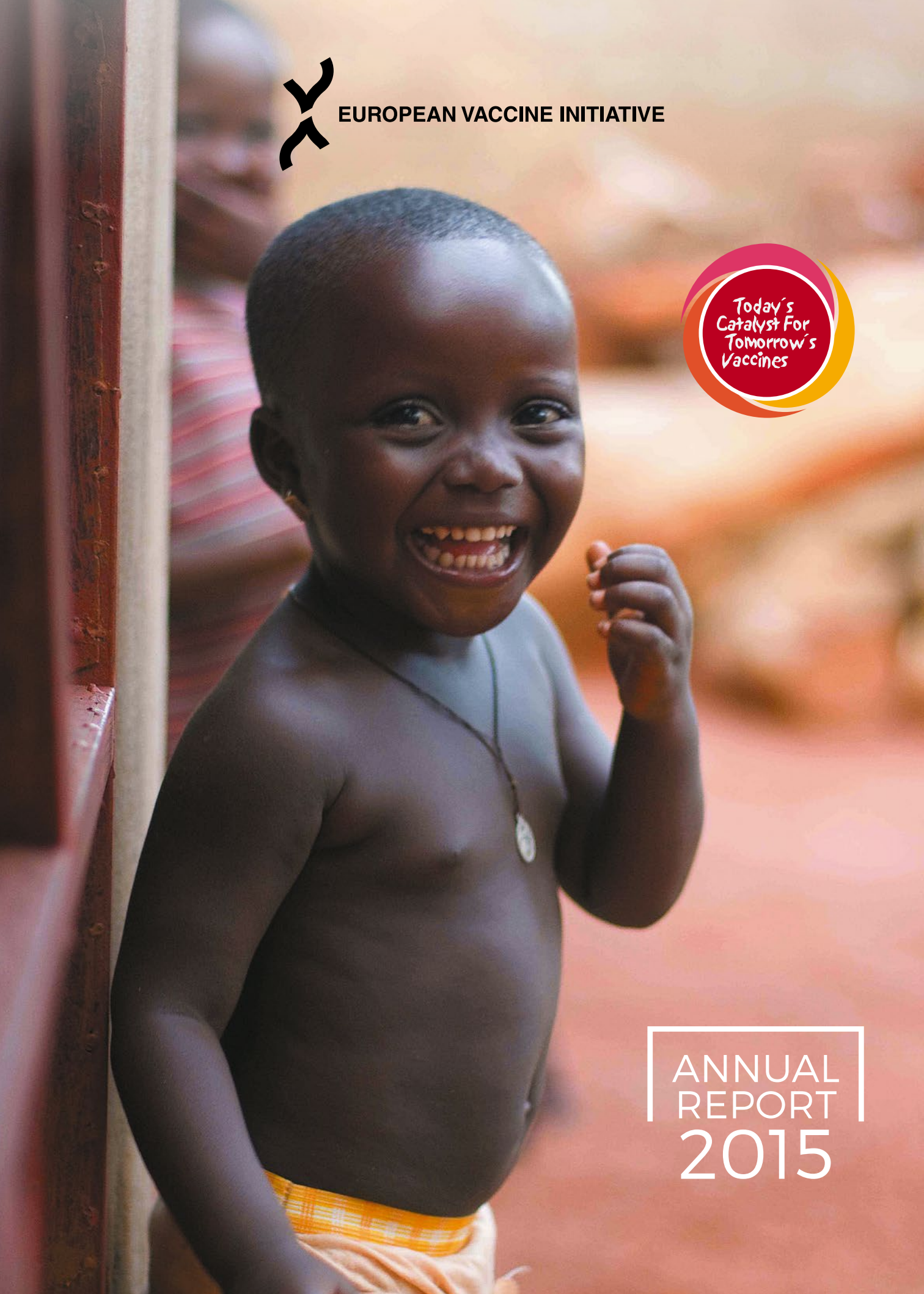
EUROPEAN VACCINE INITIATIVE
Today´s Catalyst For Tomorrow´s Vaccines
ANNUAL REPORT 2015

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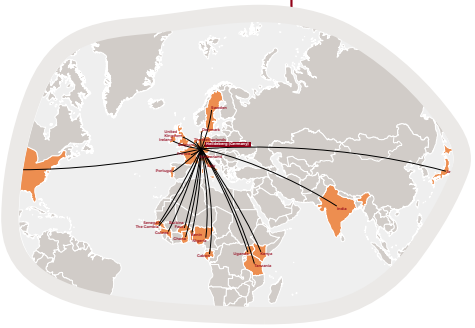


Profile

The European Vaccine Initiative (EVI) is supporting global efforts to develop effective and affordable vaccines against diseases that will have a positive impact, particularly on poor people of the world.

