinical trial. The main objective was to demonstrate 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. This was achieved by integrating capacity-building and networking in the design and implementation of phase I and II clinical trials of malaria vaccine candidates delivered using viral vectors, in East and West African adults, children, and infants.

The specific objectives are listed below:

- 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 the protection of adults and children against clinical malaria at multiple sites in East and West Africa;
- To ensure continued maintenance and further consolidation of the well-established investigational sites at level 4 and to facilitate the upgrading of the less-established sites from levels 1, 2 or 3 to levels 3 or 4 by the end of MVVC;
- To develop clinical trial capabilities, infrastructure and human resources that ensure the sustainability of the investigational 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.

The phase IIb clinical trial to assess the efficacy of the ChAd63/MVA ME-TRAP vaccine candidates in Burkinabe children aged 5–17 months reached the milestone of the last subject last visit in October after an extended follow-up during a second malaria season after vaccination.

Partners

Centre national de recherche et de formation sur le paludisme, BF
European Vaccine Initiative, DE
Kenya Medical Research Institute, KE
Kintampo Health Research Cemtre, GH
Medical Research Council, GM
Novartis Vaccines and Diagnostics, IT
ReiThera s.r.l., IT (formerly Okairòs s.r.l., IT)
Université Cheikh Anta Diop, SN
University of Oxford, UK
Vienna School of Clinical Research, AT (until 31 Jan 2013)

MVVC2

MVVC2 is an almost three-year project coordinated by EVI, building on the MVVC project which started to establish a strong network between four African partners and collaborators in Europe. This network was enlarged to include two new partners, and capacity-building efforts will be expanded during the course of MVVC2.

MVVC2 is funded by EDCTP in response to the December 2011 call "Field Trials of a New Combination Malaria Vaccine in West African Adults and Children (MVVC2)". The EDCTP grant is complemented with co-funding from EU Member States, BMBF, Irish Aid, MRC UK, Sida, and third-party contributions, with a total project budget of approximately €1,239,153. The MVVC2 consortium includes five African partners and initially five European partners.

The project aims to determine whether the vectored prime-boost malaria vaccines are compatible with the EPI vaccination schedule and whether a CSP particle in the adjuvant will show efficacy. The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines will be assessed in Gambian infants. The safety, immunogenicity and efficacy of the CSP particle in the adjuvant will be assessed in Burkinabe adults.

As part of the integrated strategy, capacity building and networking activities will be used to strengthen the clinical trial and laboratory capabilities of the African sites, allowing them to conduct the proposed clinical trials and additional health research.

The MVVC2 consortium began clinical trials at MRC, The Gambia, with the first vaccinations in May, and is preparing for the clinical trial at CNRFP, Burkina Faso. The KHRC site built

capacity in cellular immunology, and staff members from the five African partners and EVI participated in a training program on project management in clinical research.

Malaria vaccines that prevent mortality and morbidity: blood-stage vaccines

Clinical malaria occurs when malaria parasites from the genus *Plasmodium* invade red blood cells (the blood stage of the infection). Immunological studies in humans and animals have demonstrated that the immune response induced by blood-stage antigens can protect against the disease. Most antigens currently used as vaccine candidates are merozoite antigens. EVI has developed several blood-stage antigens with the intention of combining them in a second generation of malaria vaccines. The recent eradication push has brought the role of blood-stage malaria vaccines into question because they do not block transmission. However, studies in humans and animals have shown that controlling the parasite density can reduce the generation of gametocytes in the bloodstream, thus also limiting transmission.

Antigenic diversity is another challenge for the development of blood-stage vaccines. Ideally, vaccine candidates should be based on less polymorphic and more conserved antigen domains. Approaches to address this challenge include the development of recombinant antigens (AMA1-DiCo, PfMSP1 and PfEBA175, SEmalvac), recombinant full-length proteins (RH5) and synthetic peptides (P27A).

Partners

Biomedical Primate Research Centre, NL

Centre d'investigation clinique Cochin-Pasteur, FR

Centre national de recherche et de formation sur le paludisme, BF

Confarma, FR

European Vaccine Initiative, DE

Fraunhofer IME, DE

Gregory Fryer Associates Ltd, UK

Novasep (formerly Henogen), BE

Infectious Diseases Research Institute, USA

Institut national de la santé et de la recherche médicale, FR

NNE Pharmaplan GmbH, DE

Nova Laboratories, Ltd, UK

Output Pharma, DE

WIL Research, NL

AMA1-DiCo

AMA1 is a leading vaccine candidate 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 the invasion of erythrocytes by merozoites in vitro.

To investigate the role of human antibodies in naturally-acquired immunity, children in three separate endemic populations were tested for reactivity prior to the malaria transmission season, and malaria episodes throughout the subsequent transmission season were monitored. Recombinant proteins representing the different domains of PfAMA1 were used to dissect antibody reactivity in detail. In two different communities in Kenya, antibodies against domain I were significantly associated with protection from subsequent malaria infections, based on univariate analysis after adjusting for age. In one of the Kenyan cohorts and a separate Gambian cohort, antibodies to domain II were also associated with protection. However, in the Kenyan cohorts the protective associations were only seen in subjects that were parasite-slide positive at the time of pre-season serum sampling, a phenomenon noted in this area in previous studies of antibodies recognising the infected erythrocyte surface. Antibodies to domain III were very rare in all populations. These 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 prospective cohort studies covering different endemic areas. In an earlier phase of this project, a single allele of PfAMA1 FVO [25-545] was produced under GMP[1]. The product was evaluated in a phase I clinical trial with three different

[1] Faber et al., Vaccine 2008

adjuvants: Alhydrogel, GSK's AS02A and Montanide ISA720. The results were very promising, with average growth inhibition levels of up to 50% when higher vaccine dosages were combined with AS02A and Montanide ISA720[2].

One of the conclusions of this clinical trial was that polymorphism in the PfAMA1 protein must be addressed for the vaccine to be highly effective in the field.

The limited polymorphism of PfAMA1 enabled the design of three artificial PfAMA1 sequences with a very high coverage of naturally-occurring alleles (on average > 97%). This DiCo approach, recommended by the EVI SAC and approved by the EVI Board in October 2008, is expected to overcome the polymorphism found in nature, promoting a broad response to all naturally-occurring AMA1 alleles. These expectations have been met in immunogenicity studies using both rhesus monkeys and rabbits. The total budget available for the development of an AMA1-DiCo vaccine is up to €5,206,111.

The EVI-funded development of an AMA1-DiCo vaccine candidate has moved into active clinical development. In 2014, a two-centre phase Ia/Ib clinical trial began at CIC-Cochin, France, in a malaria-naïve population, and was transitioned to the malaria-exposed target population at CNRFP, Burkina Faso. The vaccination phase will be completed in early 2015.

Partners

European Vaccine Initiative, DE
ExpreS2ion Biotechnologies, DK
University of Oxford, UK

InnoMalVac

There are currently no PfRH5-based vaccine candidates in clinical development, but it was demonstrated that immunisation with full-length PfRH5 antigen is required to induce protective cross-strain antibodies.

The InnoMalVac project aims to optimise and characterise the *Drosophila* S2 cell system for the production of full-length PfRH5 protein, before commencing technology transfer, process development and GMP manufacture.

The project was successfully submitted to EVI SAC for the "Innovation and Discovery" call of summer 2012 and was initiated in June 2013 for two years. InnoMalVac has a total budget of €175,000 and it is funded by EVI with Irish Aid grant.

The project has progressed according to plan with the establishment of polyclonal S2 cell lines expressing different variants of PfRH5, and purified proteins being characterised and tested for functional antibody induction. These proteins were used in crystallisation studies, and the structure of PfRH5 in a complex with its receptor basigin and neutralising antibodies was reported in the journal Nature in August 2014[3].

The malaria vaccine group at the JI, UOXF, secured EU FP7 funding through the MultiMalVax project to advance adenovirus-poxvirus vectored vaccines encoding PfRH5 to a phase I/IIa clinical trial. Furthermore, onward funding for the GMP manufacture of the PfRH5 vaccine candidate was secured from the MRC, UK. The manufacturing is scheduled for 2015 at the CBF, UOXF.

[2] Roestenberg, Plos One 2008

[3] Wright et al., Nature 2014

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

JAIVAC-1

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 GMP conditions a bivalent malaria blood-stage vaccine candidate, and to assess its safety and immunogenicity in a phase I clinical trial.

An effective vaccine is likely to require a combination of multiple *P. falciparum* antigens. The leading blood-stage vaccine candidates 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 play important functional roles in erythrocyte invasion by *P. falciparum* merozoites. Therefore the 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 a physical mixture of two recombinant proteins: PfMSP-1_{19} (the 19-kDa, conserved C-terminal region of PfMSP-1) and PfF2 (the conserved, DBL receptor-binding domain of PfEBA-175). Both PfMSP-1_{19} and PfEBA-175 play distinct yet significant functional roles in erythrocyte 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.

Partners

ALMAC Sciences, UK
Centre hospitalier universitaire Vaudois, CH
CiToxLAB, FR
European Vaccine Initiative, DE
Gregory Fryer Associates Ltd, UK
Ifakara Health Institute, TZ
Infectious Diseases Research Institute, USA
Nova Laboratories, Ltd, UK
Output Pharma, DE
Swiss Tropical and Public Health Institute, CH
University of Lausanne, CH

P27A

This vaccine candidate is an intrinsically unstructured, hydrophilic fragment of the *P. falciparum* malaria protein PFF0165c, 104 amino acids in length[4], which was submitted in 2007 by Professor Giampietro Corradin, UNIL. It was not originally recommended for funding by the EVI SAC, but a six-month contract to evaluate this candidate with various adjuvants was signed with UNIL in September 2008 in accordance with a Board decision to help improve certain proposals. A successful proposal was submitted in response to the call in December 2008. The total budget for the development of P27A is up to €1,707,741.

The inhibition of both merozoite invasion and monocyte triggering by ADCI were investigated while using genome mining to search for novel vaccine candidates. First we considered naturally-occurring antibodies in individuals with acquired protection following exposure to the malaria parasite, and later we also considered antibodies induced by immunisation with different candidates. From a series of 95 polypeptides representing novel and unexplored alpha helical coiled coil segments of *P. falciparum* blood-stage proteins, the screening process focused on 18 novel antigens that were recognised by antibodies in exposed populations. Affinity-purified antibodies were studied in GIAs and ADCI assays, revealing that antibodies specific to 11

[4] Olugbile et al., Infection and Immunity 2009

peptides totally or partially interrupted the intra-erythrocytic development of *P. falciparum*. This occurred solely in cooperation with blood monocytes and no direct effect was observed[5].

These results support experiments showing that total immunoglobulin from protected individuals passively transferred into naïve recipients acts predominantly through a monocyte-dependent, antibody-mediated mechanism. The vaccine candidate discussed here was selected following a series of sequential screens that highlighted P27A as the target of an immune response with satisfactory characteristics for vaccine development.

The EVI-funded P27A vaccine candidate moved into active clinical development in 2014. A two-centre phase Ia/Ib clinical trial began at CHUV, Switzerland in a malaria-naïve population, and was transitioned to the malaria-exposed target population at IHI, Tanzania. The vaccination phase will be completed early in 2015.

Partners

Centre national de recherche et de formation sur le paludisme, BF

European Vaccine Initiative, DE

Research Institute for Microbial Diseases, JP

SEmalvac

The *Plasmodium falciparum* serine repeat antigen-5 (SERA5) is an abundant blood-stage antigen secreted in large amounts in the parasitophorous vacuole. It plays an essential role in the parasite life cycle and was among the first physiological substrates identified for a serine protease involved in parasite egress. A recombinant form of the SERA5 N-terminal domain (SE36) was selected for clinical development on the basis of the following achievements:

- Epidemiological studies showing high antibody titres that inversely correlate with malaria symptoms and severe disease;
- In vitro studies demonstrating the induction of antibodies that are inhibitors of parasite growth, exert antibody-dependent complement-mediated lysis of schizonts, or antibody-dependent monocyte-mediated parasite growth inhibition; and
- Animal studies demonstrating protection against *P. falciparum* challenge in non-human primates.

SE36 was prepared under GMP conditions and was formulated with aluminium hydroxide gel to yield BK-SE36. The safety and immunogenicity of BK-SE36 was demonstrated in a phase Ia clinical trial in malaria-naïve Japanese adults[6] and in a phase Ib trial conducted in healthy subjects 6–32 years of age from a malaria-endemic area in Northern Uganda[7].

The main objective of the SEmalvac project supported by the GHIT Fund is to assess the safety and immunogenicity of the recombinant *E. coli* BK-SE36 malaria vaccine candidate in healthy malaria-exposed African children 1-5 years of age living in Burkina Faso. By conducting this phase Ib clinical trial it will be possible:

- To test the vaccine candidate in a younger age group (1-5 years old);
- To generate additional safety, immunogenicity and possible efficacy data; and
- To compare clinical trial results from two different African countries with different malaria endemicity - Uganda (from the previous BK-SE36 clinical trial) and Burkina Faso.

A second objective of the SEmalvac project is to conduct a one-year follow-up study in Japanese naïve healthy volunteers from a previous phase Ia trial to evaluate the safety and immunogenicity of the BK-SE36 vaccine candidate combined with the K3 CpG adjuvant. The follow-up will provide long-term data on the safety and durability of the antibody response.

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[5] Villard et al., Plos One 2007

[6] Horii et al., Parasitology International 2010

[7] Palacpac et al., Plos One 2013

The project started in August 2014 and the total budget is ¥99,999,999.

In December 2014, the phase Ib clinical trial received ethical clearance in Burkina Faso. Immunisation of the subjects is scheduled to start in the second quarter of 2015.

Malaria blood-stage vaccines that prevent placental malaria

Placental malaria is caused by parasite-infected blood cells binding to the placental receptor CSA, and their subsequent accumulation in the placenta, from where they can infect and ultimately kill both the mother and the child. Pregnant women are particularly vulnerable to this type of malaria because their immunity is reduced during pregnancy. Women who have acquired immunity to malaria during childhood nevertheless become susceptible again during their first pregnancies. Parasites accumulate in the placenta, where a combination of altered blood flow and expression of CSA provides a new niche for parasites to sequester. Every year, more than 100 million pregnant women are threatened by placental malaria, and 80,000–200,000 children die from the infection[8]. This is a long-neglected health challenge, and currently there is no vaccine available to prevent placental malaria. Fortunately, women can acquire immunity against placental malaria and in malaria-endemic areas the average birth weight is significantly higher among second and third babies compared to the first born[9][10]. This relatively fast acquisition of protection has raised the hope that a vaccine for placental malaria can be developed.

EVI has raised funds from BMBF, Inserm, the EU and the HTF through UCPH, with further co-funding from Irish Aid, and has set up and reinforced collaboration with NIH-NIAID. The three most advanced groups dealing with this target are therefore collaborating on the development of a placental malaria vaccine. The two vaccine candidates under development offer hope for reducing the burden of malaria in pregnant women and improving the health of mothers and new-borns.

The target product profile for placental malaria vaccines differs from standard malaria vaccines. Placental malaria vaccines target young adolescent girls before childbearing age, and the vaccination should be associated with other vaccines that prevent rubella or uterine/cervical cancer caused by HPV. Depending on the other malaria vaccines available on the market, a placental malaria vaccine could also be associated with a booster dose of regular malaria vaccine in adolescent girls.

The projects focus on the distinct form of the parasite that infects the placenta. Recent research supports the development of VAR2CSA as a leading candidate for the placental malaria vaccine[11][12]. This is a member of the PfEMP1 adhesins encoded by the *var* gene family, and is specifically expressed by placental parasites. Women acquire antibodies against VAR2CSA over successive pregnancies as they become resistant to placental malaria[13]. These data suggest that vaccines based on VAR2CSA could help to block the adhesion of CSA-binding parasites to the placenta.

The 350-kDa VAR2CSA transmembrane protein has a 300-kDa extracellular region composed of six DBL domains and a cysteine-rich inter-domain, interspersed with short inter-domain regions. DBL3X is the principal target of inhibitory antibodies that prevent parasite adhesion to CSA[14][15]. 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-

8 Hartman et al., Annals of Tropical Paediatrics 2010

9 Brabin et al., Bull World Health 1983

10 McGregor et al. Transactions of the Royal Society of Tropical Medicine and Hygiene 1983

11 Baruch et al., Cell 1995

12 Su el al., Cell 1995

13 Fried et al., Nature 1998

14 Avril et al., Malaria Journal 2011;

15Dahlback et al., J Biol Chem 2011

adhesion epitopes[16][17]. These data indicate that vaccines designed to block interactions between the parasite and CSA should be based on the N-terminal region of VAR2CSA.

PAMCPH

Partners

CMC Biologics A/S, DK
European Vaccine Initiative, DE
ExpreS2ion Biotechnologies, DK
University of Copenhagen, DK

The overall objective of PAMCPH is to manufacture a vaccine that protects both the foetus and mother against the adverse effects of malaria during pregnancy. The aim of the project is to define the optimal antigen and adjuvant formulation, show that it can be produced in a scalable manner and confirm that it is safe to use in animals. In 2003, VAR2CSA was identified at CMP (UCPH) as the parasite protein which enables parasite accumulation in the placenta[18]. The aim of a VAR2CSA-based placental malaria vaccine is to induce antibodies that can hinder adhesion in the placenta followed by the destruction of infected erythrocytes in the spleen.

The technology at ExpreS2ion Biotechnologies is ideal for the expression of complex antigens, and CMC Biologics A/S has the technology and knowhow to scale up production and ensure compliance with GMP, allowing the team to take this major step towards solving a significant health problem. The overall aim of the project is to support the production of a recombinant VAR2CSA vaccine under GMP conditions, allowing it to be used in the clinical trial supported by the PlacMalVac project.

PAMCPH has a total budget of €2,000,000 and it is funded by the BMBF through KfW, with co-funding from UCPH through the HTF. The project started in September 2012 and will end in November 2015. The main achievements in 2014 were the generation and analysis of the MCB, transfer and validation of the analytical methods, upstream and downstream process transfer, and completion of the GMP engineering run at CMC Biologics A/S.

PlacMalVac

Partners

Eberhard-Karls Universität Tübingen, DE
European Vaccine Initiative, DE
Expres2ion Biotechnologies, DK
University of Copenhagen, DK
Institut de recherche pour le développement, FR
Université d'Abomey-Calavi, BN

One objective of the PlacMalVac project is to conduct a phase I clinical trial with the placental malaria vaccine developed by PAMCPH. Another objective is the development of a phase II clinical trial protocol and it implementation in a clinical trial with African women.

PlacMalVac is funded by the EU FP7 and has an overall budget of approximately €5,900,000. The project started in March 2013 and the duration is three years. The main achievements in 2014 were the preparation and submission of the draft clinical trial protocol to the EC.

16 Bordbar et al., Bioelectrochemistry 2011
17 Bigey et al., J Inf Dis 2011
18 Salanti A et al., Mol Microbiol 2003

Partners

BIOTEM, FR

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

Centre d'investigation clinique en Cochin-Pasteur, FR

CiToxLAB, FR

European Vaccine Initiative, DE

GTP Technology, FR

Infectious Diseases Research Institute, USA

Institut national de la santé et de la recherche médicale, FR

Novasep (formerly Henogen), BE

Novavax, USA (formerly ISCONOVA, SE)

Pfenex Inc., USA

Voisin Consulting Life Sciences, FR

PRIMALVAC

PRIMALVAC aims to develop a placental malaria vaccine to improve pregnancy outcomes. The main objective is to obtain proof of concept that VAR2CSA-based vaccines induce long-lasting or rapidly-boosted cross-reactive and inhibitory antibodies suitable for human use. Recombinant forms of VAR2CSA will be generated, and their immunogenic activity will be assessed, specifically their ability to elicit functional and cross-reactive antibodies against placental forms of the parasite. The candidate antigens that best meet strict immunogenicity criteria will be moved into preclinical and clinical development.