Through continuous collaboration and exchange with academia, pharmaceutical and biotechnology companies, other product development partnerships (PDPs), policy makers and donors, EVI is building a vaccine portfolio that proactively identifies critical research and development (R&D) challenges and opportunities.

EVI's Secretariat is based in Heidelberg, Germany and is governed by a Board, a Board of Stakeholders (BoS) and a Scientific Advisory Committee (SAC) of international scientific experts.

FOREWORD

Bringing up to five further candidate vaccines into clinical trials in the coming five years

Clemens Kocken,
Chairman of the European Vaccine Initiative (EVI) - European Economic Interest Grouping (EEIG)

It is both an honour and a privilege to introduce to you the achievements accomplished by EVI during the past year, as summarised in this annual report.

I will focus on **a few of the numerous EVI successes:** the clinical development of two leading blood-stage malaria vaccines candidates, P27A and AMA1-DiCo, combining phase Ia and Ib, is producing promising results. The same accelerated approach will be used for the two placental malaria vaccine candidates PRIMVAC and PAMVAC, with clinical trials scheduled to begin in 2016. EVI is bringing together outstanding researchers in placental malaria from Denmark, France and United States of America aiming to harmonise the development of these vaccines and move them through the pipeline more quickly. The new EVI project PlacID, awarded by the German Federal Ministry of Education and Research (BMBF) through Kreditanstalt für Wiederaufbau (KfW) focuses on the development of an efficient animal model for the evaluation of placental malaria vaccines. The preclinical activities of EVI diversify into universal influenza, *Staphylococcus aureus* and malaria vaccine research, plus the Japanese Global Health Innovation Technology (GHIT) funded project MVDVax, which focuses on the preclinical assessment of a new-generation of vaccine candidate against dengue virus.

EVI considers harmonisation and standardisation to be highly beneficial, and has thus become involved in harmonisation programs that will be implemented in all EVI core projects. EVI and the NIH/NIAID organised a workshop on immunoassay standardisation for universal influenza vaccines attracting more than 50 worldwide experts to discuss strategies to prioritise immunoassay validation, harmonisation and ultimately standardisation. Last year, EVI also became involved in the Innovative Medicines Initiative (IMI)-funded project FLUCOP, which aims to improve and standardise existing immunological assays to better evaluate the efficacy of future seasonal influenza vaccines. It is a special pleasure to announce that the EVI strategic plan 2016-2020 was approved by the EVI Board. The plan recommends the further pooling of resources, maximising synergies and building partnerships with other players in the vaccine R&D field, including other product development partnerships, national networks of vaccine researchers, research infrastructures, and the vaccine industry.

EVI has thus far contributed to the development of 23 vaccine candidates, 17 of which have been assessed in phase I clinical trials, and three of which have been tested in phase II trials in Africa. EVI is constantly working to strengthen partnerships and build capacity in both Africa and Europe. EVI is championing the discovery of antigens for diseases of poverty including malaria, and their introduction into the early stages of clinical development. In the coming five years, **EVI aims to bring up to five further candidate vaccines into clinical trials**, and will facilitate engagement with industry to accelerate the delivery of safe, effective and affordable vaccines.

EVI strategy

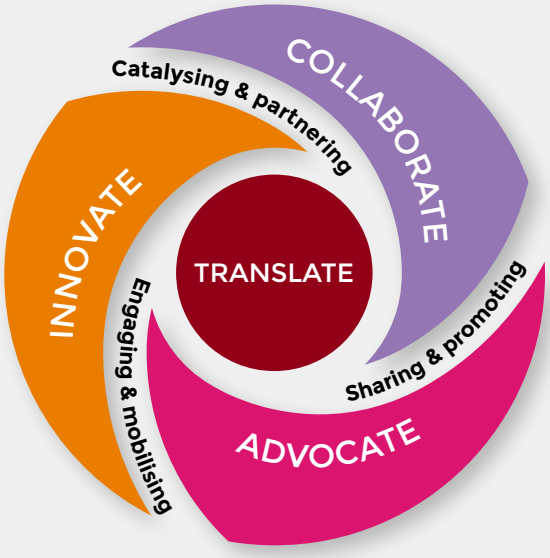
Our vision is a world free of the intolerable burden of diseases of poverty (DoP) within the coming decades.