PRIMALVAC has a total budget of €6,864,000 provided by the BMBF through KfW, EVI, Inserm, the INTS and Irish Aid. The project started in December 2011 and will last four and a half years.

The highlight of 2014 was the conclusion of process development for the VAR2CSA DBL1X-2X vaccine candidate produced in *E. coli* and the start of the GMP manufacturing. Inserm was selected as the sponsor for the clinical trial.

Malaria vaccines that prevent infection and morbidity/mortality: combination vaccines

The most effective malaria vaccines are likely to be based on a multi-stage product, i.e. a combination of antigens targeting several stages of the malaria parasite life cycle.

Partners

European Vaccine Initiative, DE
GlaxoSmithKline, BE
Novartis Vaccines and Diagnostics s.r.l., IT
ReiThera s.r.l., IT (formerly Okairos s.r.l., IT)
Université Pierre et Marie Curie, FR
University of Oxford, UK

MultiMalVax

The aim of the EU FP7 MultiMalVax project, which started in October 2012 with a budget of €6,000,000, is to assess 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 advances in the design of vaccines against all four stages of the *P. falciparum* life-cycle now allow the testing of multi-stage multi-component vaccines for the first time, with strong chances of success.

These advances are:

- The availability of a new vectored prime-boost vaccination regime based on the ChAd technology that has been found to induce exceptionally potent CD8+ T-cell responses and high titres of antibodies against multiple malaria antigens;
- 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 virus antigen in RTS,S;
- The use of a vector technology screen to identify the blood-stage antigen PfRH5 as the first antigen to induce potent strain-transcending neutralisation of blood-stage parasites in vitro as determined by GIAs; and
- The demonstration that vector-induced antibodies against two mosquito-stage antigens can achieve 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 immuno-monitoring, key functional assays for vaccine-induced immunogenicity, and sporozoite and blood-stage parasite challenges to measure efficacy prior to field testing.

This collaboration includes one SME, two universities, two global pharmaceutical companies and EVI, and will provide complementary abilities to accelerate the development of this promising vaccine product.

The main achievement in 2014 was the GMP production of the ChAd63 and MVA vectors expressing PfRH5 and mosquito-stage antigens, and the start of the clinical trial assessing the PfRH5 vectored vaccines. Following a competitive call, the Southampton NIHR Wellcome Trust Clinical Research Facility, UK, was selected as the clinical trial site for the mosquito-stage antigens.

Universal influenza vaccine

Current influenza vaccines afford only limited protection against seasonal as well as pandemic influenza. Because influenza viruses can accumulate three or four amino acid substitutions per year and frequently undergo antigenic changes to escape population immunity, vaccine composition must be updated regularly and new vaccines must be administered on an annual basis. The development of a universal influenza vaccine that can provide broad coverage against different strains within a subtype or even across subtypes has thus become a key public health priority in both industrialised and low-and-middle-income countries.

Partners

Biomedical Primate Research Centre, NL

Central Veterinary Institute, NL

ETNA BIOTECH s.r.l., IT

European Vaccine Initiative, DE

Instituto de Biologia Experimental e Tecnológica, PT

National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency, UK

Redbiotec AG, CH

EDUFLUVAC

In order to address the problem of antigenic drift and annual vaccine reformulation, the EU FP7 EDUFLUVAC consortium proposes to develop a combinatorial immunisation strategy to educate the immune system towards cross-recognition and coverage against antigenic drift during seasonal influenza virus exposure. The strategy, developed by Ed Remarque at BPRC, is based on the success of the DiCo approach used for the development of a new malaria vaccine candidate in the AMA1-DiCo project. With a budget of €4,647,149, EDUFLUVAC aims to develop a novel influenza vaccine candidate encompassing a combination of multiple influenza HA and/or NA antigenic variants within a single subtype. The project will test the hypothesis that this vaccine concept, using the proven technology of baculovirus-derived VLPs, will elicit broad neutralising immunity that will confer longer-lasting and broader protection against multiple strains of influenza virus.

The antibody response is broadened because the increased relative concentration of common epitopes dilutes out strain-specific epitopes. This will be achieved by testing the ability of a combination of historic HA variants to protect against a variety of modern isolates. Thus, the overall strategy of the EDUFLUVAC project will be to select HA and NA antigens representing antigenic drift within relevant subtypes and generate baculovirus vectors expressing one or more HAs. VLPs will be tested in immunological studies using mice before the further selection of vaccine candidates. Proof of principle will then be demonstrated for the EDUFLUVAC strategy in challenge studies using ferret and non-human primate models. Furthermore, an optimised process suitable for the GMP-compliant production of VLPs will be developed. The project will take note of new influenza vaccine regulatory guidance and will be geared towards the development of a complete IMPD ready for transfer into GMP production for early-phase clinical testing. Finally, the knowledge generated in the project will be disseminated through networking activities including targeted workshops.

The main achievements of 2014 include the generation of baculovirus vectors expressing selected HA and NA antigens, the preparation of baculovirus-derived VLPs and their use for mouse immunisation studies.

Paratyphoid vaccine

Systemic enteric fever in humans is often caused by *Salmonella typhi* and *Salmonella paratyphi A*, resulting in 27 million new cases worldwide and 200,000 deaths each year[19], with the highest number of cases in South and Southeast Asia. However, there are no vaccines against *Salmonella paratyphi A*, which is emerging as a major cause of pandemic enteric fever that is clinically indistinguishable from diseases caused by *Salmonella typhi*.

The limited investment in vaccine antigen discovery and the absence of defined correlates of protection for paratyphoid fever are holding back the development of strategies to prevent this disease. The step from early vaccine concepts to expensive field trials needs new and innovative approaches. Furthermore, because *Salmonella paratyphi* is a human-restricted pathogen, there is no animal model that allows the protective efficacy of vaccines to be evaluated.

Partners

European Vaccine Initiative, DE
Novartis Vaccines Institute for Global Health, IT
University of Oxford, UK
Wellcome Trust Sanger Institute, UK

PIM

The PIM project was selected for funding by the EVI SAC and approved by the EVI Board in 2013. The overall objective is to pursue advances that lead to the control of paratyphoid infection by improving the selection of vaccine candidates.

To advance the development of paratyphoid vaccines, PIM aims to develop the first controlled human model of paratyphoid infection that will provide a unique opportunity to study the immune response to *Salmonella paratyphi A*, identify potential correlates of protection and evaluate the efficacy of vaccine candidates by providing early proof of the vaccine concept.

This two-year project has a total budget provided by EVI of €325,000 complemented by co-funding from the BMGF.

In 2014, the clinical trial received ethical and regulatory approval allowing the human challenge study to commence. The first volunteer was challenged in May 2014: healthy volunteers have been challenged with escalating doses of *Salmonella paratyphi A* in order to give a clinical/laboratory attack rate of 60–75%.

New vaccine technologies and a vaccine against *Staphylococcus aureus*

Novel and potent immunogenic tags have recently shown promise. IMAXIO, a French biotechnology company, has developed IMX313, a small DNA sequence that can be fused to an antigen gene of interest. Recombinant proteins fused to IMX313 spontaneously auto-assemble into a heptamer and thus present the antigen of interest seven times to the immune system. Oligomerisation significantly increases both the B and T cell immunogenicity of the antigen, therefore improving the efficacy of related vaccine candidates. IMX313 is compatible with subunit, DNA and viral vector vaccines, but is also synergistic with regular adjuvant technologies. This technology has been tested since 2013 in a phase I clinical trial of a TB vaccine candidate and it is undergoing preclinical development for vaccine candidates against malaria and *Staphylococcus aureus*.

Staphylococcus aureus, including MRSA, is one of the most important bacterial pathogens responsible for skin lesions and deep infections. It causes approximately 16,000 deaths annually in Europe and 19,000 in the USA. Treatment is difficult and expensive and may require the prolonged intravenous administration of antimicrobials. The emergence of highly antibiotic-resistant *Staphylococcus aureus* strains, such as MRSA, has created a serious global public health threat and a growing economic burden. Because recent vaccine candidates against *Staphylococcus*

19 Buckle GC et al, J Glob Health, 2012

aureus have not proven effective and therefore have not been licensed by the FDA or EMA, there is an urgent need to develop new vaccine strategies against this pathogen.

Partners

European Vaccine Initiative, DE
Imaxio SA, FR
Preclin Biosystems AG, CH
University of Oxford, UK

BELLEROPHON

BELLEROPHON is an EU FP7 project with a budget of approximately €5,500,000, which commenced in September 2013 and will last three years

The aim of the BELLEROPHON project is to design, manufacture, and evaluate in a phase I clinical trial a novel *Staphylococcus aureus* vaccine candidate targeting both the cellular and humoral immune responses. It is designed to protect against both MRSA and more sensitive *Staphylococcus aureus* strains.

The BELLEROPHON project comprises four European institutions involved in vaccine development, each contributing specialist expertise and technology. Imaxio, a French biotechnology company focusing on immunology, was the leader of the project application. The JI (UOXF, UK) is an academic institution with key expertise in *Staphylococcus aureus* antigens and viral vector delivery systems, and is the project coordinator. EVI assists with project management and advises on GMP production and clinical development aspects. The fourth member is Preclin Biosystems, a Swiss CRO with strong expertise in preclinical efficacy models for infectious diseases.

The main achievements of 2014 were the selection of the antigen composition of the vaccine candidate and the first annual meeting that was held in October in Lyon, France.

Factors influencing vaccination

NIDs represent a major public health burden, raising awareness of their widespread distribution throughout low-income countries. NIDs are caused by diverse infectious agents and predominantly by different types of worms, which are prevalent in tropical regions. Although most infections are asymptomatic, heavy infections result in significant morbidity. Following concerted advocacy and major philanthropic donations, population-based national programmes for the integrated control of worms have been scaled up over the last few years. These programmes raise important questions about the public health implications of co-infection and treatment for other diseases such as malaria, HIV/AIDS and TB[20]. Indeed there is growing epidemiological evidence of interactions between worms and these diseases. The most recent estimates indicate that approximately two billion people are infected with worms, 300,000,000 are severely affected and ~50% of cases involve children. Infections include schistosomiasis and several species of intestinal worms, also known as soil-transmitted helminths. According to WHO, schistosomiasis affects almost 240 million people worldwide and more than 700 million people live in endemic areas. The infection is prevalent in tropical and sub-tropical areas, especially in poor communities without potable water and adequate sanitation[21]. Given the considerable geographic overlap, co-infections of worms with HIV, TB and malaria affect tens of millions of people including children and adults. Preliminary epidemiological data from a small number of studies suggest that ~25% of those affected by HIV, malaria or helminth infections are co-infected.

[20] Eziefula AC et Brown M, Current Opinion in Infectious Diseases, 2008

[21] http://www.who.int/en/

Partners

Academisch Medisch Centrum bij de Universiteit van Amsterdam, NL

Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, NL

Agence nationale de recherches sur le sida et les hépatites virales, FR

Centre Hospitalier Universitaire Vaudois, CH

Eberhard Karls Universitaet Tübingen, DE

Ecole Polytechnique Federale de Lausanne, CH

European Vaccine Initiative, DE

EuroVacc Foundation, NL

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

Ifakara Health Institute, TZ

Institut national de la sante et de la recherche Medicale, FR

Istituto Nazionale Malattie Infettive L.Spallanzani – IRCCS, IT

Kenya Medical Research Institute, KE

London School of Hygiene and Tropical Medicine, UK

Ludwig Maximilians Universität München, DE

Malaria Consortium LBG, UK

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

National Institute for Medical Research - Mbeya Medical Research Program, TZ

Swiss Tropical and Public Health Institute, CH

University of Ibadan, NI

University of Oxford, UK

Vaccine and Gene Therapy Institute Florida, USA

IDEA

Worm infections, HIV, TB and malaria have been studied extensively, but the potential impact of co-infections has been addressed only recently. First, the interaction between these diseases may increase the disease burden on society because effective vaccines are not yet available. Second, although worm, HIV, TB and malaria-specific immune responses have been the target of extensive investigations, the precise immune correlates of protection remain unknown for all these diseases. Third, there is little information about worm-induced immunity and its ability to modulate HIV, TB and malaria-specific immune responses. Fourth, there is limited data concerning 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 because the limited available data suggest the effectiveness of vaccines is reduced in subjects with worm infections.

IDEA is a five-year EU-funded project with 20 consortium members coordinated by CHUV and has a total budget of €10,300,000.

The primary objective of IDEA is to determine whether and how the presence of worm infections modulates:

- The functional and molecular profile of HIV, TB and malaria-specific immune responses;
- The immunological markers of HIV, TB and malaria-specific immune responses associated with better control of pathogen replication and associated disease;
- The clinical course of HIV, TB and malaria;
- Vaccination and vaccine-induced immune responses against HIV, TB and malaria

EVI and UOXF are joint leaders of a work package studying the effect of worm infections on immune responses following vaccination against malaria, TB and HIV.

The main achievements in 2014 for activities involving EVI were the ethical and regulatory approval of two stand-alone phase I clinical trials to study the influence of helminth infection on TB and HIV vaccine-induced immunity. Both clinical trials were initiated successfully.

Policy

EVI continued to engage with several EU member states to lobby for the provision of further PDP funding. Activities with EVI involvement included the organisation of and participation in parliamentary events in different EU Member States. The first major success was achieved in 2014 in the Netherlands. Following the favourable evaluation of previous Dutch public funding to PDPs by the Dutch government, and the joint lobbying activities of a coalition of several leading PDPs including EVI, the Dutch government renewed its commitment to support PDPs with fresh funding from 2015 onwards. Other EU Member States are expected to take decisions on the future funding of PDPs during 2015.

Partners

European Advanced Translational Research Infrastructure in Medicine, NL

European Vaccine Initiative, DE

Sclavo Vaccines Association, IT

Vaccines Europe / European Federation of Pharmaceutical Industries and Associations, BE

IPROVE

IPROVE is an EU FP7 policy project with a budget of €496,367 aiming to establish a clear vision of the priority technologies and innovations for immunisation required to address infectious and non-infectious diseases that threaten public health. IPROVE uses a bottom-up approach involving all key stakeholder groups in the European vaccine-development field to analyse the entire vaccine innovation chain, from the identification of needs and conceptualisation to vaccine discovery and development, including interventions necessary to improve education curricula, and vaccine perception and awareness among the public. The principal outcome of IPROVE will be a comprehensive roadmap to provide guidance for strategic decisions in future EU vaccine R&D projects. During 2014, the first two stakeholder consultation meetings were organised, the first on vaccine SMEs and the second on training and communication in vaccines and vaccinology.

AMA1-DiCo

The long-term real-time stability analysis of the AMA1-DiCo drug product is underway. Extension of the shelf life of the drug product has been certified by the qualified person of Nova Laboratories Ltd.

InnoMalVac

UOXF collaborated with ExpreS2ion Biotechnologies to produce polyclonal S2 cell lines expressing seven different variants of PfRH5.

The C-tag purification process (based on the C-terminal four amino acids) was chosen because it gave much greater yields compared to the original His-tag (C-terminal six histidine residues). The new C-tag purification process is in the final stages of process development for GMP production.

The purified proteins were characterised using different assays to select the best candidate. GIAs and ELISA analysis were completed and from these data the PfRH5 variant v2.0-Ctag (3D7 sequence) was chosen and progressed to GMP process development and manufacturing. It is anticipated that GMP production will commence at the CBF in Oxford in the first quarter of 2015.

Furthermore, the S2 cell system, C-tag and GMP process were presented to the MHRA, UK, in February 2014, resulting in a very positive evaluation.

P27A

The long-term real-time stability analysis of the drug product is underway. Extension of the shelf life of the drug product has been certified by the qualified person of Nova Laboratories Ltd.

SEmalvac

The long-term stability analysis of the BK-SE36 vaccine was performed and a shelf life extension certificate was provided by the quality assurance division of BIKEN in Japan. The IMPD was reviewed by EVI prior to regulatory submission in Burkina Faso.

PAMCPH

Early in the development process, the Swedish MPA was approached for scientific advice on the processing and testing of the product. A meeting was then organised between CMP (UCPH) and EKUT, and the German regulatory authorities (PEI) where issues relating to process development were clarified.

Analytical methods were developed to support process development and to guarantee the quality of the vaccine. The methods were transferred and validated, and the reports were finalised.

The downstream process was developed in parallel to upstream development, consistency runs and upscaling, all of which were achieved successfully.

The MCB was released in September and the first 100-L engineering batch was produced before the GMP run. The material will be used for method validation and toxicological safety studies performed by the CRO Huntingdon Life Sciences. These studies started in November and the report is expected by the end of March 2015. Furthermore, a virus validation study was developed and will be performed on the engineering batch.

The documents for GMP production are being prepared and the release of the drug product is expected by March 2015.

PRIMALVAC

GTP Technology concluded process development for the production of FCR3 VAR2CSA DBL1X-2X in *E. coli* and appropriate analytical methods were developed. The technology was

successfully transferred to the CMO Novasep, the GMP manufacturer of the placental malaria vaccine candidate. The MCB was released in November, the pilot batch was produced and released in December, and GMP manufacturing started towards the end of 2014. The drug product should be released by April 2015. Toxicology studies will be performed by CiToxLAB in early 2015.

MultiMalVax

ReiThera (formerly Okairos) produced and released the ChAd63 PfRH5 GMP batches. The CMO IDT manufactured and released the MVA PfRH5 vector GMP batch. IMPDs were developed and the shelf life of ChAd63 PfRH5 was extended to May 2016.

ChAd63 and MVA vectors were generated for several mosquito-stage antigens and GMP manufacturing of the Pfs25-IMX313 expression vectors was completed in 2014.

Process development was successful for the R21 particles and the material for toxicology studies was produced. R21 should be available for clinical trials in the second quarter of 2015.

EDUFLUVAC

Redbiotec generated baculovirus vectors expressing the selected influenza HA and NA antigenic variants. The vectors were transferred to iBET, where suitable culture conditions for insect cell lines were screened allowing the production of VLPs. Following optimisation of the upstream and downstream processes, iBET prepared VLPs that were subsequently used for mouse immunisation studies at ETNA Biotech. Supporting analytical activities are being developed for the characterisation of the VLPs.

PIM

The NVGH308 strain of *S. paratyphi A* used for the development of the controlled human infection model was isolated from a case of human paratyphoid infection in Nepal and was produced under GMP conditions. Full microbiological characterisation was carried out and the antibiotic sensitivity of the strain was demonstrated, followed by genome sequencing at the Sanger Institute in Cambridge.

Real-time stability testing of the challenge strain is underway at GenIbet BioPharmaceuticals in Portugal. Before the microbial challenge, each dose is prepared in sodium bicarbonate at the required dilution and the viability of the bacteria is confirmed.

BELLEROPHON

During 2014, the BELLEROPHON project focused on the optimisation and validation of the vaccine candidate. Pre-clinical batches of the recombinant proteins with and without the IMX-tag were produced and analysed for immunogenicity. The generation of viral vectors expressing the antigens is underway. The most promising formulated candidates were selected for preclinical efficacy testing. The immunisation regimes were optimised in terms of sequences and codons, the final antigen composition was identified and the type of IMX tag was chosen. The selection and testing of different mouse models is underway.

DELIVERY PLATFORMS, ADJUVANTS AND VIRAL VECTORS

A variety of delivery platforms is currently used in malaria vaccine development and several adjuvants have been assessed for their ability to increase the immunogenicity of malaria antigens.

EVI has filled vials of aluminium hydroxide under GMP conditions at Nova Laboratories Ltd for use in its preclinical and clinical trials. Please contact EVI at contact.us@euvaccine.eu for further information.

MVVC

The malaria antigen ME-TRAP was delivered in a prime boost strategy using two different vectors: ChAd63 and MVA.

MVVC2

The malaria antigen ME-TRAP will be delivered in a prime boost strategy using two different vectors: ChAd63 and MVA. The adjuvant used to administer the R21 CSP particles will be Matrix M, provided by Novavax.

AMA1-DiCo

GLA-SE and aluminium hydroxide as a comparator are being used as adjuvants in the phase Ia/Ib clinical trial. EVI has purchased GMP-grade GLA-SE and SE from IDRI, under a clinical supply agreement between EVI, Inserm and IDRI.

InnoMalVac

PfRH5 is expressed as a recombinant protein in *Drosophila* S2 cells, and the project team is currently negotiating with GSK for access to the AS01B adjuvant.

JAIVAC

The adjuvant selection included aluminium hydroxide, AS02A, Montanide ISA 51 and Montanide ISA 720. Based on the immunogenicity determined by ELISA, IFA and parasite growth inhibition data, Montanide ISA 720 was recommended for further clinical development. JAIVAC-1 was expressed in E. coli.

P27A

Two adjuvants are being used in the clinical trials: aluminium hydroxide as a reference adjuvant because it has shown promising results in preclinical studies, and GLA-SE from IDRI. EVI has purchased GMP-grade GLA-SE and SE from IDRI, under a clinical trial agreement between EVI, CHUV, IHI, IDRI and Swiss TPH.

SEmalvac

The malaria antigen SE36 is adsorbed onto aluminium hydroxide in the BK-SE36 vaccine.

PAMCPH / PlacMalVac

The selected adjuvants are aluminium hydroxide (Alhydrogel) and the MPL analogue GLA-SE. Access to the GLA-SE adjuvant is being negotiated with IDRI.

PRIMALVAC

The selected adjuvants are aluminium hydroxide (Alhydrogel) and GLA-SE. An agreement for access to GLA-SE for preclinical studies and clinical trials has been signed by Inserm and IDRI. Alhydrogel filled by EVI at Nova Laboratories Ltd will be used for the clinical trial.

MultiMalVax

The malaria antigens ME-TRAP, PfRH5 and the transmission-blocking antigen will be delivered in a prime boost strategy using two different vectors: ChAd63 and MVA. The transmission blocking antigen will be fused to the Imaxio IMX313 tag to enhance immunogenicity. The R21 CSP particle will be administered in adjuvants, probably AS01B and Matrix M.

EDUFLUVAC

The EDUFLUVAC project will use VLPs to deliver multiple influenza HA and/or NA antigenic variants. In 2014, following careful selection of the antigen strains, the assembly of baculovirus vectors began at Redbiotec AG, Switzerland, and VLP production in insect cells began at iBET, Portugal.

BELLEROPHON

The technology used for the design of the vaccine candidate is based on a new protein tag (IMX313) from Imaxio, which will be fused to the selected *S. aureus* antigens. The IMX313 tag spontaneously auto-assembles into a heptamer, which produces a seven-fold aggregation of the fused antigen of interest and thus enhances its presentation to the immune system. Viral vectors developed at UOXF will also be tested for the expression of the vaccine antigens.

CLINICAL DEVELOPMENT

EVI has selected clinical trial sponsors and investigational centres for several core projects. The selection process includes preliminary selection based on capacities and costs, followed by an assessment by an external auditor and the Quality Assurance Director of EVI. The selection of a sponsor is based on the assessment results and is further recommended by the EVI SAC and approved by the EVI Board.

MVVC

The MVVC project conducted a series of clinical trials to determine whether a prime-boost vaccine combination using ChAd63 ME-TRAP and MVA ME-TRAP is safe and immunogenic and will achieve efficacy in the target population.

A phase Ib clinical trial of these vaccine candidates was carried out at MRC, The Gambia, in adults and in infants aged 5–12 months and 10 weeks. The vaccine candidates achieved a good safety profile and good immunogenicity data were obtained. No SAEs related to the vaccine candidates were reported. The safety and immunology results of the phase Ib adult clinical trials were published in PLOS ONE[22] and Molecular Therapy[23]. A manuscript is in preparation for the phase Ib clinical trial in children and infants.

Phase IIb adult efficacy trials have been completed at KEMRI and UCAD. The KEMRI phase IIb trial showed 67% efficacy against PCR positivity and a manuscript has been submitted for publication. However, the UCAD phase IIb clinical trial data did not reproduce the KEMRI results. A manuscript is in preparation.

A phase Ib lead-in/IIb clinical trial in the target age group (5–17 month old infants and children) commenced in the fourth quarter of 2012 at CNRFP. The last of the 700 subjects was enrolled in August 2013, and the subjects were followed-up for a second malaria season peaking in July to October. The clinical trial ended in October 2014, data analysis is ongoing and the results are expected in the first half of 2015.

The recruitment and follow-up of subjects enrolled in the baseline epidemiological studies at UCAD and CNRFP in the fourth quarter of 2011 continued during the year and follow-up was completed in 2013. All recruitment targets have been met at both sites. The results of the baseline study at CNRFP were published in Clinical and Vaccine Immunology[24].

MVVC2

This project aims to determine whether malaria-vectored prime-boost vaccines are compatible with the EPI vaccination schedule and whether a CSP particle in the adjuvant will be safe, immunogenic and efficacious.

The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines will be assessed in Gambian infants 1–16 weeks of age at the MRC in a truly South-South collaborative clinical trial with the support of the UCAD team. The clinical trial started in the first quarter of 2014 and the 8- and 16-week-old infants were vaccinated, revealing good vaccine safety profiles. The vaccination of 1-week-old infants commenced in December 2014.

The safety, immunogenicity and efficacy of the CSP particle in adjuvant will be assessed in African adults at the CNRFP, Burkina Faso. This clinical trial is expected to start in 2015.

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[22] Ogwang C. et al. PLOS One 2013

[23] Kimani D. et al. Molecular Therapy 2014

[24] Nébié I et al. Clinical and Vaccine Immunology 2014

AMA1-DiCo

The AMA1-DiCo phase Ia/Ib clinical trial is a staggered, randomised, double-blind, multi-centre trial. It aims to evaluate the safety and immunogenicity of a 50-µg dose of the AMA1-DiCo malaria vaccine candidate with GLA-SE and aluminium hydroxide adjuvant, in healthy European adults not previously exposed to *P. falciparum* and in healthy African adults previously exposed to the parasite.

The sponsor of the clinical trial is Inserm, France. Prof Odile Launay (CIC-Cochin, Paris, France) is conducting the clinical trial arm in the non-exposed population, and Dr Sodiomon Sirima (CNRFP, Ougadougou, Burkina Faso) is conducting the clinical trial arm in the exposed population.

Ethical and regulatory approval has been granted for both arms of the clinical trial. The vaccination phase in France took place between January and September 2014 and the phase Ia subjects will be followed until February 2015. The vaccination phase in Burkina Faso started in July 2014 and is scheduled to finish in January 2015. The phase Ib subjects will be followed until June 2015.

JAIVAC-1

This year the team finalised the integrated clinical and statistical clinical trial report and the sent the publication to PLOS ONE for peer review.

P27A

The P27A phase Ia/Ib clinical trial is staggered, randomised, single-blind, antigen and adjuvant dose-finding, multi-centre. The clinical trial aims to evaluate the safety and immunogenicity of the P27A malaria vaccine candidate with GLA-SE and aluminium hydroxide adjuvant, in healthy European adults not previously exposed to *P. falciparum* and in healthy African adults previously exposed to the parasite.

The sponsor of the clinical trial is CHUV, Switzerland. Prof François Spertini (CHUV, Switzerland) is conducting the evaluation of the vaccine in the non-exposed population, and Dr Seif Shekalaghe (IHI, Bagamoyo, Tanzania) will conduct the clinical trial arm in the exposed population.

Ethical and regulatory approval has been granted for both arms of the clinical trial. The vaccination phase in Switzerland took place from March to July 2014 and the phase Ia subjects will be followed until January 2015. The vaccination phase in Tanzania took place from July to December 2014 and the phase Ib subjects will be followed until June 2015.

SEmalvac

The clinical trial will assess the safety and immunogenicity of the recombinant *E. coli* BK-SE36 malaria vaccine candidate in healthy malaria-exposed African children 1-5 years of age living in Burkina Faso. The principal investigator of the clinical trial is Dr Sodiomon Sirima (CNRFP, Ougadougou, Burkina Faso) and the sponsor is Nobelpharma (Japan).

The clinical trial application has been prepared and submitted to the ethical committees in Burkina Faso. Following ethical clearance in December 2014, the dossier will be submitted to the regulatory agency in early January 2015. The vaccination phase should begin by May 2015.

PlacMalVac

The first phase Ia/Ib clinical trial will be designed to assess the safety and immunogenicity of different doses of the selected VAR2CSA vaccine candidate in healthy adult subjects not previously exposed to malaria (i.e. first-in-human and dose escalation at EKUT, Tübingen, Germany) and in exposed subjects from malaria-endemic areas in the target group (i.e. randomised, controlled, dose-finding at CERPAGE, Cotonou Benin). The sponsor will be EKUT, Germany, and the principal investigators will be Dr Benjamin Mormüller (EKUT, Tübingen, Germany) and Dr Saadou Issifou (CERPAGE, Benin).

EVI has appointed an independent auditor, who conducted an ICH-GCP audit of the sponsor and EKUT investigational site in November 2014 with a positive outcome.

The draft clinical trial protocol was prepared and will be finalised when the results of the toxicology study are available in March 2015. The phase Ia arm of the clinical trial should start at EKUT in early summer 2015, and the phase Ib at CERPAGE in early autumn 2015.

PRIMALVAC

The PRIMALVAC project will carry out a phase Ia/Ib clinical trial in healthy adult subjects not previously exposed to malaria and in exposed subjects in malaria-endemic regions in sub-Saharan Africa. The clinical trial will be designed to assess the safety and immunogenicity of different doses of the VAR2CSA DBL1-2 vaccine candidate in aluminium hydroxide and GLA-SE. In a competitive tender, Inserm was selected as the sponsor. Prof. Odile Launay (CIC-Cochin, Paris, France) and Dr Sodiomon Sirima (CNRFP, Ougadougou, Burkina Faso) will conduct the clinical trial. The draft clinical trial protocol has been prepared and will be finalised in the second quarter of 2015 with the clinical trial anticipated to start in the second half of 2015.

MultiMalVax

The aim of the MultiMalVax project is to develop the concept of a highly-effective multi-stage malaria vaccine to proof-of-concept phase II efficacy testing in Europe, prior to clinical trials in malaria-endemic areas. The overarching aim of this four-year clinical development programme is to show safety, immunogenicity and efficacy at each stage of the parasite life cycle using a multi-stage malaria vaccine, which could provide a deployable high-efficacy product for use in malaria-endemic areas.

The blood-stage malaria vaccine trial using the PfRH5 antigen delivered by viral vectors started at UOXF in mid-2014. Subjects received the ChAd63-PfRH5 vaccine candidate at different doses followed or not by an MVA-PfRH5 boost. The pre-erythrocytic vaccine trial using the RTS,S biosimilar R21, and the transmission-blocking vaccine trial, are expected to start in mid-2015. The call for the selection of the investigational site was re-launched in July 2014. Four applications were received from four different European countries. The proposal of Prof Saul Faust from Southampton NIHR Wellcome Trust Clinical Research Facility was recommended to the PSC by a selection committee (two representatives of UOXF and two representatives from EVI). The PSC approved the recommendation during its meeting in Siena during the annual meeting of the project. The sponsor is now in charge of the contract negotiation with the principal investigator. The first pre-erythrocytic combination vaccine trial was performed to assess the combination of RTS,S with the ME-TRAP vectored vaccines in a phase IIa efficacy trial, showing increased efficacy compared to each single component.

PIM

The PIM project aims to develop the first controlled human challenge model of paratyphoid infection that can be used to investigate the pathogenesis and immunobiology of infection, identify biomarkers and evaluate the efficacy of vaccine candidates.

To determine the dose of *Salmonella paratyphi A* required for the development of the human challenge model, healthy volunteers were challenged with escalating doses of *Salmonella paratyphi A* in order to give a clinical/laboratory attack rate of 60–75%. The clinical trial application received ethical approval by the South Central – Oxford A ethics committee in February 2014, and regulatory approval from NHS R&D was received in March 2014. The first volunteer was challenged in May 2014.

Immunological and transcriptomic analysis will be used to characterise the immune response and to identify factors associated with resistance to infection.

BELLEROPHON

Preparations for the clinical trial of the *S. aureus* vaccine candidate will begin during the fourth quarter of 2015. The clinical trial will take place in the UK in healthy adult subjects 18–50 years of age.

IDEA

The IDEA work package that measures the impact of intestinal helminth infections on the immune response to malaria, TB and HIV vaccines is led jointly by UOXF and EVI.

The add-on studies for malaria vaccine trials (GMZ2) in Lambaréné, Gabon, were completed early in 2013. Samples were analysed by PCR and microscopy to detect parasites. Cell-based and functional immunoassays were carried out to study the influence of helminth infection on vaccine-induced immunity, and unblinding of the data is expected in 2015.

The TB trial aims to examine the effect of *Schistosoma mansoni* infections on the immunogenicity of the MVA 85A TB vaccine candidate in African adolescents, positive or negative for *Schistosoma mansoni,* vaccinated with BCG. The clinical trial protocol was approved by the regulatory and ethical authorities and the clinical trial started in June 2014. Enrolment of subjects took place in three schools in Uganda and was completed by the end of November 2014. The last follow up is expected at the end of January 2015 and data analysis is expected to start in March 2015.

The HIV clinical trial aims to evaluate the safety and immunogenicity of HIV vaccine candidates, including a DNA prime followed by a NYVAC boost in HIV-free adult participants with or without underlying schistosomiasis infections. After protocol approval by UVRI IRB, the proposed NYVAC vaccine had to be changed due to its reactogenicity in ongoing external studies. The replacement vaccine AIDSVAX B/E protein was remanufactured in 2014. The amended protocol with the new vaccine was approved by the UVRI Science and Ethics Committee and by the UNCST in May 2014. The clinical trial application was approved by the NDA in Uganda in October 2014. The clinical trial started in November 2014 and the recruitment of 70 subjects is underway.

CAPACITY BUILDING, WORKSHOPS, TRAINING

Capacity building

MVVC

The infrastructure and laboratory equipment upgrade was completed at the CNRFP site in Banfora (Burkina Faso) and at the UCAD research site in Keur Socé (Senegal). Both sites are now functioning effectively.

Several exchange visits took place to reinforce collaborations, especially between the African project partners.

MVVC2

As part of the MVVC2 capacity building activities, immunology facilities at the KHRC, Ghana, have been secured and made available. The laboratory facilities have been established and equipment is currently being sourced. An exchange visit between KHRC and CNRFP will be organised to set up the immunology laboratory by sharing resources and expertise.

Other exchange visits took place during the year to reinforce collaborations, especially between the African project partners. An exchange visit was organised at KEMRI in January 2014 for Issiaka Soulama (CNRFP) for the evaluation of qPCR techniques and corresponding training, as needed for the CNRFP clinical trial which will begin mid-2015.

A true example of South-South collaboration is the exchange of expertise and laboratory personnel between the MRC, The Gambia, and the UCAD. The UCAD staff will gain

experience in paediatric malaria clinical trials while two UCAD laboratory technicians support immunological analysis at the MRC.

P27A

The construction of the outpatient wing started at BCTU, Tanzania. The cost of the outpatient wing is being met in part by an EDCTP P27A-CTB strategic primer grant.

IDEA

In 2014, considerable capacity building was achieved in collaboration with The SchistoVac consortium, and others including the Wellcome Trust-funded Makerere University UVRI research training programme in infection and immunity in Uganda. The IDEA project provides opportunities for postgraduate research and contributes to the development of emerging African centres of excellence in both parasitological and immunological techniques. To facilitate collaboration and coordination between field sites, the centre at Bagamoyo has become a reference hub in Tanzania for stool analysis for helminth infection and for stool PCR. The centre at UVRI has also developed as a hub for training in immunology and bioinformatics, with plans in place for further training of scientists from Nigeria.

Workshops

MVVC2

A three-day workshop on project management for clinical research professionals within the MVVC2 project was organised by EVI in collaboration with KHRC at the KHRC conference centre in Kintampo, Ghana. The workshop was conducted by IAoCR. Participants from the five African MVVC2 partner institutions (MRC, The Gambia, KEMRI, Kenya, CRNFP, Burkina Faso, UCAD, Senegal, and KHRC, Ghana) and from EVI, Germany, attended this workshop.

During the workshop, the participants were trained in project management techniques and equipped with the skills and techniques needed to manage their clinical research projects as part of the integrated strategic capacity building component of MVVC2.

The course applied standard project management techniques to the definition, planning and implementation of clinical trial projects.

The course was very well appreciated by all participants, and the varied professional background of the participants resulted in many interesting discussions.

IPROVE

- **Workshop on Vaccine SMEs, 15 May 2014, Brussels, Belgium**

The workshop set out to discuss the following core thematic areas:

- Mobilising new ideas to improve R&I contributions from vaccine/immunology SMEs;
- Enhancing the competitiveness of SMEs in their interactions with public authorities and large companies;
- Elaborating strategies to enhance the involvement of SMEs in EU R&I activities in the vaccine arena;
- Improving access to risk/venture capital, and increasing the effectiveness of funding at the EU level.

The workshop included 16 SMEs from eight EU countries, as well as high-level representatives from EC DG Research and Innovation, EIB, EIT and from large vaccine companies. The participating experts' views on potential solutions and suggested recommendations for action at the EU and national levels, concerning the specific areas addressed by the workshop, were summarised in a report to the EC submitted in September 2014.

- **Workshop on Training & Communication on vaccines and vaccinology, 28 October 2014, Brussels, Belgium**

This workshop covered topics concerning current training needs in vaccine R&D and vaccinology, and communication and perception issues related to vaccination. Each of the workshop sessions prepared a list of proposed actions at the EU level to address the needs and gaps identified during the workshop. The workshop was attended by approximately 50 participants from public research organisations, universities, industry, public health, civil society organisations, and funders and policy makers. The workshop report will be submitted to the EC in 2015.

Training

MVVC

Massamba Syll, UCAD, Senegal, successfully completed two MSc degrees in "Biologie et Contrôle des Parasites" and "Analyses Physicochimiques et Management de la Qualité en Santé" at UCAD in January 2014. The thesis title is "Quality assessment of Keur Socé's Research and Training Centre laboratory in compliance with ISO 15 189". The work of the three PhD students is progressing well, the main results of their studies were published in peer-reviewed journals and they are expected to graduate in 2015. Francis Ndungu from KEMRI completed his postdoctoral research at KEMRI (his funding from MVVC ended in December 2013). He recently won an independent research grant from the MRC to continue his research at KEMRI.

P27A

Catherine Mkindi registered as a PhD student at the University of Basel and continued her research focusing on the analysis of the immune responses induced by the malaria peptide P27A delivered with either Alhydrogel or GLA-SE in Tanzanian subjects. The PhD fellowship is supported by the EDCTP P27A-CTB grant.