The EVI portfolio is targeting several infectious diseases including malaria, dengue, influenza, para-typhoid and *Staphylococcus aureus* infections. Malaria has been the major target since the foundation of EVI, leading to the development of 24 malaria antigen combinations in 37 vaccine formulations, with 17 vaccine candidates advancing into phase I clinical trials. EVI is expanding, not only by targeting other diseases but also by strengthening capacity building and the harmonisation of vaccine development in Europe and Africa.

The EVI strategic plan for the last five years ended in 2015, successfully addressing all of the five-year priorities and achieving more than anticipated. Nine projects instead of the planned five were selected for proof of concept and validation of the vaccine candidate in a phase I clinical trial, and two new vaccines were advanced to phase IIb clinical development instead of phase Ib. The 2016-2020 strategic plan is now available and will be launched in 2016. EVI has identified four synergistic themes – innovation, translation, collaboration and advocacy – around which the architecture of the strategic plan has been consolidated.

The synergetic themes will be translated into four specific actions: the development of new technology, preclinical development, clinical development, and harmonisation and capacity strengthening.

Over the next five years, EVI aims to advance up to five candidate vaccines into clinical trials, and facilitate engagement with industry to accelerate the delivery of safe, effective and affordable vaccines.



Governance events

Members of EVI Board as of 31 December 2015

The EVI Board is the ultimate and exclusive decision making body of the European Economic Interest Grouping (EEIG). In accordance with Article 8. of the Statutes, it acts collectively and the full Members are jointly and severally liable for the actions of the EEIG.

Wolfgang Herzog
Heidelberg University, Germany

Carla Hoitink
Institute for Translational Vaccinology, Bilthoven, The Netherlands

Clemens Kocken
Biomedical Primate Research Centre, Rijswijk, The Netherlands

Claude Leclerc
Institut Pasteur, Paris, France

Ruairi Brugha
Royal College of Surgeons, Dublin, Republic of Ireland

David Salisbury
Jenner Vaccine Foundation, Oxford, United Kingdom

Martin Trillsch
Substitute for Wolfgang Herzog, Legal Council, University Clinical Centre, Heidelberg, Germany

Marita Troye-Blomberg
Wenner Gren Institute, Stockholm University, Vice Chair, Sweden

Members of EVI Board of Stakeholders as of 31 December 2015

The EVI Board of Stakeholders consists of EVI donors and stakeholders from vaccine development and low income populations.

Charles de Taisne
Sanofi Pasteur, Marcy l'Etoile, France

Suresh Jadhav
Serum Institute of India, Pune, India

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

Jean-Paul H. Prieels
Consultant, Belgium

Sodiomon Bienvenu Sirima
Chairman, CNRFP, Ouagadougou, Burkina Faso

Marcel Tanner
Swiss Tropical and Public Health Institute, Basel, Switzerland

Members of EVI SAC as of 31 December 2015

The independent Scientific Advisory Committee (SAC) makes recommendations to the EVI Board on scientific direction and technologies as well as on the choice of applications for funding.

Chetan Chitnis
Institut Pasteur, Paris, France

Giuseppe Del Giudice
Novartis Vaccines and Diagnostics, Research Center, GSK, Italy

Joachim Hombach
World Health Organization, Switzerland

Ingeleif Jónsdóttir
Landspitali University Hospital, Iceland

Michael Lanzer
Chair of parasitology unit at HD, Germany

Nancy Le Cam Bouveret
Consultant, Canada

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

James Searl Robertson
Retired, United Kingdom

Mahamadou Aly Thera
Mali

Aissatou Toure
Institut Pasteur de Dakar, Senegal

Members of EVI Finance and Risk Management Committee (FRMC) as of 31 December 2015

The Finance and Risk Management Committee is appointed by the EEIG-Board to assist the EEIG-Board in discharging its oversight responsibilities.
The Finance and Risk Management Committee will provide independent and timely advice to the EEIG-Board on the financial reporting process and the judgements associated therewith to ensure the balance, transparency and integrity of the financial information submitted to the EEIG-Board, Board of Stakeholders, and donors, on an on-going basis and to the auditors for annual audit.