EDUFLUVAC

In relation to the EDUFLUVAC project, iBET team members attended the following courses and workshops in 2014:

- Vaccines: Bioprocess Development and Commercialisation, Portugal, was attended by ntonio Roldao, Marcos Sousa, Ricardo Silva, Sofia Carvalho;
- Single-Use Technologies for Rapid Manufacturing, UK, was attended by Marcos Sousa;
- Animal Cell Technology course – 4th edition, Spain, was attended by Sofia Carvalho;
- Integrative Structural Biology tools for the study of protein-ligand interactions, Portugal, was attended by Sofia Carvalho;
- VI Latin American Symposium on Cell Culture Technology, Chile, was attended by Antonio Roldao.

In May 2014, the EVI financial team provided the Redbiotec team with detailed instructions concerning financial accounting in the EDUFLUVAC project.

BELLEROPHON

Yuko Yamaguchi, UOXF, attended the following training programmes:

- Human and Veterinary Vaccinology course, UOXF, UK;
- Statistics with SPSS, Comparing Biological Data Using Nonlinear Model Fitting

Amy Flaxman, UOXF, attended the following training programmes:

- Home Office: animal handling, Introduction to Phlebotomy, UOXF, UK;
- Flow Cytometry Course, University of York, UK

Elizabeth Allen, UOXF, attended following training programmes:

- Home Office: animal handling, Introduction to Phlebotomy, UOXF, UK;
- Flow Cytometry Course, University of York, UK

IDEA

In 2014, the IDEA project provided fellowships to nine Masters students at UVRI, Uganda, CERMEL, Gabon and IHI, Tanzania, and to 16 PhD students at UVRI, Uganda, IHI, Tanzania, University of Ibadan, Nigeria and KEMRI, Kenya.

IDEA continues to contribute to the Immunology Short Course, Immunology in the Tropics, at the faculty of UVRI. A course on the evolution of the immune system, malaria and helminth immunology took place in March 2014. IDEA contributed to the course faculty including world leaders in these fields from IDEA and Schistovac institutions in East Africa and Europe.

In collaboration with MUII, IDEA contributed to the development of a curriculum in Bioinformatics, specifically a component on the analysis of microarray and multiplex gene array and cytokine data. Two courses in R programming were held at UVRI, and individuals have also undertaken recommended on-line training in R.

HARMONISATION

The progress of research into the development of vaccines against diseases of poverty depends on the ability to compare the efficacy of experimental vaccines from different laboratories. EVI is working across Europe to harmonise specific aspects of vaccine development, including adjuvant testing and numerous assays commonly used to determine experimental vaccine efficacy. EVI's current efforts focus on the harmonisation of clinical trial design and functional immunoassays for two different placental malaria vaccine candidates. EVI seeks to develop a level of standardisation for several key assays through agreement on standardised laboratory procedures, preparations and reagents.

MVVC

The antibody and T-cell assays are now standardised among the consortium centres. The antibody assays for baseline studies were centralised in KEMRI and data were normalised by using standard controls with known antibody concentrations in each plate. The T-cell assays use an identical protocol, with identical operating procedures, an achievement made possible by a series of exchange trips and collaboration with a quality control network. Reagents for ELISpot assays were purchased from agreed suppliers and were standardised among the centres. In addition, the sites involved in the immunogenicity studies are part of the OPTIMALVAC network to process shared samples, and an agreement was reached among the sites for specific responses and controls.

MVVC2

The MVVC2 consortium has expanded the MVVC harmonisation efforts on immunoassays to include KHRC, and those concerning qPCR to include CNRFP. This will ensure that the sites generate comparable results in the MVVC2 project and in future clinical trials.

AMA1-DiCo

Ed Remarque (BPRC) has supplied AMA1 antigens and/or GIA standards to the following organisations/individuals:

- NIBSC (EuriPred project, Paul Boyer): AMA1 antigen, GIA strains and standards;
- UOXF (Simon Draper): GIA standard;
- Fraunhofer IME (Holger Spiegel): AMA1 proteins, GIA standard;
- IRD Benin (David Courtin): AMA1 antigens;
- IMT Antwerp: AMA1 antigens;
- Jaffu Chilonga, Tanzania: AMA1 antigens;
- Karolinska University Hospital (Klara Sonden): AMA1 antigens

Ed Remarque (BPRC) has provided support for the establishment of ELISA protocols at CIC-Cochin Pasteur in the context of the AMA1-DiCo phase Ia/Ib clinical trial.

P27A

The project is in the process of harmonising the immunological assays between the CHUV and IHI teams during the course of the P27A phase Ia/Ib clinical trial.

Placental Malaria

- **EVI workshop on the clinical development of a placental malaria vaccine**

An EVI workshop on placental malaria vaccine clinical development was held on 24 April 2014 at Institut Pasteur in Paris. The aim of the workshop was to bring together researchers representing the PRIMALVAC, PAMCPH and PlacMalVac projects, and a panel of worldwide experts.

During this workshop, the placental malaria community committed to working together on the clinical development strategy for a placental malaria vaccine. Agreements were reached concerning the preferred product characteristics of a placental malaria vaccine at an early development stage; the implementation of the first draft of a clinical development plan for a placental malaria vaccine; and the harmonised phase Ia/Ib staggered clinical trial design, allowing the placental malaria vaccines to be compared across clinical trial centres. The community also agreed to harmonise immunoassays for the assessment of immunogenicity.

The outcome of this workshop was a report that was shared with the placental malaria community and policy makers, describing the status of the immunoassays and their harmonisation, preferred product characteristics, the clinical development plan, and the clinical trial phase Ia/Ib design.

- **EVI workshop on immunoassay harmonisation for placental malaria vaccines**

Following the EVI workshop on clinical development, a second EVI workshop was held in Brussels on 19 November 2014 aiming to establish and harmonise functional immunoassays in order to compare the efficacy of the two placental malaria vaccine candidates currently under development in the PAMCPH/PlacMalVac and PRIMALVAC projects. The two teams involved in these projects agreed to develop a harmonised immunoassay platform allowing the comparison of their results and providing some evidence of efficacy before committing to clinical development. The following placental malaria assays will be harmonised:

- Measurement of antibody titre by ELISA;
- Measurement of antibody recognition of the surface of infected erythrocytes by flow cytometry;
- Measurement of CSA-binding inhibition by antibodies using a Petri dish-based binding inhibition assay.

Reference reagents and SOPs will be exchanged, and discussions to achieve harmonisation are continuing.

MultiMalVax

UOXF is a member of the MVVC and MVVC2 consortia and was part of the OPTIMALVAC network and thus involved in antibody and T-cell assay harmonisation activities. In addition, the phase I clinical trial assessing the blood-stage antigen PfRH5 is being conducted at the CCVTM, UOXF, and the Southampton NIHR Wellcome Trust CBF, and clinical activities are harmonised across these centres.

EDUFLUVAC

A list of reagents, controls, SOPs and materials was created and circulated within the consortium with the aim of harmonising EDUFLUVAC's activities. The following SOPs were exchanged among iBET, Redbiotec and NIBSC and implemented accordingly:

- Cryopreservation, thawing and routine maintenance of Sf9 and Hi5 insect cells;
- Baculovirus amplification, storage and titration;
- Downstream processing of influenza VLPs;
- Characterisation of influenza VLPs (including haemagglutination assay, HA deglycosylation assay, ELISA, western blot, SRID and neuraminidase activity assay)

In addition, iBET and NIBSC coordinated their activities to quantify HA in influenza VLPs by IDMS.

PIM

The development of a controlled human model of paratyphoid infection will provide a valuable tool for the evaluation of vaccine candidate efficacy, allowing the direct comparison of clinical features, laboratory parameters and biomarkers, and the identification of correlates of protection.

Furthermore, such a model will allow researchers to develop and harmonise novel immunoassays and diagnostic tools for enteric fever.

IDEA

The harmonisation of immunological assays and diagnostic methods across the IDEA study sites continued in 2014. SOPs for the isolation and stimulation of dendritic cells, monocytes, B cells, CD4 and CD8 T cells were shared among the partners, as well as protocols for PBMC isolation and cryopreservation, ELISpot, functional polychromatic flow cytometry, PCR and Luminex technology. There was also further harmonisation of the criteria used to evaluate clinical symptoms, disease progression and response to therapy. There was also a significant focus on the harmonisation of Luminex data analysis. A data-cleaning SOP was developed to import the data into statistical programs in a unified manner, and this was distributed among the partners. In addition, a protocol for principal component analysis has been established and shared with all partners to promote a similar data analysis strategy and comparable outcomes.

MVVC

The MVVC annual meeting was held on 13–14 January in Kilifi, Kenya. The partners presented their latest results and updates of the activities in the different work packages, and the next steps were discussed.

MVVC consortium was selected for the malaria vaccine studies' session at the 7th EDCTP forum, 30 June - 2 July, Berlin, Germany:

- Nicola Viebig (EVI, Heidelberg, Germany) presented "Integrating capacity building and networking in the design and conduct of clinical trials in East and West Africa";
- Nébié Issa Ouédraogo (CNRFP, Ouagadougou, Burkina Faso) presented "Assessing chimpanzee adenovirus serotype ChAd63 neutralising antibodies prior to the implementation of a candidate malaria vaccine regimen based on viral vectors";
- Alfred B. Tiono (CNRFP, Ouagadougou, Burkina Faso) presented "Safety and immunogenicity of heterologous prime-boost immunisation with candidate vaccines ChAd63 ME-TRAP and MVA ME-TRAP in healthy Burkinabè children aged 5-17 months";
- Badara Cisse (UCAD, Dakar, Senegal) presented "Efficacy study of ChAd63-MVA ME-TRAP prime-boost vaccination against *Plasmodium falciparum* infection in healthy adults in Senegal".

Muhammed O. Afolabi (MRC, Fajara, The Gambia) presented "Digitised audio questionnaire for assessment of informed consent comprehension in a low literacy African research population: development and psychometric evaluation" at the cross cutting session at the 7th EDCTP forum, 30 June - 2 July, Berlin, Germany.

Adrian Hill (UOXF, Oxford, UK) presented "Towards a multi-antigen multi-stage malaria vaccine" at Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK.

Danny Wright (UOXF, Oxford, UK) presented "Immunogenicity of ChAd63 + MVA ME-TRAP in Senegalese adults" at Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK.

Georgina Bowyer (UOXF, Oxford, UK) presented "Humoral Immunogenicity of ChAd63_MVA ME-TRAP vaccination in African infants and children" at Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK.

The MVVC consortium was also very well represented at the 63rd ASTMH Meeting, 2–6 November, New Orleans, USA:

- Muhammed O. Afolabi (MRC, Fajara, The Gambia) presented "Development and evaluation of multimedia informed consent tool for a low literacy African research population";
- Katie Ewer (UOXF, Oxford, UK) presented "Potent cellular and humoral immunogenicity of ChAd63 MVA ME-TRAP in African infants and children";
- Victorine Mensah (UCAD, Dakar, Senegal) presented "Immunogenicity and efficacy of ChAd63-MVA ME-TRAP prime-boost vaccination against Plasmodium falciparum infection in healthy adults in Senegal" at the 63rd ASTMH Meeting, 2–6 November, New Orleans, USA;
- Alfred B. Tiono (CNRFP, Ouagadougou, Burkina Faso) presented "Efficacy, safety and immunogenicity of heterologous prime-boost immunization with the candidate malaria vaccines ChAd63 ME-TRAP and MVA ME-TRAP in 5-17 month old Burkinabe infants and children";

- Amy Ndaw (UCAD, Dakar, Senegal) presented "Chimpanzee adenovirus serotype 63 neutralizing antibodies assessment, prior to evaluation of a candidate malaria vaccine regimen based on viral vectors: Preliminary results from a survey in Senegal".

Alfred Tiono (CNRFP, Ouagadougou, Burkina Faso) presented "Preliminary results of phase I/IIb clinical trial with ChAd63 ME-TRAP and MVA ME-TRAP" at the EVI Rendez-Vous, 3 December, Paris, France.

MVVC2

The MVVC2 annual meeting was held on 15 January in Kilifi, Kenya. The partners presented updates on their recent results and activities in the different work packages and the next steps were discussed.

Adrian Hill (UOXF, Oxford, UK) presented "Towards a multi-antigen multi-stage malaria vaccine" at Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK.

Muhammed Afolabi (MRC, The Gambia) presented "Phase I/IIb safety and immunogenicity of CHAd63/MVA ME-TRAP vaccine candidates co-administered with EPI vaccines in infants" at the EVI Rendez-Vous, 3 December in Paris, France.

AMA1-DiCo

On World Malaria Day, EVI published a press release "Neue Impfstoffkandidaten gegen Malaria gehen in klinische Entwicklungsphase", by Market Wire, highlighting the recent achievements of the two blood-stage vaccine candidates under development: AMA1-DiCo and P27A.

Odile Launay (CIC-Cochin Pasteur, France) and Adama Gansané (CNRFP, Ouagadougou, Burkina Faso) gave an update on "AMA1-DiCo clinical trial phase Ia/Ib" at the EVI Rendez-Vous, 3 December, Paris, France.

InnoMalVac

Outreach related to the project:

- Waynflete Tutor for 6th Formers – Malaria and Vaccines, Magdalen College School, March 2014, Oxford, UK;
- Year 6 Talk – Malaria and Vaccines, Dragon School, May, Oxford, UK;
- 750th Anniversary Weekend – Talk on Malaria & Ebola Vaccines, Merton College, September, Oxford, UK.

Simon Draper (UOXF, UK) presented the project at:

- Hammersmith Imperial College (Guest Seminar – John Humphrey Lecture Series), January, London, UK;
- Integrated MSc in Immunology - Lecture, UOXF, January, Oxford, UK;
- Human and Veterinary Vaccinology Course - Lecture, UOXF, January, Oxford, UK;
- Bachelor of Medicine Pathology Course for 2nd Year Medics – Lecture, UOXF, January, Oxford, UK;
- MSc in Molecular and Cellular Biology of Tropical Diseases and Vectors – Lecture, LSTM, January, Liverpool, UK;
- Edinburgh Immunology Group, Edinburgh University (Guest Seminar), February, Edinburgh, UK;
- Immunology in the Tropics Course, MRC Uganda / UVRI, March, Entebbe, Uganda;
- British Society of Parasitology Conference (Invited Speaker), April, Cambridge, UK;
- Gordon Research Conference (Invited Speaker and Discussion Leader), June, Rhode Island, USA;

- Lister Prize Seminar, June, Oxford, UK;
- University of Oslo (Guest Seminar), August, Oslo, Norway;
- MultiMalVax annual meeting (WP leader), Novartis, September, Siena, Italy;
- Symposium of Infectious Diseases in Africa, University of Cape Town, October, Cape Town, South Africa;
- EVIMalaR Cluster 1 & 4 Meeting (Invited Speaker), October, Copenhagen, Denmark;
- Vaccinology in Africa Course, JI/ILRI, October, Nairobi, Kenya;
- University of Ghent (Guest Seminar), November, Ghent, Belgium.
- Dunn School of Pathology "Bug Session" (Guest Seminar), November, Oxford, UK;
- EVI Rendez-Vous (Invited Speaker), 3 December, Paris, France.

P27A

On World Malaria Day, EVI published a press release "Neue Impfstoffkandidaten gegen Malaria gehen in klinische Entwicklungsphase", by Market Wire, highlighting the recent achievements of the two blood-stage vaccine candidates under development: AMA1-DiCo and P27A.

François Spertini (CHUV, Lausanne, Switzerland) and Seif Shekalaghe (IHI, Bagamoyo, Tanzania) presented "P27A clinical trial phase Ia/Ib update" at the EVI Rendez-Vous, 3 December, Paris, France.

SEmalvac

The SEmalvac project kick-off meeting took place in Heidelberg on 8–9 October where the CNRFP, RIMD and EVI consortium partners discussed the BK-SE36 phase Ib clinical trial implementation in Burkina Faso.

In October, EVI published a press release on the GHIT and EVI websites presenting SEmalvac, the newly awarded EVI project aiming to assess the safety and immunogenicity of the BK-SE36 malaria vaccine candidate in healthy malaria-exposed African children 1-5 years of age living in Burkina Faso.

PAMCPH

Ali Salanti (UCPH, Copenhagen, Denmark) presented "VAR2CSA vaccines" at the 63rd ASTMH meeting, 2–6 November, New Orleans, USA.

Philippe Deloron (IRD, Benin) presented "VAR2CSA antigen: production and clinical development" at the EVI Rendez-Vous, 3 December, Paris, France.

Wian de Jongh and Charlotte Dyring (ExpreS2ion, Copenhagen, Denmark) presented the production phase of the project at:

- PEPTALK (poster presentation), 13–17 January, Palm Springs, CA, USA;
- New Cells New Vaccines, 17–20 March, Delaware, USA;
- PEGS Boston (oral presentation), 4–9 May, Boston, USA;
- DCB9 Animal Cell Cultures - Expression and Engineering (oral presentation), 22–23 May, Vejle, Denmark;
- Merck Millipore Upstream seminar (oral presentation), 27–28 May, Bordeaux, France;
- BioProcess summit (oral presentation), August, Boston, USA;
- Insectinov ADEBIOTECH (oral presentation) 2–3 December, Romainville, France;
- Veterinary Vaccines (oral presentation), December, Brussels, Belgium.

PlacMalVac

On World Malaria Day (25 April), EVI published a press release on CORDIS Wire and the EVI websites: "Joint efforts to defeat malaria affecting pregnant women and their babies.". This highlighted the progress in placental malaria vaccine development and summarised the main conclusions of the EVI workshop held in April on the harmonisation of clinical development for the PlacMalVac and PRIMALVAC placental malaria vaccine candidates.

The PlacMalVac first annual meeting was held on 22–23 April in Paris, France, where the consortium members presented their achievements for each work package.

PRIMALVAC

On World Malaria Day (25 April), EVI published a press release on CORDIS Wire and the EVI website: "Joint efforts to defeat malaria affecting pregnant women and their babies.". This highlighted the progress in placental malaria vaccine development and summarised the main conclusions of the EVI workshop held in April on the harmonisation of clinical development for the PlacMalVac and PRIMALVAC placental malaria vaccine candidates.

Benoit Gamain (Inserm, France) published an article on World Malaria Day in the Huffington Post on the burden of placental malaria and recent achievements in vaccine development: http://www.huffingtonpost.fr/benoit-gamain/vaccin-contre-le-paludisme-femmes-enceintes_b_5204102.htmlPublications

Nicola Viebig (EVI, Heidelberg, Germany) presented "PRIMALVAC: VAR2CSA as a placental malaria vaccine candidate" at the BioMalPar conference, 14–16 May, Heidelberg, Germany.

Benoit Gamain (Inserm, Paris, France) presented "Developing a VAR2CSA-based vaccine" during the symposium: "Developing PfEMP1-Based Vaccines for Malaria" at the 63rd ASTMH meeting, 2–6 November, New Orleans, USA.

Hervé Ginisty (GTP Technology, Labège, France) presented "Vaccine process development (PRIMALVAC Project)" at the EVI Rendez-Vous, 3 December, Paris, France.

MultiMalVax

The MultiMalVax consortium met face to face for the third time during the annual meeting on 15-16 September in Siena, Italy. The partners presented their scientific achievements and discussed future activities for each work package.

Adrian Hill (UOXF, Oxford, UK) presented "Towards a multi-antigen multi-stage malaria vaccine" at Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK.

Carly Bliss (UOXF, Oxford, UK) presented "Development of an in vitro *Plasmodium* parasite killing assay for the evaluation of cell-mediated immune responses following vaccination with pre-erythrocytic malaria vaccine candidates" at Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK.

Thomas Rampling (UOXF, Oxford, UK) presented "Safety, immunogenicity and efficacy of the combination malaria vaccine regimen of RTS,S/AS01B with ChAd-MVA vectored vaccines expressing ME-TRAP" at the 63rd ASTMH Meeting, 2–6 November, New Orleans, USA.

Catherine Collins (UOXF, Oxford, UK) presented "Enhancing pre-erythrocytic stage vaccine efficacy with the development of a highly immunogenic virus-like particle vaccine and a multi-component vaccine strategy" at the 63rd ASTMH Meeting, 2–6 November, New Orleans, USA.

Adrian Hill (UOXF, Oxford, UK) presented "Development of a multi-component multistage malaria vaccine – here we are" at the EVI Rendez-Vous, 3 December in Paris, France.

EDUFLUVAC

The first EDUFLUVAC annual meeting took place in Carcavelos, Portugal, on 15–16 October. During this two half-day meeting, current and future EDUFLUVAC activities were discussed and the participants were able to visit the laboratories and the facilities at iBET and GenIbet, where the influenza VLPs, containing the HA NA proteins, are currently being produced and characterised.

Paula Alves (iBET, Portugal) presented "Insect cell technology as a vaccine producing platform" at the 16th European Congress on Biotechnology on 13–16 July, Edinburg, Scotland.

Paula Alves (iBET, Portugal) presented "Universal flu vaccine based of diversity covering approach: antigen selection and production" at the EVI Rendez-Vous, 3 December, Paris, France.

PIM

Andrew Pollard (Oxford Vaccine Group, UOXF, UK) presented an update of the paratyphoid human challenge study at the Grand Challenges Meeting, BMGF, 7 October, Seattle, USA.

Hazel Dobinson (Oxford Vaccine Group, UOXF, UK) presented the human paratyphoid infection model as an example to understand recruitment and participant satisfaction with the challenge models at the CORVAC meeting, December, Lille, France.

Iain Milligan and Malick Gibani (Oxford Vaccine Group, UOXF, UK) presented "Development of a paratyphoid human infection model to accelerate vaccine development" at the EVI Rendez-Vous, 3 December in Paris, France.

BELLEROPHON

The first BELLEROPHON annual meeting took place on 1–2 October in Lyon, France. During the meeting, the consortium partners presented their scientific achievements over the last year and discussed future plans. The independent scientific advisory committee acknowledged the results generated in the project and gave valuable recommendations to the team.

Elizabeth Allen (UOXF, UK) presented "MRI based quantification of abscess volumes in mice following *S. aureus* i.v. challenge", abstract 7 at the ISSSI meeting, 26–29 August, Chicago, USA.

Pauline van Diemen (UOXF, UK) presented "Partial protection against *Staphylococcus aureus* i.v. challenge with a vector vaccine", abstract 252 at the ISSSI meeting, 26–29 August, Chicago, USA.

Yuko Yamaguchi (UOXF, UK) presented "Evidence for control of *S. aureus* nasal carriage by innate lymphocyte populations in humans: a cross sectional study", abstract 267 at the ISSSI meeting, 26–29 August, Chicago, USA.

Yuko Yamaguchi (UOXF, UK) presented the project at the BSI congress, 1–4 December, Brighton, UK.

Alexandre Le Vert (IMAXIO, Lyon, France) presented "Combining cellular and humoral immune responses as a vaccine strategy against *Staphylococcus aureus* pathogen" at the EVI Rendez-Vous, 3 December, Paris, France.

IDEA

The IDEA annual meeting was held on 17–18 June in Vienna, Austria. All partners presented their latest achievements and discussed future activities.

Akim Ayola (CERMEL, Gabon) presented "Helminths and malaria" at the EVI Rendez-Vous, 3 December, France.

PUBLICATIONS

EVI

Leroy O, Geels M, Korejwo J, Dodet B, Imbault N, Jungbluth S. Roadmap for the establishment of a European vaccine R&D infrastructure. *Vaccine,* 2014 32(51):7021-4 (TRANSVAC)

Mark J Geels, Regitze L Thøgersen, Guzman CA, Ho MM, Verreck F, Collin N, Robertson JS, McConkey SJ, Kaufmann SHE, Leroy O. TRANSVAC Research infrastructure – results and lessons learned from the European network of vaccine research and development. *Vaccine,* 2014 (in press) (TRANSVAC)

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de Barra E, Hodgson SH, Ewer KJ, Bliss CM, Hennigan K, Collins A, Berrie E, Lawrie AM, Gilbert SC, Nicosia A, McConkey SJ, Hill AV. A phase Ia study to assess the safety and immunogenicity of new malaria vaccine candidates ChAd63 CS administered alone and with MVA CS. *PLoS One*, 2014, 9(12)

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Salim N, Schindler T, Abdul U, Rothen J, Genton B, Lweno O, Mohammed AS, Masimba J, Kwaba D, Abdulla S, Tanner M, Daubenberger C, Knopp S. Enterobiasis and strongyloidiasis and associated co-infections and morbidity markers in infants, preschool- and school-aged children from rural coastal Tanzania: a cross-sectional study. *BMC Infectious Diseases*, 2014, 14(1):644

Chachage M, Podola L, Clowes P, Nsojo A, Bauer A, Mgaya O, Kowour D, Froeschl G, Maboko L, Hoelscher M, Saathoff E, Geldmacher C. Helminth-associated systemic immune activation and HIV co-receptor expression: response to albendazole/praziquantel treatment. *PLOS Neglected Tropical Diseases*, 2014, 8(3)

Knopp S, Salim N, Schindler T, Karagiannis Voules DA, Rothen J, Lweno O, Mohammed AS, Singo R, Benninghoff M, Nsojo AA, Genton B, Daubenberger C. Diagnostic accuracy of Kato-Katz, FLOTAC, Baermann, and PCR methods for the detection of light-intensity hookworm and *Strongyloides stercoralis* infections in Tanzania. *Am J Trop Med Hyg*, 2014, 90(3):535-45

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Katherine E. Wright, Kathryn A. Hjerrild, Jonathan Bartlett, Alexander D. Douglas, Jing Jin, Rebecca E. Brown, Joseph J. Illingworth, Rebecca Ashfield, Stine B. Clemmensen, Willem A. de Jongh, Simon J. Draper, Matthew K. Higgins, Structure of malaria invasion protein PfRH5 with erythrocyte basigin and blocking antibodies. *Nature,* 2014 515: 427-30

MVVC

Ndiath M, Faye B, Cisse B, Ndiaye JL, Gomis GF, Dia AT and Gaye O. Identifying malaria hotspots in Keur Soce health and demographic surveillance site in context of low transmission. *Malaria Journal,* 2014, 13:453

Kangoye DT, Nebie I, Yaro JB, Debe S, Traore S, Ouedraogo O, Sanou G, Soulama I, Diarra A, Tiono A, Marsh K, Sirima SB, Bejon P. *Plasmodium falciparum* malaria in children aged 0-2 years: the role of foetal haemoglobin and maternal antibodies to two asexual malaria vaccine candidates (MSP3 and GLURP). *Plos One*, 2014, 9(9)

Nébié I, Edwards NJ, Tiono AB, Ewer KJ, Sanou GS, Soulama I, Sanon S, Diarra A, Yaro JB, Kangoye D, Imoukhuede EB, Hill AV, Sirima SB. Assessment of chimpanzee adenovirus serotype 63 neutralizing antibodies prior to evaluation of a candidate malaria vaccine regimen based on viral vectors. *Clin Vaccine Immunol.* 2014, 21(6):901-3

Kimani D, Jagne YJ, Cox M, Kimani E, Bliss CM, Gitau E, Ogwang C, Afolabi MO, Bowyer G, Collins KA, Edwards N, Hodgson SH, Duncan CJ, Spencer AJ, Knight MG, Drammeh A, Anagnostou NA, Berrie E, Moyle S, Gilbert SC, Soipei P, Okebe J, Colloca S, Cortese R, Viebig NK, Roberts R, Lawrie AM, Nicosia A, Imoukhuede EB, Bejon P, Chilengi R, Bojang K, Flanagan KL, Hill AV, Urban BC, Ewer KJ. Translating the immunogenicity of prime-boost immunisation with ChAd63 and MVA ME-TRAP from malaria naïve to malaria-endemic populations. *Mol Ther.*, 2014, 22(11):1992-2003

Afolabi MO, Adetifa JU, Imoukhuede EB, Viebig NK, Kampmann B, Bojang K. Early phase clinical trials with human immunodeficiency virus-1 and malaria vectored vaccines in The Gambia: frontline challenges in study design and implementation. *Am J Trop Med Hyg.*, 2014, 90(5):908-14

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Afolabi MO, Bojang K, D'Alessandro U, Imoukhuede EB, Ravinetto MR, Larson JH, McGrath N, Chandramohan D. Multimedia informed consent tool for a low literacy African research population: Development and pilot-testing. *J Clin Res Bioeth.*, 2014; 5(3):178

Afolabi MO, Bojang K, D'Alessandro U, Ota MOC, Imoukhuede EB, Ravinetto MR, Larson JH, McGrath N, Chandramohan D. Digitised audio questionnaire for assessment of informed consent comprehension in a low literacy African research population: Development and psychometric evaluation. *BMJ Open.*, 2014, 4

MOVIES

EVI has collaborated with A. Longuet (Evening Bay) to prepare the following movies highlighting the progress in fighting diseases of poverty.

- Fighting malaria – Malaria Vectored Vaccines Consortium: https://www.youtube.com/watch?v=63MAPCzzHqY
- Malaria vaccine development at EVI: https://www.youtube.com/watch?v=ToU9Pl4HyY4
- Fighting placental malaria https://www.youtube.com/watch?v=21apcE849-g

German launch event "Horizon 2020", 28–29 January, Berlin, Germany

The event was organised by the BMBF to celebrate the launch of the new EC framework programme Horizon 2020 at the end of 2013. Representatives from BMBF and the EC presented the structure of the new framework programme to the participants and outlined the most important differences compared to previous programmes. EVI was represented by Stefan Jungbluth.

Inauguration of ECRIN-ERIC, 30 January, Brussels, Belgium

EVI was invited to attend the inauguration of the European Clinical Research Infrastructure Network - European Research Infrastructure Consortium, and was represented by Sophie Houard.

Global Vaccine and Immunization Research Forum, 4–6 March, Washington, USA

The Global Vaccine and Immunization Research Forum is derived from the Global Vaccine Research Forum, organised successfully by WHO for a number of years. Building on that tradition, the meeting has now been expanded and was co-hosted by WHO, NIH-NIAID, and BMGF. The GVIRF served as a forum for the discussion of the R&D component of the Global Vaccine Action Plan developed in the framework of the Decade of Vaccines Collaboration and endorsed by the 2012 World Health Assembly. Odile Leroy, who is a member of the scientific organising committee, chaired a workshop entitled "Vaccines against neglected infectious diseases and innovative vaccine research: the point of view of industry and biotech companies".

New Horizons for Vaccine Research and Innovation, 12–13 March, Brussels, Belgium

The conference was a follow-up to the "Innovation Convention" with more than 2000 participants under the patronage of the Commission President Manuel Barroso, which took place on the previous two days. The objectives of the conference, which included 200 top scientists and policy makers, was to raise awareness, to analyse current bottlenecks, to come up with innovative solutions, and to give strategic input into future policies and funding actions for vaccine research under the new EU Framework Programme for Research and Innovation 'Horizon 2020'. Odile Leroy gave a presentation entitled "Product Development Partnership".

RBM advocacy meeting, 24–25 March, Geneva, Switzerland

This was a meeting of the advocacy working group of RBM in which the participants discussed and prepared the advocacy strategy for the global malaria community for 2014 and beyond. EVI was represented by Stefan Jungbluth.

Communicating European Health Research Network, 20 March, Berlin, Germany

The CommHERE meeting is an opportunity to exchange ideas and experiences with other network members, i.e. scientific coordinators and managers of EU-funded research projects as well as professionals in communication. Nathalie Imbault participated in the workshop.

Virus-like particles as vaccines, vectors and adjuvants, 31 March – 2 April, Fondation Mérieux, Veyrier-du-Lac, France

The meeting discussed vaccine failures observed with soluble proteins illustrating that the size and/or spatial assembly of the surface proteins is critical for the induction of a protective immune response. Antigen design and the mechanism of action specific to VLPs with regard to adaptive and innate immune responses were discussed in depth. These issues are particularly relevant to the EDUFLUVAC project coordinated by EVI, which aims to develop a universal influenza vaccine based on VLPs. This meeting brought together key players in VLP vaccine technology in particular university and industrial experts on nanoparticle characterisation (Neil Ranson, University of Leeds, Vironova). Sophie Houard participated in the workshop

BioMalPar conference, 14–16 May, Heidelberg, Germany

Nicola Viebig attended the meeting and presented a poster on the PRIMALVAC project. The meeting is a good platform to interact with scientists involved in basic malaria research, which is the basis of future product development.

Parliamentary Breakfast organised by the German Network for NTDs, 22 May, Berlin, Germany

Breakfast hosted by G Kippels, MP of the German Parliament, in order to discuss the objectives of the German Network which was at the time still in the preparatory phase. EVI was represented by Stefan Jungbluth.

Phacilitate: Partnering for Vaccine Emerging Markets, 28–29 May, Amsterdam, the Netherlands

The 2nd Annual Phacilitate Partnering for Biologic Emerging Markets event was designed to bring together senior decision-makers from the leading Western life sciences stakeholders and their counterparts from key emerging nations and regions, including Asia Pacific, India, Eastern Europe, Turkey and Russia, Latin America and South Africa. Odile Leroy gave a presentation entitled "Malaria Vaccines".

Common Barriers in Vaccine Research and Development, 19–20 June, Washington D.C., USA

The workshop was sponsored by NIH-NAID and was attended by Odile Leroy who was the chair of the session on "Natural history and clinical studies to define correlates of protection".

7th EDCTP Forum, 30 June – 2 July, Berlin, Germany

Under the theme of "The partnership journey: New horizon for better health", the forum was attended by 358 participants from 25 African countries and 18 other countries around the world. EVI was represented by Nathalie Imbault, Nicola Viebig, Odile Leroy and Stefan Jungbluth. As part of a session on MVVC, Nicola Viebig presented an overview of MVVC activities.

Parliamentary Round Table on "EDCTP & Research and Development for Poverty-Related and Neglected Diseases", 3 July, Berlin, Germany

Nathalie Imbault, Odile Leroy and Stefan Jungbluth attended this event organised by DSW. Odile Leroy gave an overview of EVI's EDCTP-funded projects to highlight the added value to Germany's research agenda and to show how PDPs collaborate with EDCTP.

Scientific Symposium of the Institut Pasteur International Network, 10–13 September, Paris, France

This three-day scientific conference attended by Nathalie Imbault was an opportunity to establish first contact with scientists based in endemic areas.

5th international influenza conference organised by the ESWI, 14–17 September, Riga, Latvia

This conference offered a useful platform to discuss the most recent advances in influenza research, control, prevention and treatment. Given EVI's recent involvement in the development of a universal flu vaccine (EDUFLUVAC), the EVI team members attending this conference benefited from meeting leading influenza scientists and discussing their work. In particular, important networking activities were initiated with other EU-funded projects on universal flu vaccines. EVI was represented by Flavia D'Alessio, Odile Leroy and Sophie Houard.

Launch of the German Network for NTDs, 22 September, Berlin, Germany

EVI was represented by Stefan Jungbluth during the official launch of the German network which was legally established in August 2014.

Challenges in Malaria Research: Core science and innovation, 22–24 September, Oxford, UK

Internationally renowned speakers presented their insights into core science and innovation in malaria research. EVI was represented by Nicola Viebig.

IABS, Human Challenge Trials in Vaccine Development: Scientific and Regulatory Issues, 29 September – 1 October, Strasbourg, France

The IABS workshop focused on human challenge trials as a tool that can help to overcome some of the hurdles inherent in vaccine development and to better understand host-pathogen interactions. Human challenge studies also face a series of scientific, ethical and regulatory issues related to their design and execution, and their use for regulatory decision-making and vaccine development. The IABS workshop brought together representatives from academia, industry, regulatory authorities and public health agencies to discuss the scientific and regulatory framework required for the safe and ethical conduct of human challenge trials. EVI was represented by Flavia D'Alessio, Odile Leroy and Sophie Houard.

4th Joint Conference of the German Society for Hygiene and Microbiology and the Association for General and Applied Microbiology, 5–8 October, Dresden, Germany

The meeting covered microbiological research and application in Germany. Leading international and national scientists presented their latest data. The scientific program brought together experts from the fields of basic science in microbiology, environmental microbiology, technical microbiology, medical sciences and diagnostics. The meeting provided an opportunity to discuss the latest research relevant to the BELLEROPHON project, which aims to develop vaccine candidates against the bacterial pathogen *Staphylococcus aureus,* and also to build networks with other researchers in the field. EVI was represented by Sophia Hundt.

Parliamentarian Evening on Innovative Research for Health in Developing Countries, 8 October, Berlin, Germany

This parliamentary evening was co-organised by EVI, DNDi, and MVI-PATH. At the event, the participating PDPs presented an overview of their current activities and their role in research and development for neglected, poverty-related diseases. EVI was represented by Stefan Jungbluth.

6th international conference on corporate sustainability and responsibility, 8–10 October, Berlin, Germany

The forum explores global themes of corporate social responsibility in its manifold dimensions. EVI was represented by Stefan Jungbluth.

Developing Countries' Vaccine Manufacturers Network Annual General Meeting 2014, 27–29 October, New Delhi, India

The theme of the DCVMN 15th annual general meeting was "Vaccines, our shared responsibility". This international event attended by Nathalie Imbault allowed EVI to initiate and strengthen contacts with vaccine producers for future collaborations, focusing on the development and GMP production of EVI's portfolio of vaccine candidates.

ASTMH 63th Annual Meeting, 2–6 November, New Orleans, USA

The ASTMH annual meeting is one of most important events of the year for those involved in tropical medicine and the event is always well attended. This year's meeting covered the usual diseases addressed by the event but also included several special conferences on the Ebola crisis in West Africa. EVI was represented by Nicola Viebig and Stefan Jungbluth.

Improving health in developing countries for those most in need – The role of product development partnerships in combatting poverty-related and neglected diseases, 5 November, Den Haag, the Netherlands

This hearing of the Standing Committee on Foreign Affairs of the Dutch Parliament provided an opportunity to learn more about poverty-related and neglected diseases and the innovations helping fight them. The PDP representatives demonstrated how their model helps to advance the development of new health tools by explaining how they address research gaps, work with partners, strengthen national capacity, manage portfolios and bring their innovative products to patients in developing countries. Clemens Kocken, Chair of EVI Board, and Odile Leroy attended this event.

Strategy meeting of the German NTD Network, 11 November, Würzburg, Germany

Members and observers of the recently launched German network discussed the development and implementation of the network's strategy. EVI was represented by Stefan Jungbluth.

Global launch of the G-Finder 2014 report, 9 December, London, UK

The latest G-Finder report was presented This is the most comprehensive report to date on public, philanthropic and industry funding for neglected diseases R&D. EVI was represented by Stefan Jungbluth.

GOVERNANCE

The year 2014 was highly productive for the EVI governing bodies, with the development of the new strategic plan.

The process of the development of the new strategic plan started in March with the selection of Mansour Yaich, an external consultant with extensive experience in vaccine development in industrial and product development partnership settings. A series of meetings with the EVI SAC and Board were held, as well as consultations (written and telephone interviews) with external international stakeholders.

EVI Scientific Advisory Committe

The EVI SAC met face to face three times:

- For the kick-off of the development of the new strategic plan on 29 April;
- For the development of the new strategy on 7 October, and;

For the annual review of the portfolio and finalisation of the executive summary of the new strategic plan on 2–3 December.

The EVI SAC also held one teleconference on 29 July for projects requiring specific attention.