Clemens Kocken
Biomedical Primate Research Centre, Rijswijk, The Netherlands

Terry McWade
Chair of FRMC

Martin Trillsch
Legal Council, University Clinical Centre, Heidelberg, Germany

Members of EVI Secretariat as of 31 December 2015

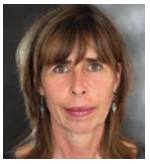
The Secretariat implements policies and strategies recommended by EVI Scientific Advisory Committee and approved by the EVI Board. The Secretariat is led by an Executive Director who is appointed by the EVI Board, and is governed by Rules of Procedure.

Odile Leroy
Executive Director

Flavia D'Alessio
Project Manager

Sandra Hauenstein
Accounting Assistant

Nicolas Havelange
Production Director, Consultant



Sophie Houard
Vaccine Development Leader

Sophia Hundt
Project Manager

Nathalie Imbault
QA, and External Relations & Communication Director

Jill Iversen
Retired, ad hoc assistant

Stefan Jungbluth
Head of Business Development

Roland Kleine
Administrative Assistant

Thorsten Kohaut
Finance Manager

Sten Larsen Finnsson
Finance and Human Resources Director

Brenda Okech
Vaccine Manager Assistant, Consultant

Harry Van Schooten
Business Developer, Consultant

Oliver A. Schraidt
Project Manager

Nicola Viebig
Leader, Strategic Research

Regitze Thoegersen
Programme Manager

Eric Nébié
EDCTP/TDR fellow

2015 governance events

The EVI governing bodies had another highly productive year in 2015, with the finalisation of the new strategic plan 2016-2020.

Development of the new strategic plan began in March 2014 and continued with a series of meetings with the EVI SAC and Board. The final strategic plan was recommended for approval by the EVI SAC on 8 December and approved on 10 December by the EVI Board.

EVI Scientific Advisory Committee (SAC)

The EVI SAC met face-to-face twice:

For the review of vaccine development projects and the development of the new strategic plan on **24 March**.

For the annual review of the portfolio and finalisation of the new strategic plan on **8-9 December**.

In **October**, the EVI SAC recommended Chetan Chitnis, Nancy Le Cam Bouveret and Dominique Mazier for EVI SAC membership. Chetan Chitnis and Nancy Le Cam Bouveret joined the EVI SAC for the meeting in December, and Dominique Mazier will join in early 2016.

EVI Board

The EVI Board met twice:

For the first of the usual biannual meetings to approve the annual report, the development of the new strategic plan, on **12 May**;

For the second biannual meeting on **10 December**, where the new strategic plan 2016-2020 was approved.

The EVI Board also held two teleconferences on **15 March** and **17 September** for regular updates on EVI activities.

In **November**, the EVI Board approved Chetan Chitnis, Nancy Le Cam Bouveret and Dominique Mazier for EVI SAC membership, by written consent.

EVI Board of Stakeholders (BoS)

The EVI BoS met jointly with the EVI Board **on 12 May and 10 December**.

Marcel Tanner, Swiss TPH, Switzerland, was elected as a member of the BoS in **December 2014**, and was welcomed on board during the May meeting.

EVI Rendez-Vous

Finally, on **9 December**, the now traditional EVI Rendez-Vous took place, for the second 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.

EVI Finance and Risk Management Committee (FRMC)

The FRMC held four teleconferences for:

The approval of the 2014 internal audit report on **27 January**;

The approval of the annual financial audit report on **22 April**;

The approval of the scope of work of internal audit on **2 September**; and

The approval of the 2015 internal audit report on **30 November**.

The risk management and internal audit functions are fully operational. 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 the EVI Steering Committee. The project-specific risks are reviewed bimonthly. The fourth internal audit took place in **November**.