At the most recent EVI SAC meeting in December, Mahamadou Thera was proposed as Chair to take over the responsibilities of Alister Craig's, who decided to relinquish his SAC membership after six years of outstanding commitment. This recommendation was approved by the EVI Board.

EVI Board

The EVI Board met twice:

- For the first of the usual bi-annual meetings to approve the annual report, the kick-off of the development of the new strategic plan, and to approve the integration of Institut Pasteur, Paris, as a full member of EVI EEIG on 30 April, and;
- For the second bi-annual meeting on 4 December, where Professor Claude Leclerc, Professor and Head of the Immune Regulation and Vaccinology Unit at the Institut Pasteur, represented Institut Pasteur for the first time, having been introduced to EVI and the responsibilities of the Board on 17 November.

The EVI Board also held two teleconferences on 10 March and 14 August for topics which required urgent attention.

EVI Board of Stakeholders

The EVI BoS met once jointly with the EVI Board on 4 December, where Marcel Tanner, Swiss TPH, Switzerland, was elected as a member of the BoS.

The FRMC held two teleconferences:

- For the approval of the internal audit report and the election of Terry McWade as chair on 3 March, and;
- For the approval of the annual financial audit report on 15 April.

EVI

Finally, on 3 December the now traditional EVI Rendez-Vous took place, for the first time at Institut Pasteur in Paris. The international experts participating in the annual review of EVI's portfolio showed keen interest in the latest progress of EVI's diverse projects.

The EVI Secretariat has put in place risk management and internal audit functions. The risk register is updated monthly and shared with the FRMC and SAC at each meeting. The

non-project-specific risks are reviewed monthly by EVI Steering Committee. The project-specific risks are reviewed bi-monthly. The third internal audit took place at the end of the year.

All EVI documentation is now stored in the document management system (Xerox DocuShare®) where it can be accessed by the internal auditor and the financial auditors.

Participants at EVI SAC, BoS and Board face to face meetings

EVI-EEIG Board and BoS meetings

3 April, RCSI, Dublin

EEIG Board:

Carla Hoitink, Intravacc, the Netherlands

Clemens Kocken (chair), BPRC, the Netherlands

David Salisbury, Jenner Vaccine Foundation, UK

Marita Troye-Blomberg (vice-chair), Stockholm University, Sweden

Ruairi Brugha, RCSI, Republic of Ireland

Terry McWade (chair of FRMC), Jadhav, Republic of Ireland

Diarmuid O'Donovan (vice-chair of BoS), Irish Health Service Executive, representing Irish Aid, Republic of Ireland

Sam McConkey (SAC, non-voting member), RCSI, Republic of Ireland

From EVI: Odile Leroy, Sten Larsen, Jill Iversen, Nathalie Imbault (Secretary of EVI Board and BoS), and Mansour Yaich (External Consultant Vaxyn)

4 December, Institut Pasteur, Paris, combined with a BoS Meeting

EEIG Board:

Claude Leclerc, Institut Pasteur, France

Clemens Kocken (chair), David Salisbury, Marita Troye-Blomberg (vice-chair), Ruairi Brugha, Alister Craig (chair of EVI SAC)

BoS:

Charles de Taisne, Sanofi Pasteur, France

Lorraine Gallagher, Irish Aid, Republic of Ireland

Sodiomon Bienvenu Sirima (chair), CNRFP, Burkina Faso

Suresh Jadhav, SII, India

From EVI: Odile Leroy, Sten Larsen, Jill Iversen, Nathalie Imbault (Secretary of EVI Board and BoS) and Mansour Yaich (External Consultant Vaxyn)

EVI SAC

29 April, RCSI, Dublin

Alister Craig (chair), Liverpool School of Tropical Medicine, UK

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

Ingileif Jonsdottir (vice-Chair), Landspitali University Hospital, Iceland

James Robertson (vice-chair), Consultant, UK

Michael Lanzer, Heidelberg University, Germany

Samuel McConkey, RCSI, Republic of Ireland

EVI Secretariat and Mansour Yaich (External Consultant Vaxyn)

7 October, Sheraton Paris Airport Hotel & Conference Centre

Aissatou Touré, Institut Pasteur de Dakar, Senegal

Guiseppe Del Guidice, James Robertson, Samuel McConkey

Mahamadou Thera, University of Bamako, Mali

2–3 December, Institut Pasteur, Paris,

Aissatou Touré, Alister Craig (chair), Guiseppe Del Guidice, Ingileif Jonsdottir (vice-chair), James Robertson (vice-chair), Mahamadou Thera, Samuel McConkey.

EVI Secretariat and Mansour Yaich (external consultant Vaxyn)

FUNDRAISING

In 2014, EVI together with other partner organisations received funds that allowed the continuation of ongoing projects and successfully mobilised new funds which enabled the launch of one new project relating to vaccine development: SEmalvac. A total of €684,619 was raised in 2014.

In addition to EVI, the consortium of the SEmalvac project includes the RIMD at Osaka University, Japan, and the CNRFP, Burkina Faso. SEmalvac will clinically test a novel malaria vaccine candidate (BK-SE36) primarily in young children, who account for most malaria deaths. The project builds on the promising results of a previous clinical trial and aims to generate more safety and efficacy data. The partners will also conduct a follow-up study on Japanese men who have previously been immunised with the vaccine containing a different adjuvant.

ROADMAPS

Malaria Vaccine Technology Roadmap

MVFG published the updated MVTR[25] in November 2013 to highlight recent changes in malaria epidemiology, based on the reduction in transmission rates achieved thanks to more effective control measures. The updated strategy of the roadmap aims to develop vaccines with a protective efficacy of at least 75% against both *Plasmodium falciparum* and *Plasmodium vivax*, and transmission-blocking vaccines with substantial efficacy. The newly developed vaccines should be available to the international public health community by 2030.

Following the launch of the MVTR, EVI hosted a workshop "Malaria vaccine development in Europe – preparing for the future" on 20–21 November 2014 in Brussels, Belgium. The workshop brought together experts from the European, North American and African malaria vaccine communities to set out key strategic activities for the coming years, and to integrate European vaccine development with global activities in the context of the updated MVTR.

The workshop addressed four major topics:

- Innovation and discovery, correlates and surrogates of protection;
- Combination vaccines;
- Clinical aspects of development and CHMI;
- Capacity building in GMP manufacturing and clinical trial infrastructure.

Major conclusions:

Effective malaria vaccines are indispensable tools alongside other methods for prevention, diagnosis and treatment, if the ambitious aims of the global malaria community are to be achieved: the prevention of malaria disease and deaths by progressive malaria elimination and ultimately malaria eradication worldwide. The development of the RTS,S vaccine, which is likely to be licensed in 2015, and encouraging results from recent phase I and II clinical trials of other vaccine candidates, have provided proof of concept, demonstrating that the development of malaria vaccines is technically feasible. The malaria community is now moving towards multi-antigen, multi-stage vaccine candidates comprising several antigen components targeting the different life cycle stages of the *Plasmodium* parasite. This approach is expected to give better protection. However, the development of next generation malaria vaccines with high efficacy will require continuous collaboration and integration within the global malaria community, together with sustained political and financial support and commitment from policy makers and funding organisations supporting global health R&D.

The major recommendations and outcomes for each of these four areas, which should guide the European malaria research community in fulfilling the MVTR, will be summarised in a future publication.

[25] http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1

Table 1: Statement of financial position as of 31 December 2014

	Notes	EUR 2014	EUR 2013
Current assets			
Cash and cash equivalents:			
Cash and banks - key accounts		1,830,384.37	6,235,688.64
Time deposits		4,000,000.00	0.00
Total cash and cash equivalents		**5,830,384.37**	**6,235,688.64**
Current accounts and receivables:			
Other receivables		29,627.05	5,784.83
Prepaid expenses		9,451.17	13,554.48
Total current accounts and receivables		**39,078.22**	**19,339.31**
Total current assets		**5,869,462.59**	**6,255,027.95**
Non-current assets			
Tangible fixed assets, net	**2**	26,184.85	32,899.03
Total non-current assets		**26,184.85**	**32,899.03**
Total assets		**5,895,647.44**	**6,287,926.98**
Current liabilities			
Creditors	**3**	660,101.24	501,031.63
Accrued expenses	**4**	1,023,423.23	537,163.27
Provisions	**5**	29,454.55	34,202.91
Deferred income	**6**	2,770,271.39	4,089,642.25
Total current liabilities		**4,483,250.41**	**5,162,040.06**
Equity of organisation			
Unrestricted operating funds		1,412,397.03	1,125,886.92
Total equity of the organisation		**1,412,397.03**	**1,125,886.92**
Total equity and liabilities		**5,895,647.44**	**6,287,926.98**

Table 2: Statement of comprehensive income for the year as of 31 December 2014

	Notes	EUR 2014	EUR 2013
Income	7		
Turnover from sales		35,522.95	250.00
Public institutional funding:	7		
Governmental & public international organisations		3,119,175.65	2,569,910.37
European Union		1,457,325.00	4,431,970.11
European and Developing Countries Clinical Trial Partnership (EDCTP)		411,461.52	2,203,000.49
Total public institutional funding	7	**4,987,962.17**	**9,204,880.97**
Other income net		(74,446.94)	492,143.45
Total income		**4,949,038.18**	**9,697,274.42**
Social mission expenditure			
Research & vaccine development expenditure:	8		
EVI vaccine development projects		1,905,722.94	1,864,726.53
EU-funded research and vaccine development projects		1,457,063.89	4,430,385.95
EDCTP-funded research and vaccine development projects		411,461.52	2,203,000.49
Advocacy & communications expenses		205,857.66	192,180.11
Total social mission expenditure		**3,980,106.01**	**8,690,293.08**
Supportive social mission expenditure	8		
Training, quality assurance and project development		59,292.85	60,282.23
Fundraising		114,802.27	170,657.54
Governance		191,965.08	64,441.02
Total supportive social mission expenditure		**366,060.20**	**295,380.79**
Non-social mission expenditure	8		
General executive administration		329,058.37	344,875.76
Total non-social mission expenditure		329,058.37	344,875.76
Total expenditure		**4,675,224.58**	**9,330,549.63**
Operating surplus / (loss)		273,813.60	366,724.79
Other income (expenses)			
Financial income, net	7	12,696.51	11,850.08
Total other income (expenses), net		**12,696.51**	**11,850.08**
Net surplus for the year prior to allocations		286,510.11	378,574.87
Allocation / (release) to restricted operating funds in equity		0.00	0.00
Allocation / (release) to unrestricted operating funds in equity		286,510.11	378,574.87
Net surplus for the year after allocations		**0.00**	**0.00**

Table 3: Funds flow statement

For the year ended 31 December 2014 (with 2013 comparative figures)

Funds flow from operations	EUR 2014	EUR 2013
Net surplus for the year	286,510.11	378,574.87
Depreciation of fixed assets	14,599.04	17,700.34
Increase (decrease) in provisions	(4,748.36)	(29,031.07)
(Increase) Decrease in other receivables	(23,842.22)	9,035.47
(Increase) Decrease in prepaid expenses	4,103.31	12,560.19
Increase (decrease) in creditors	159,069.61	160,235.62
Increase (decrease) in accrued expenses	486,259.96	256,548.22
Increase (decrease) in deferred income	(1,319,370.86)	1,328,869.19
Funds flow from operations	**(397,419.41)**	**2,134,492.83**

Funds flow from investing activities	EUR 2014	EUR 2013
(Increase) Decrease of investments in tangible fixed assets	(7,884.86)	(5,650.39)
Funds flow from investing activities	**(7,884.86)**	**(5,650.39)**

Funds flow from financing activities	EUR 2014	EUR 2013
Cash increase (decrease)	(405,304.27)	2,128,842.44
Cash and cash equivalents – beginning of year	6,235,688.64	4,106,846.20
Cash and cash equivalents – end of year	**5,830,384.37**	**6,235,688.64**

Statement of changes in equity for the year ended 31 December 2014 (EUR)

Internally generated funds as of 31 December 2013	Opening balance	Allocation	Internal fund transfers	Closing balance
Paid-in capital	0.00	-	-	0.00
Surplus for the year	0.00	378,574.87	(378,574.87)	0.00
Restricted operating funds	0.00	-	0.00	0.00
Unrestricted operating funds	747,312.05	-	378,574.87	1,125,886.92
Capital of the organisation	**747,312.05**	**378,574.87**	**0.00**	**1,125,886.92**
Internally generated funds as of 31 December 2014				
Paid-in capital	0.00	-	-	0.00
Surplus for the year	0.00	286,510.11	(286,510.11)	0.00
Restricted operating funds	0.00	-	0.00	0.00
Unrestricted operating funds	1,125,886.92	-	286,510.11	1,412,397.03
Capital of the organisation	**1,125,886.92**	**286,510.11**	**0.00**	**1,412,397.03**

NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR 2014

Note 1 - Significant Accounting Policies

(a) General comment

EVI fully complies with the demands of German General Accepted Accounting Principles (GAAP) and continuously empowers its staff working on projects to participate in budget control and the control of spending. For an organization of its size, EVI does much more controlling than legally required to meet the highest standards. EVI operates an extensive continuous internal control system of financial management to meet the highest standards for public fund management. EVI diversifies its financial tasks and, despite its relatively small Secretariat, ensures the extensive and detailed control of all transactions by staff in the Finance Unit, the Executive Director and the empowered project leaders. EVI carefully monitors its liquidity and plans its fundraising to meet liquidity targets years in advance as part of risk management. EVI has established 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 employees. EVI accounting method is accrual based, with consideration for projects governed by external guidelines.

The financial presentation in this report is based on the International Financial Reporting Standard (IFRS) as endorsed by the EU and is prepared in addition to the German General Accepted Accounting Principles (GAAP) & the German commercial code - Handelsgesetzbuch (HGB) statements which is the legal basis of the operation of the European Vaccine Initiative – EEIG.

The financial statements prepared in accordance with IFRS as endorsed by the EU include:

a) Statement of Financial Position

b) Statement of Comprehensive Income (activity based method)

c) Funds flow statement

d) Statement of changes in Equity

e) Notes and additional performance report.

Negative amounts are shown within brackets as required by standard.

(c) Funding parties

EVI is currently funded by Governmental agencies (Irish Aid, GHIT, BMBF) and the EU 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 want to support a good cause that combats 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 to the Profit and Loss (PNL), and - if eligible – are offset by corresponding amounts of income released from the deferred income. Only income generated from sales or other economic activity is directly recognised as income in the PNL.

(e) Payables

All amounts payable by EVI are charged to the PNL in the cost-relevant year on the basis of accrual based accounting. Payables are identified, evaluated and approved by the relevant project leaders for proof of deliverables and milestones. The Finance Unit then post them accordingly to the respective accounts.

(f) Social mission expenditure

Social mission expenditures are expenses made in accordance with the purposes defined in EVI Mission and Vision.

(g) Investment income and interest receivable

Interests received on EVI funds are included in the PNL in the year for which it is receivable.

(h) Primary and secondary commerce

EVI's primary focus is to develop vaccines that combat diseases of poverty. As a secondary commerce, EVI may sell services and products in the form of lecturing, workshops and debates where needed as well as utilising to the full extent any surplus of product available.

(i) 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 EU/EDCTP and other similar projects

(j) Time recording

EVI operates, on a 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 employees, which are segmented in defined dimensions in detail, and are posted to the accounting system as such.

(k) 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 their areas 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.

The annual work plan and budget are approved by the EVI-EEIG Board. They include funding for projects subcontracted to partners and current expenditures required to achieve the objectives for the year. Budget revisions are approved by the EVI-EEIG Board on an ad-hoc basis. All expenditures incurred on behalf of a project or for any EVI activity are recorded on an accrual basis.

(l) Tangible fixed assets

Tangible fixed assets are presented as the acquisition cost less accumulated depreciation. Depreciation is charged to the statement of operations on a straight-line basis over the estimated useful lives of the tangible fixed assets.

The rates of depreciation are based on the following estimated useful lives:

- Office fittings and equipment: four years
- IT equipment: four years

(m) Credit risk, cash-flow management

EVI's liquid assets are maintained in low-risk short- term deposits. At the balance sheet date, there are no significant concentrations of credit risk. The maximum exposure is primarily represented by the carrying amounts of the financial assets in the balance sheet, including accounts receivable and cash

(n) Provisions

A provision is recognised on the balance sheet when the organisation has a legal or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.

Provisions are measured according to the management's best estimates of the expenditure required to settle that obligation on the balance sheet date.

(o) Equity

Funds held by EVI as equity:

Equity are utilised as a strategic reserve for research and development for the organisation. EVI does not pay out any dividends or similar benefits to its shareholders as stipulated by the statutes of the organisation.

(p) Foreign currencies

Transactions in foreign currencies are translated into euro at rates prevailing on the date of the transaction using xe.com, with the exception of Danish Kroner which is politically fixed at an exchange rate of 7.45. EVI has, for the year 2014, made use of the following currencies: EUR, DKK, INR, USD, GBP and XOF.

(q) Financial Auditors

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

The auditor issues an annual 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 an 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 made public. The opinion is shown in German and an English translation is prepared by the auditor.

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

Note - 2 Tangible fixed assets (EUR)	
Net carrying amounts 31/12/2013	
Beginning of the period 01/01/2013	44,948.98
Additions	5,650.39
Disposals	0.00
End of the period 31/12/2013	50,599.37
Depreciation / amortisation 2013	17,700.34
End of the period 31/12/2013	**32,899.03**
Net carrying amount 31/12/2014	
Beginning of the period 01/01/2014	32,899.03
Additions	8,020.79
Disposals	0.00
End of the period 31/12/2014	40,919.82
Accrued amortisation 2014	135.93
Depreciation / amortisation 2014	14,599.04
End of the period 31/12/2014	**26,184.85**

Note - 3 Creditors	EUR 2014	EUR 2013
Creditors for grant linked payments	607,156.13	484,419.72
Other creditors	52,945.11	16,611.91
Total	**660,101.24**	**501,031.63**

Note - 4 Accrued expenses	EUR 2014	EUR 2013
Accrued paid leave	101,016.61	81,420.99
Accrued payables (grants linked)	812,750.50	72,163.00
Accrued direct costs	22,513.96	38,154.39
Accrued indirect costs	65,504.08	345,288.39
Accrued other expenses	21,638.08	0.00
Total	**1,023,423.23**	**537,026.77**

Note - 5 Provisions (EUR)

Carrying period as per 31/12/2013	
Tax provisions	20,431.10
Social charges provisions	918.32
Other provisions	12,853.49
Total provisions 31/12/2013	**34,202.91**
Carrying period as per 31/12/2014	
Tax provisions	19,149.35
Social charges provisions	6,463.70
Other provisions	3,841.50
Total provisions 31/12/2014	**29,454.55**

Note - 6 Deferred income (EUR)

Cumulative donations committed to EVI as of 31 December 2014 and current deferred income

Donors	Contract currency	Total commitment in currency	Total commitment in euro	Income as per statement of operations	Costs as per statement of operations	**Remains as deferred income**
Irish Aid - IE	EUR	5,000,000.00	5,000,000.00	1,000,000.00	1,510,111.88	**(964,478.86)**
BMBF/KfW - DE	EUR	4,512,025.00	4,512,025.00	1,149,734.00	1,474,880.98	**237,588.99**
GHIT - JP	JPY	7,999,995.00	684,619.00	425,786.93	133,899.24	**291,887.69**
European Union - FP7	EUR	16,229,077.00	20,729,077.00	937,616.76	1,457,325.00	**174,008.03**
European Development Clinical Trial Partnership	EUR	9,137,281.00	9,137,281.00	92,576.97	411,461.52	**(352,969.74)**
EVI reserve funds	EUR	3,321,642.18	3,321,642.18	319,326.19	256,773.09	**3,384,195.28**
Total donations			**43,384,644.18**	**3,925,040.85**	**5,244,451.71**	**2,770,231.39**

Note - 7 Income / realised (EUR)

Funding used per project (restricted and unrestricted)

	Irish Aid	BMBF	GHIT	EU	EDCTP
EVI vaccine development projects	389,735.36	1,323,677.59	132,206.24	0.00	0.00
Supportive EVI development costs	519,539.44	0.00	0.00	0.00	0.00
EU research and development projects	0.00	0.00	0.00	1,457,325.00	0.00
Supportive EU development costs	39,764.86	0.00	0.00	0.00	0.00
EDCTP research and development projects	0.00	60,103.75	0.00	0.00	411,461.52
Supportive EDCTP development costs	7,054.16	0.00	0.00	0.00	0.00
Executive administration	554,018.06	91,099.64	1,693.00	0.00	0.00
Internal allocations	0.00	0.00	0.00	0.00	0.00
Total income	**1,510,111.88**	**1,474,880.98**	**133,899.24**	**1,457,325.00**	**411,461.52**

	Utilisation of reserve funds	Total income pr. activity	Unused overheads and interest	Total income
EVI vaccine development projects	0.00	1,845,619.19	0.00	1,845,619.19
Supportive EVI development costs	5,559.40	525,098.84	0.00	525,098.84
EU research and development projects	0.00	1,457,325.00	0.00	1,457,325.00
Supportive EU development costs	0.00	39,764.86	0.00	39,764.86
EDCTP research and development projects	0.00	471,565.27	0.00	471,565.27
Supportive EDCTP development costs	0.00	7,054.16	0.00	7,054.16
Executive administration	(318,013.44)	328,797.26	0.00	328,797.26
Internal allocations	0.00	0.00	286,510.11	286,510.11
Total income	**(312,454.04)**	**4,675,224.58**	**286,510.11**	**4,961,734.69**

Note - 8 Social & non-social mission expenditure	Notes	EUR 2014	EUR 2013
EVI vaccine development projects			
P27A	(a)	283,442.26	317,947.01
AMA1-DiCo	(a)	87,286.35	177,318.16
ADJUVANT	(a)	0.00	5.29
JAIVAC	(a)	0.00	1,645.75
CSVAC	(a)	0.00	56,942.43
PAMCPH	(a)	479,988.29	376,034.09
PRIMALVAC	(a)	843,689.30	375,867.36
SPOROVAC	(a)	7,047.82	64,822.99
InnoMalVac	(a)	5,818.00	152,911.64
PIM	(a)	6,140.93	295,660.77
Leishmaniasis	(a)	0.00	31,130.44
SEmalvac	(a)	132,206.24	0.00
Supportive vaccine development costs	(a)	525,098.84	393,938.63
Total EVI vaccine development projects		2,370,718.03	2,244,224.56
EU-funded research and development projects			
MultiMalVax		62,172.33	49,718.90
EMVDA		0	(19,153.04)
TRANSVAC		763,333.09	2,834,327.93
IDEA		59,746.67	44,641.09
PlacMalVac		103,225.50	96,663.12
BELLEROPHON		117,990.97	44,077.16
EDUFLUVAC		292,216.47	1,379,972.81
IPROVE		58,378.86	137.98
INYVAX		0.00	0.00
OPTIMALVAC		0.00	0.00
Supportive project development costs		39,764.86	58,475.63
Total EU-funded research and development projects		1,496,828.75	4,488,861.58
EDCTP-funded research and development projects			
MVVC		129,921.02	1,400,293.09
P27A-EDCTP		139,280.05	36,028.31
MVVC 2		142,260.45	765,252.39
BMBF-EDCTP		60,103.75	14,440.60
eICT - EDCTP		0.00	1,426.70
Supportive project development costs		7,054.16	35,146.64

Note - 8 Social & non-social mission expenditure	Notes	EUR 2014	EUR 2013
Total EDCTP-funded research and development projects		478,619.43	2,252,587.73
Executive administration			
Executive administrative management costs		329,058.37	344,875.76
Total executive administration		329,058.37	344,875.76
Total of all project-related expenditure	**(b)**	**4,675,224.58**	**9,330,549.63**

(a) Breakdown of research and development coordination expenditure per activity	EUR 2014	EUR 2013
1 - Project development	409,965.43	303,435.11
2 - Process development	35,002.68	450,726.52
3 – Production	795,811.88	450,989.38
4 - Clinical trials	748,577.99	772,334.70
5 - Other support services	41,039.01	27,977.77
6 - International collaboration	289,348.63	185,561.04
7 - Quality Assurance	50,972.41	53,200.04
TOTAL	**2,370,718.03**	**2,244,224.56**

(b) Presentation of EVI expenditures per nature of expenses	EUR 2014	EUR 2013
6010 Payables - EVI program related	1,691,666.82	1,593,496.67
6060 Payables - EDCTP program related	122,973.72	1,956,371.41
6070 Payables - EU program related	854,921.62	3,516,072.82
7099 Salary costs (also includes in house consultants)	1,199,423.13	1,253,829.87
7100 Contract service expenses	117,861.74	144,569.21
7200 Facility & equipment maintenance expenses:	70,085.69	53,188.86
7300 Equipment, hardware & software	15,179.99	20,035.99
7400 Travel & meetings expenses:	296,961.45	322,390.63
7500 Other direct expenses:	34,774.34	56,590.92
8000 Indirect business expenses:	248,256.72	400,399.74
9000 Board, BoS and SAC expenses:	18,764.24	8,820.78
9100 EU ESAC, SAC and SC expenses:	4,355.12	4,782.73
9299 Total expenses	**4,675,224.58**	**9,330,549.63**

INDEPENDENT AUDITOR'S REPORT

To: European Vaccine Initiative EEIG, Heidelberg

We have reviewed the accompanying Statement of Financial Position, the Statement of Comprehensive Income, the Funds Flow Statement and the Statement of Changes in Equity as well as certain Notes to the Financial Presentation, (together "the Financial Presentation") of European Vaccine Initiative EEIG as at December 31, 2014.

Management's Responsibility for the Financial Presentation

Management is generally responsible for the preparation and fair presentation of German GAAP financial statements. In addition to German GAAP, management chose to prepare this Financial Presentation in accordance with IFRS as endorsed by the EU and as such remains also responsible for the preparation and fair presentation of this IFRS Financial Presentation and for such internal control as management determines is necessary to enable the preparation of the financial presentation that is free from material misstatement, whether due to fraud or error.

Auditor's Responsibility

Our responsibility is to express an opinion on the German GAAP financial statement based on our audit. We conducted our audit in accordance with International Standards on Auditing. Those standards require that we comply with ethical requirements and plan and perform the audit to obtain reasonable assurance about whether the financial statement is free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statement. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statement, whether due to fraud or error. In making those risk assessments, the auditor considers internal control relevant to the entity's preparation and fair presentation of the financial statement in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates, if any, made by management, as well as evaluating the overall presentation of the financial statement.

We have issued a separate audit opinion on the German GAAP financial statements as at December 31, 2014 of European Vaccine Initiative EEIG, Heidelberg dated March 31, 2015.

Our audit engagement also included the review of the accompanying Financial Presentation in accordance with IFRS as endorsed by the EU.

We believe that the evidence we have obtained in connection with the review of the accompanying Financial Presentation in accordance with IFRS as endorsed by the EU is sufficient and appropriate to provide a basis for our opinion.

Opinion

In our opinion, the Financial Presentation presents fairly, in all material respects, the financial position of European Vaccine Initiative EEIG as at December 31, 2014 in accordance with IFRS as endorsed by the EU relevant to preparing such Financial Presentation.

FALK GmbH & Co KG
Wirtschaftsprüfungsgesellschaft
Steuerberatungsgesellschaft

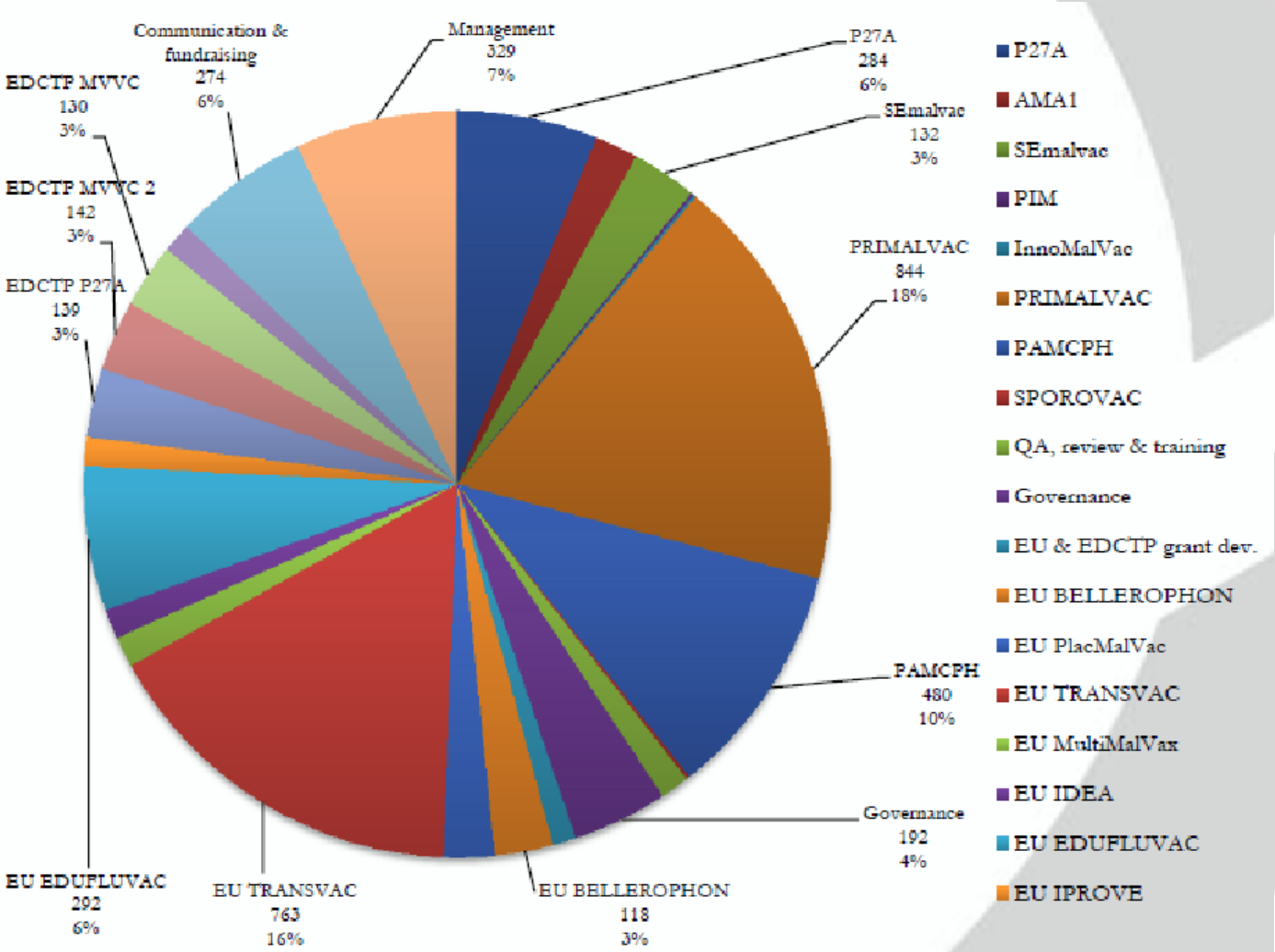
(Meyer)	(Ahrens)
Wirtschaftsprüfer Steuerberater	Wirtschaftsprüfer Steuerberater CPA (IL USA)

FINANCIAL PERFORMANCE REPORT

The year 2014 was again a very exciting year for EVI. We have achieved promising results in our vaccine development projects, which have progressed through vaccine production towards clinical trials. The EU/EDCTP projects have efficiently met their targets for substantial deliverables and milestones, and the EVI-coordinated project EDUFLUVAC has successfully completed its first financial reporting task. The EVI Secretariat has, in the current reporting period, once again shown a conscientiousness level of achievement in all areas of EVI activities and has efficiently coped with a heavy workload that confirms the need for and relevance of EVI. EVI is as always indebted to its grant providers for their strong support, and the EVI Secretariat would like to extend heartfelt thanks to Irish Aid, BMBF, GHIT, EDCTP and the EU for their invaluable encouragement.

Error! Reference source not found. shows EVI's cost activity over the current reporting period, during which expenditure covering the broad portfolio of EVI, EDCTP and EU projects has produced major achievements given the level of funding. The financial conclusion of the current reporting period is that the performance of EVI has been continuously resilient, and that funds are properly utilised to accelerate the development of vaccines against diseases of poverty.

Figure 1: Total EVI activity 2014 (€'000 and in %)



The key ratios presented in Table 4 reflect EVI's 2014 operations.

Table 4: Key ratios

Management percentage			
Year	Upper threshold	Result	Direct investment percentage of each euro donated
2012	7%	2.2%	98%
2013	7%	3.7%	96%
2014	7%	7.0%	93%

For each euro donated to EVI in 2014, 93 cents on average was directly invested into the development of vaccines against poverty-related diseases.

Table 5: Quick ratios

Indicators	Ratios results	
	Figure	Qualification
Quick ratio (liquidity)	3.42	Good
Gross operating profit ratio (financial autonomy)	0.00	Good
Profitability	8.12	Good
Solvency	3.17	Good
Indicators	**Noteworthy value results**	
	Figure	**Qualification**
Equity flag	3.17	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 EU

The key indicators provided in Table 6 reflect EVI's 2014 operations.

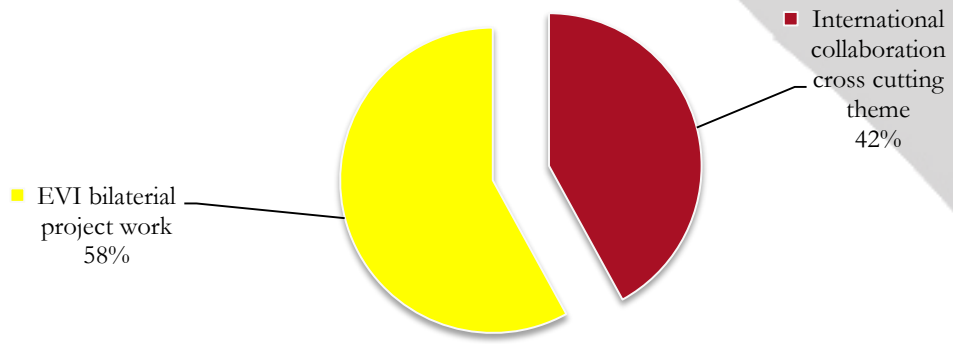
Table 6: Key financial indicators

Annual growth margin	$\frac{\text{Current period} - \text{Previous period}}{\text{Previous period}}$	(49)%
Annual OPEX (operating expenses)	$\frac{\text{OPEX for the period}}{\text{Net Revenue for the period}}$	70%
Working capital as percentage of revenue	$\frac{\text{Total Current Assets} - \text{Total Current Liabilities}}{\text{Net Revenue for the quarter} \times 4}$	481%
Return on assets	$\frac{\text{Net Income for the quarter} \times 4}{(\text{Beginning-of-quarter Total assets} + \text{End-of-quarter Total Assets})/2}$	5%
Return on equity	$\frac{\text{Net Income for the quarter} \times 4}{(\text{Beginning-of quarter Total S/E} + \text{End-of-quarter S/E})/2}$	23%

International collaboration

In 2014, 42% of EVI's activities were direct international collaborations with partners and stakeholders from Europe, Africa, Asia and North America, whereas 58% represented bilateral work, which by its nature also counts as international collaboration (see Figure 2).

Figure 2: International collaborations (in %)



EVI project activities

Over the past year, the activity of the EVI vaccine portfolio has increased, especially the pregnancy associated malaria vaccine development projects (PAMCPH and PRIMALVAC).

Figure 3: EVI portfolio investment (€'000 and in %)

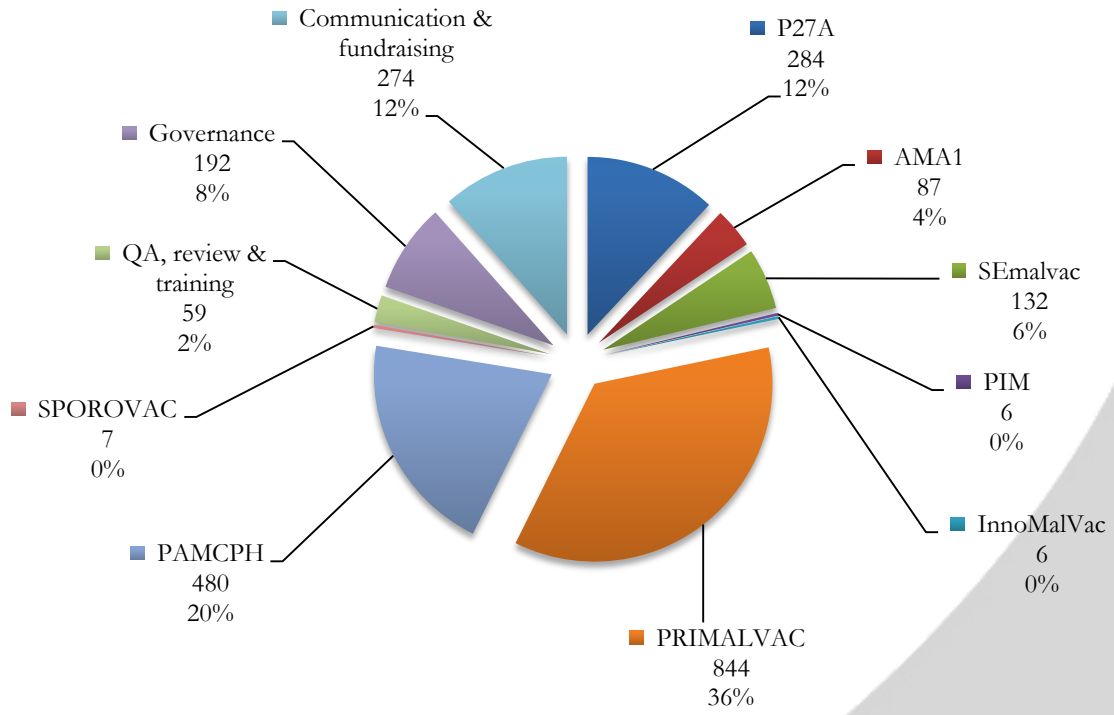
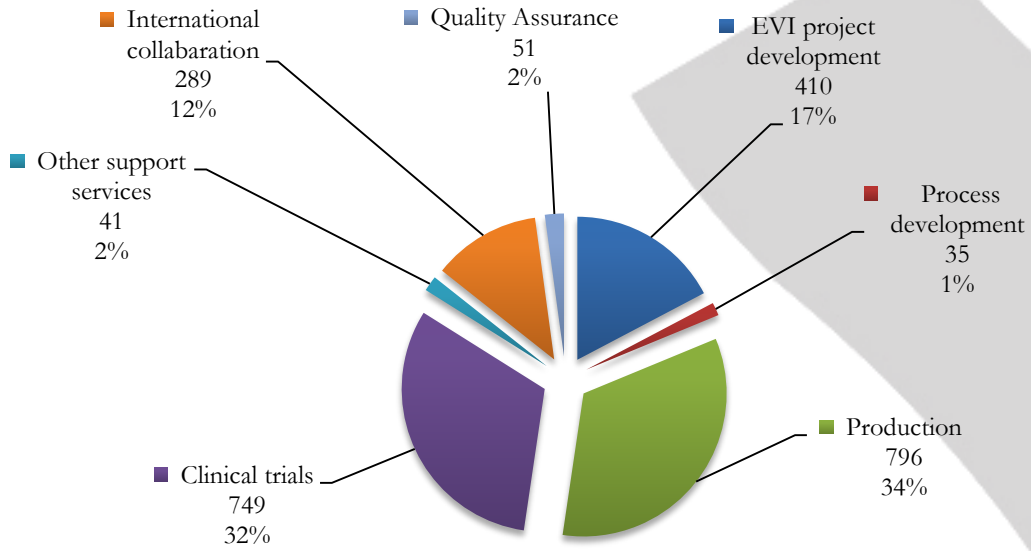


Figure 4: Portfolio investment type (€'000 and in %)Figure 4 shows that investment in 2014 was dominated by GMP production and clinical trials (up to 66%). Investment over the next year will continue to be dominated by clinical trials, especially for the placental malaria vaccine development projects (PAMCPH and PRIMALVAC) but also for the clinical development of P27A and AMA1-DiCo.