Participants in the EVI SAC, BoS and Board face-to-face meetings
EVI-EEIG Board and BoS meetings ■ 12 May, Institut Pasteur, Paris, combined with a BoS Meeting: EEIG Board: Carla Hoitink, Intravacc, Netherlands - Claude Leclerc, Institut Pasteur, France - Clemens Kocken (chair), BPRC, Netherlands - David Salisbury, Jenner Vaccine Foundation, UK - Ruairi Brugha, RCSI, Republic of Ireland ■ **BoS:** Jean-Paul Prieels, consultant, Belgium - Marcel Tanner, Swiss TPH, Switzerland - 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)
10 December, Institut Pasteur, Paris: EEIG Board: Claude Leclerc, Clemens Kocken (chair), David Salisbury, Suresh Jadhav (BoS member), Samuel McConkey (substitute for Ruairi Brugha), RCSI, Republic of Ireland, Ingeleif Jonsdottir (vice-chair of EVI SAC), Landspitali University Hospital, Iceland - Terry McWade (chair of FRMC), 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)
EVI SAC ■ 24 March, RCSI, Dublin: Joachim Hombach, WHO, Switzerland - Ingeleif Jonsdottir (vice-chair) - James Robertson (vice-chair), consultant, UK - Samuel McConkey ■ **From EVI**: Odile Leroy, Stefan Jungbluth, Jill Iversen, Nathalie Imbault (Secretary of EVI Board and BoS), and Mansour Yaich (External Consultant, Vaxyn)
8 and 9 December March, Institut Pasteur, Paris: Chetan Chitnis, Institut Pasteur Paris, France - Guiseppe Del Guidice, GlaxoSmithKline, Italy Joachim Hombach, Ingeleif Jonsdottir (vice-chair), Michael Lanzer, Heidelberg University, Germany - Nancy Le Cam Bouveret, Montreal, Canada - James Robertson (vice-chair) - Mahamadou Ali Thera (chair), Malaria Research and Training Centre, Mali - Aissatou Touré, Institut Pasteur de Dakar, Senegal

Fundraising: a serious financial perspective

In 2015, EVI and its partner organisations secured new funding that allowed the continuation of current projects, resulting in a 27% increase in co-funding alone compared to all previous years of operation. Total mobilised resources to support the EVI portfolio for the development of new vaccines against diseases of poverty increased by €2,814,819, which is committed to EVI projects in 2015 including the abovementioned co-funding. Furthermore, the EVI secured a new joint collaboration project funded by IMI, bringing the total fundraising in 2015 to €16,813,984.

The successfully mobilised new funds enabled the launch of one new project (MVDVax) relating to dengue vaccine development supported by GHIT funds to the tune of **€460,103**. In addition, two EVI projects (PRIMALVAC and PAMCPH) where awarded with supplemental funding in 2015 by the BMBF through KfW, as well as the new project PlacID aiming to develop a new preclinical model for the evaluation of placental malaria vaccines.

EVI was also proud to receive its first private donation of **US$400,000** from the Japanese company Nobelpharma Ltd, for the continuation of the SEmalvac project, shared equally between EVI and our clinical investigational partner CNRFP in Burkina Faso. EVI is honoured to be the link for a strong cooperative program of vaccine development between Asian, European and African institutions.

At the same time, EVI has once again shown excellence in achieving joint collaborations with our partners across Europe, first with the new project FLUCOP, which is coordinated by Sclavo Vaccines Association, University of Siena and Sanofi Pasteur. The total budget is **€13,999,165** and the funding allocated to EVI supports dissemination activities.

During the preparation of this annual report in early 2016, EVI secured the new coordinated IMI project VAC2VAC, more than half of which is co-funded by private industrial partners in the EFPIA. The total budget is just below