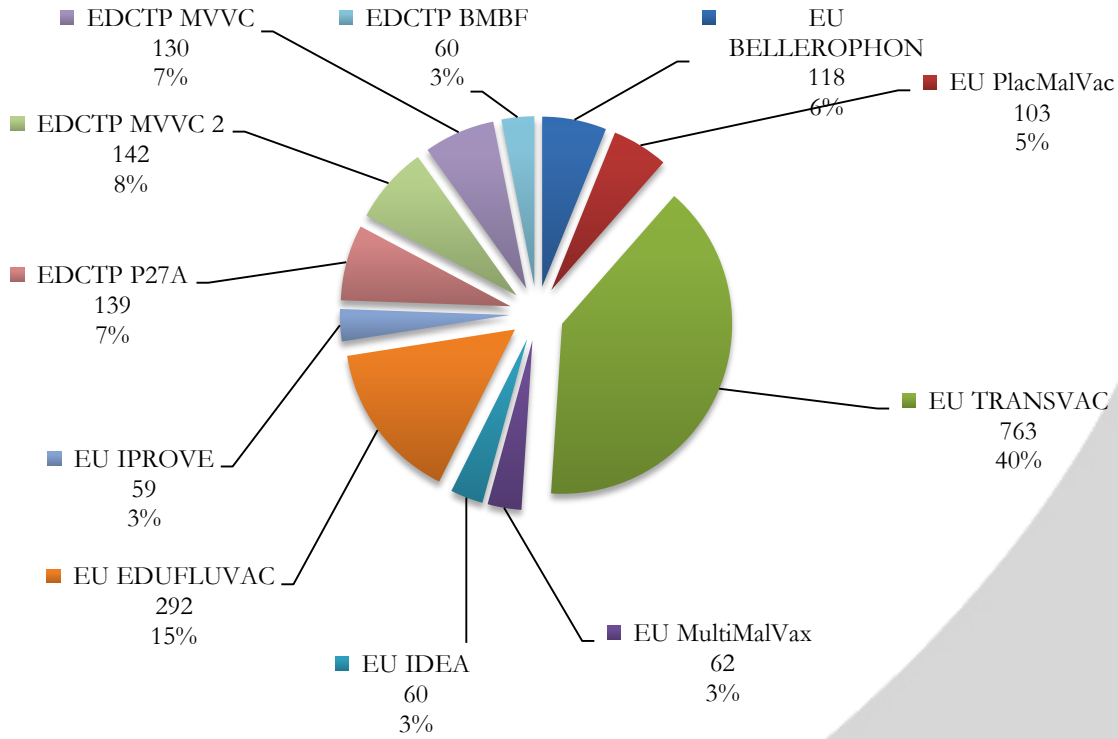
Figure 4: Portfolio investment type (€'000 and in %)



EVI, EU and EDCTP activities

In addition to the EVI portfolio of specific investments in vaccine development projects, EVI is also involved in several EU and EDCTP funded projects. Figure 5 shows the expenditure on all these projects.

Figure 5: EU and EDCTP activity (€'000 and in %)

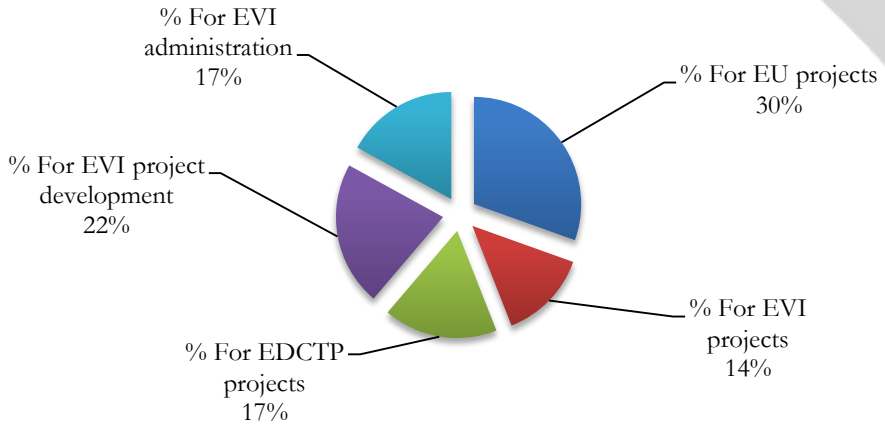


Personnel hours in the current reporting period

In 2014, EVI managed to maintain its pace on the EU and EDCTP projects as reflected in Figure 6. Although staff spent 17% of their time on administration, overall management expenditure only accounted for 7% of EVI's global expenditure.

By the end of 2014, most personnel were based at the EVI headquarters in Heidelberg, Germany, and only three staff members were sited outside of Germany, two of whom worked at the registered office in Denmark and one in Belgium.

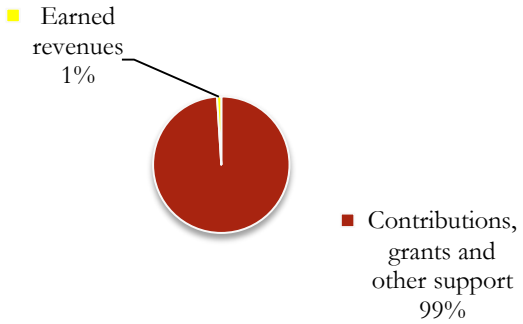
Figure 6: Personnel hours – percentages dedicated to different activities



Income and expenditure composition

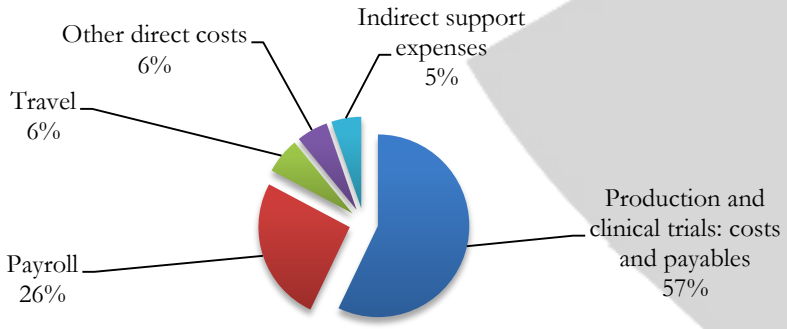
EVI's income consists almost entirely of public funding from the EU, EU Member State government grants, GHIT and EDCTP, with only 1% from other sources in 2014.

Figure 7: Income - percentages from different sources



The major components of EVI's costs continue to reflect the outsourcing of production, clinical trials and other grant payments. Secondary costs include payroll costs, which are strongly linked to the EU and EDCTP projects, and of course EVI core vaccine projects.

Figure 8: Expenditure – percentage dedicated to different activities



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

Table 7: Financial audits

Completed by FALK & Co	
BMBF grant financial audit 2013	Successful, no qualifications
EDCTP project financial audit 2009-2014	Successful, no qualifications
EVI organisational audit 2013	Successful, no qualifications
Continued internal control by Prentis & Co.	
Internal control	Successful, no qualifications

Table 8: Donations and grants received (EUR)

BMBF / KfW	1,108,006
BMBF / EDCTP	41,728
EU IDEA	32,952
EU IPROVE	42,937
EU TRANSVAC	850,356
EDCTP MVVC	65,386
EDCTP P27A	26,993
Irish Aid	1,000,000
GHIT	425,787

Table 9: Interest earned (EUR)

Interest Danish accounts	84
Interest German accounts	12,613
Total	12,697

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

Table 10: Personnel as of 31 December 2014

First Name	Last Name	Title/Function in EVI	Location
Odile	Leroy	Executive director	Germany
Nathalie	Imbault	Quality assurance, external relations and communication, director	Germany
Roland	Kleine	Office clerk	Germany
Thorsten	Kohaut	Finance manager	Germany
Nicola	Viebig	Project manager	Germany
Sophia	Hundt	Project manager	Germany
Sandra	Hauenstein	Accounting assistant	Germany
Stefan	Jungbluth	Business unit leader	Germany
Nicolas	Havelange	Production, director*	Belgium
Sophie	Houard	Vaccine development leader	Belgium
Flavia	D'Alessio	Project manager	Germany
Sten	Larsen	Finance and human resource, director	Denmark
Jill	Iversen	Webmaster*	Denmark
Regitze Louise	Thoegersen	Program manager	Denmark
Harry	Van Schooten	Public health and business development advisor*	The Netherlands

*Consultant

Male	6	
Female	9	
Total Staff of EVI 31 December 2014	**15**	**(11.62 FTE)**

Table 11: Income and expenses (EUR)

Income realised	
Contributions, grants and other support	
Revenue from indirect contributions	(74,446.94)
National government agency grants	3,119,175.65
EU grants	1,457,325.00
EDCTP grants	411,461.52
Total contributions, grants and other support	**4,987,962.17**
Earned revenues	
Interest on savings/short-term investments	12,696.51
Non-inventory sales – gross	35,522.95
Total earned revenues	**48,219.46**
Total income realised	**4,961,734.69**
Direct and indirect project expenditure **	
Grants, contracts and direct assistance	
Contracts - program-related	1,691,666.82
Benefits paid to or for MVVC consortium members	122,973.72
Benefits paid to or for EU consortium members	854,921.62
Total payables	**2,669,562.16**
Salaries and wage expenses	
Salaries and wages, international staff	195,378.17
Salaries and wages, German staff	399,841.21
Social maternity refunds	(768.32)
Payroll taxes, etc.	247,878.80
In-house consultancies	67,711.36
Temporary employees by the hour	27,971.54
Statutory social security expenses	231,756.25
Contributions to health and safety agency	5,878.68
Voluntary social benefits not subject to wage tax	3,187.82
Employee benefit expenses	992.00
Holiday pay accrued	19,595.62
Total salary cost	**1,199,423.13**
Contract service expenses	
Accounting fees	51,601.30
Legal fees	2,254.53
Professional fees - other	64,005.91
Facility and equipment maintenance expenses	
External computer services	1,688.92
Software licenses	9,806.56
Software licenses – SUB*	918.00
Repairs and maintenance	38,344.54
Publishing costs including copying and printing	16,660.58

Publishing costs including copying and printing – SUB*	1,458.00
Books, subscriptions, references	1,209.09
Equipment, hardware and software	
Minor hardware purchases	415.43
Minor software purchases	39.99
Minor furniture, fixed equipment, vehicle parts	125.53
Depreciation and amortisation	14,599.04
Travel and meetings expenses	
Travel (flights)	90,349.21
Travel (train, ferry, taxi, others)	37,808.72
EU travel (train, ferry, taxi, others)	166.63
Travel (refund for use of own travel means)	1,541.99
Hotel and other accommodation costs	73,411.12
Conferences, conventions, meetings	16,143.06
EU conferences, conventions, meetings	8,136.13
EDCTP conferences, conventions, meetings	25,456.04
Travel allowances for employees	17,764.14
Restaurants, catering and other travel provisions	11,452.55
EU restaurants, catering and other travel provisions	1,155.98
External staff training costs	13,575.88
Total travel costs	**296,961.45**
Other direct expenses	
Insurance	15,268.35
Membership dues - organisation	225.00
Internal staff training costs	2,982.00
Advertising expenses	11,489.29
Contingency provisions	2,906.66
Other expenses	1,903.04
Indirect business expenses	
Cleaning costs	23.48
Telephone and telecommunications	17,411.01
Broadband and other internet connections	1,255.31
Postage and shipping	5,514.66
Office supplies	4,527.32
Printing and copying	78.82
Fees and charges	9,888.99
Hosting agreement costs	64,999.99
Fines, penalties, judgements	227.31
Organisational (corporate) expenses	144,329.83
EVI Board, BoS and SAC expenses	
Board travel costs	667.55
SAC meetings	11,100.00

SAC travel costs	6,996.69
EU ESAC, SAC and SC expenses	
SAC travel costs	86.15
SAC meetings	1,600.00
SAC travel costs	2,668.97
Total expenses	**4,675,224.58**

Result of the year

2014 Result (EUR):	
Transferred to equity – Reserved for R&D	**286,510.11**

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

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

Table 12: Major payables (EUR)

EVI project payments	Project relevance	Amount
Output	AMA1/P27A	26,386.82
Novalabs	AMA1/P27A	18,502.75
Novasep	AMA1	14,904.00
CNRFP	SEmalvac	115,095.00
Confarma	AMA1	8,320.00
Fraunhofer	AMA1	24,629.99
Ifakara	P27A	820.45
Almac	P27A	867.73
Inserm	PRIMALVAC	731,899.63
CHUV	P27A	334,000.00
UCPH	PAMCPH	415,000.00
Wil Research	AMA1	108.80
IDRI	AMA1/P27A	1,131.65
EDCTP project payments	**Project relevance**	**Amount**
UOXF	MVVC	(3,722.38)
UCAD	MVVC	43,383.08
MRC Gambia	MVVC2	83,313.02
EU project payments	**Project relevance**	**Amount**
REDBIOTEC	EDUFLUVAC	91,588.53
HZI	TRANSVAC	(29,249.32)
MPIIB	TRANSVAC	115,307.09
LIONEX	TRANSVAC	65,488.90
UREG	TRANSVAC	54,218.33
BPRC	TRANSVAC	210,358.94
TBVI	TRANSVAC	28,841.06
CVI	TRANSVAC	149,625.35
UNIL	TRANSVAC	8,957.06
UOXF	TRANSVAC	133,269.90
LSHTD	TRANSVAC	26,515.78

Table 13: Expenditures by project

Project code	Amount spent (incl. partner pay) (EUR)	As percentage
P27A	283,442.26	6.06%
AMA1-DiCo	87,286.35	1.87%
PAMCPH	479,988.29	10.27%
PRIMALVAC	843,689.30	18.05%
SPOROVAC	7,047.82	0.15%
InnoMalVac	5,818.00	0.12%
PIM	6,140.93	0.13%
SEmalvac	132,206.24	2.83%
Communication	205,857.66	4.40%
Fundraising	67,983.25	1.45%
Quality assurance	3,357.18	0.07%
Development and review	5,553.25	0.12%
Training	50,382.42	1.08%
Governance	191,965.08	4.11%
EU grant	39,764.86	0.85%
EU MultiMalVax	62,172.33	1.33%
EU TRANSVAC	763,333.09	16.33%
EU IDEA	59,746.67	1.28%
EU PlacMalVac	103,225.50	2.21%
EU BELLEROPHON	117,990.97	2.52%
EU EDUFLUVAC	292,216.47	6.25%
EU IPROVE	58,378.86	1.25%
EDCTP MVVC	129,921.02	2.78%
EDCTP P27A	139,280.05	2.98%
EDCTP MVVC 2	142,260.45	3.04%
EDCTP BMBF	60,103.75	1.29%
EDCTP grant	7,054.16	0.15%
Management	329,058.37	7.04%
TOTAL	**4,975,224.58**	**100.00%**

Table 14: Balance overview of donor and EU/EDCTP funds (EUR)

Donator/Grant	Type	Balance 31/12 2013	Received 2014	Cost 2014	Balance 31/12 2014
IE Irish Aid	Core	**(454,367)**	1,000,000	1,510,112	**(964,479)**
EVI Board Funds	Core	**3,076,725**	0	283	**3,076,442**
DE BMBF/KfW	Restricted	**548,200**	1,108,006	1,419,560	**236,646**
DE BMBF	Restricted	**14,536**	41,728	55,321	**943**
JP GHIT	Restricted	**0**	425,787	133,899	**291,888**
EU TRANSVAC	Restricted	**(154,266)**	861,728	763,333	**(55,871)**
EU EDUFLUVAC	Restricted	**401,434**	0	296,513	**104,921**
EU BELLEROPHON	Restricted	**241,134**	0	117,991	**123,143**
EU PlacMalVac	Restricted	**142,750**	0	103,226	**39,524**
EU IDEA	Restricted	**6,288**	32,952	60,008	**(20,768)**
EU MultiMalVax	Restricted	**56,515**	0	62,173	**(5,658)**
EU IPROVE	Restricted	**(138)**	42,937	54,082	**(11,284)**
EDCTP MVVC	Restricted	**(189,964)**	65,386	129,921	**(254,499)**
EDCTP eICT	Restricted	**(198)**	198	0	**0**
EDCTP MVVC2	Restricted	**59,102**	0	142,260	**(83,158)**
EDCTP P27A	Restricted	**96,975**	26,993	139,280	**(15,312)**
EVI administration	Core	**244,917**	319,289	256,413	**307,793**
EVI equity reserves	Core	**1,125,887**	286,510	0	**1,412,397**
Total core		**2,993,162**	**1,605,799**	**766,808**	**3,832,153**
Total restricted		**1,222,367**	**2,605,715**	**3,477,567**	**350,515**
Total EVI funds		**4,215,529**	**4,211,514**	**4,244,375**	**4,182,668**

Table 15: EVI inventory value estimated (EUR)

P27A	139,440.00
AMA1-DiCo	87,885.00
Adjuvants	8,960.00
Total	**236,285.00**

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

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

Table 16: EVI finished production inventory

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/14	Changes 2014	Quantity 31/12/14
NOVALABS	ALMy001	P27A vaccine	P27A Line A	ALMy001	885	(182)	703
NOVALABS	ALMy001	P27A vaccine	P27A Line B	ALMY001	822	(0)	822
NOVALABS	EVIy003	AMA1 - DiCo vaccine	pfAMa1 DiCo 60 µg Lyophilised	EVIy002	971	(67)	904
NOVALABS	EVIy002	Adjuvant	Alhydrogel Line A	EVIy003	1666	(176)	1490
NOVALABS	EVIy002	Adjuvant	Alhydrogel Line B	EVIy003	1596	(39)	1557

Cash management (bank accounts)

Cash in German key accounts (EUR)	5,762,152.46
Cash in German secondary account (EUR)	11,700.08
Cash in Danish bank (EUR)	43,138.00
Cash in UK bank (EUR)	13,393.83

Hosting costs

EVI is hosted by the UHEI with the following costs:

Hosting costs – Legal support €65,000

Total 2014 service charges €65,000.00 (2013 = €65,000.00)

Remuneration of governing bodies

Remuneration of governing bodies travel and subsistence costs are refunded to EVI BoS and EVI SAC members in connection with meetings and conferences including an honorarium to SAC members. Hotel costs are paid for EVI Board members.

We formally sign and approve the EVI annual financial report for the year 2014 ending 31 December 2014 in accordance with the 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: / / 2015

Sten Larsen, EVI Finance Director

Date: / / 2015

Odile Leroy, EVI Executive Director

Date: / / 2015

Clemens Kocken, Chair of EVI-EEIG Board

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