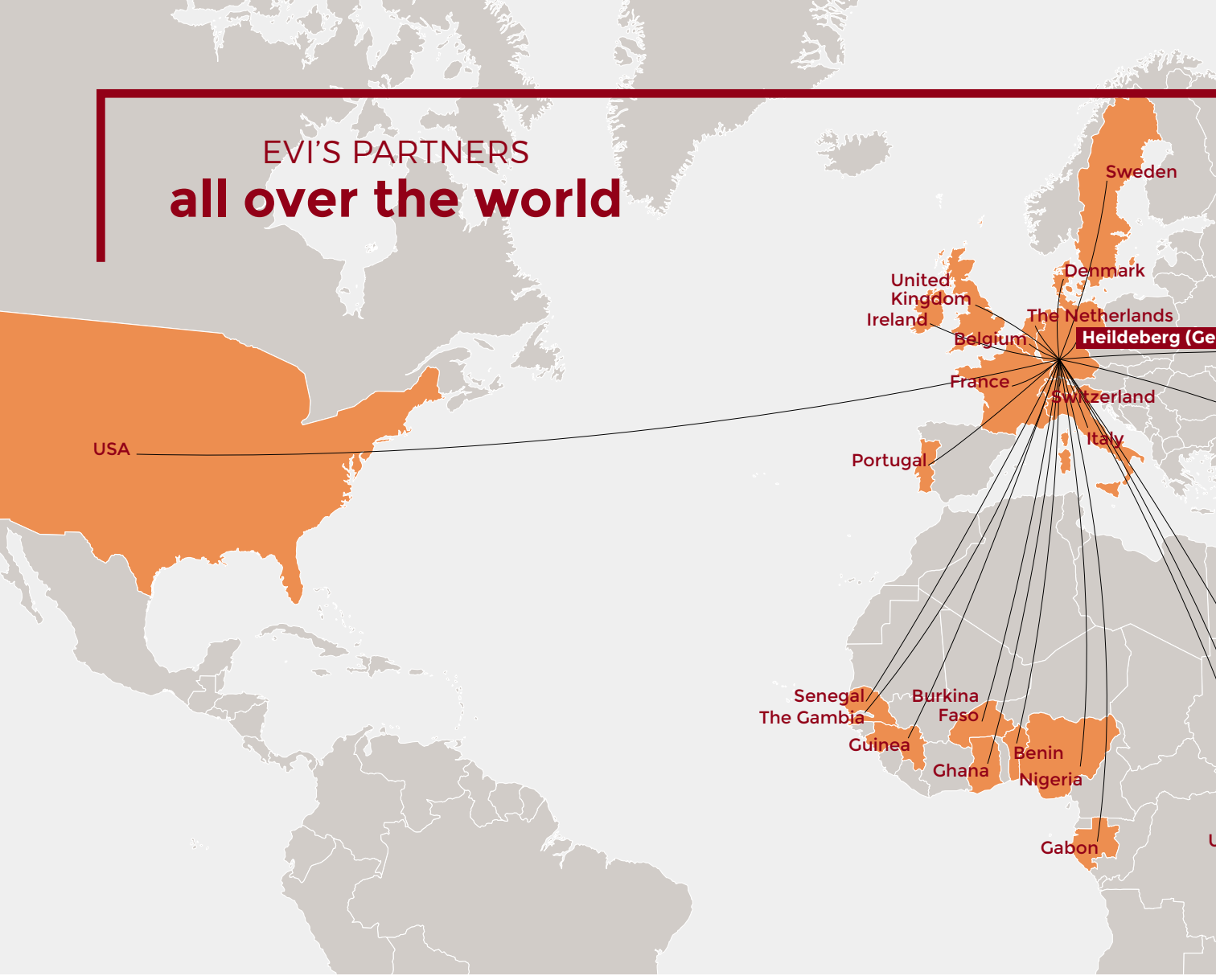
€16 million and we look forward to discussing this success story in next year's annual report.

The EVI's ability to secure co-funding and achieve remarkable levels of return on investment for our donors is an ongoing story of success, underpinned by strong fiscal management and a highly dedicated governance team including the EVI secretariat, which we will build on in the future.

EVI extends its thanks to all our supporters. We would also like to express our greatest appreciation for the donations that help us to achieve our mission of eradicating diseases of poverty.

EVI'S PARTNERS

all over the world



Belgium
- GlaxoSmithKline
- Novasep (formerly Henogen)
- EU PDP Coalition
- European Immunisation and Vaccine Advocacy Coalition
- Vaccines Europe / European Federation of Pharmaceutical Industries and Associations
- Gent University

Benin
- Institut de recherche clinique du Benin
- Université d'Abomey-Calavi

Burkina Faso
- Centre national de recherche et de formation sur le paludisme

Denmark
- CMC Biologics A/S
- ExpreS2ion Biotechnologies
- University of Copenhagen

France
- Institut Pasteur, Paris
- BIOTEM
- CiToxLAB
- Confarma
- GTP Technology
- Imaxio SA
- Sanofi Pasteur
- Agence nationale de recherches sur le sida et les hépatites virales
- Centre d'investigation clinique Cochin-Pasteur
- Commissariat à l'énergie atomique et aux énergies alternatives
- Institut de recherche pour le développement
- Institut national de la santé et de la recherche médicale
- Université Pierre et Marie Curie
- Creapharm
- QUINTEN
- Vaxyn
- Voisin Consulting Life Sciences

Gabon
- Centre de recherches médicales de Lambaréné
- Fondation international de l'hôpital de Dr Albert Schweitzer de Lambaréné

Germany
- Ruprecht-Karls-Universität Heidelberg
- IDT Biologika
- NNE Pharmaplan GmbH
- Output Pharma
- Eberhard-Karls Universität Tübingen
- Fraunhofer IME
- Ludwig-Maximilians-Universitaet München
- Paul-Ehrlich-Institut

Ghana
- Kintampo Health Research Centre

India
- Zydus Cadilla
- DiagnoSearch Life Sciences Pvt. Ltd.

Ireland
- Royal College of Surgeons in Ireland

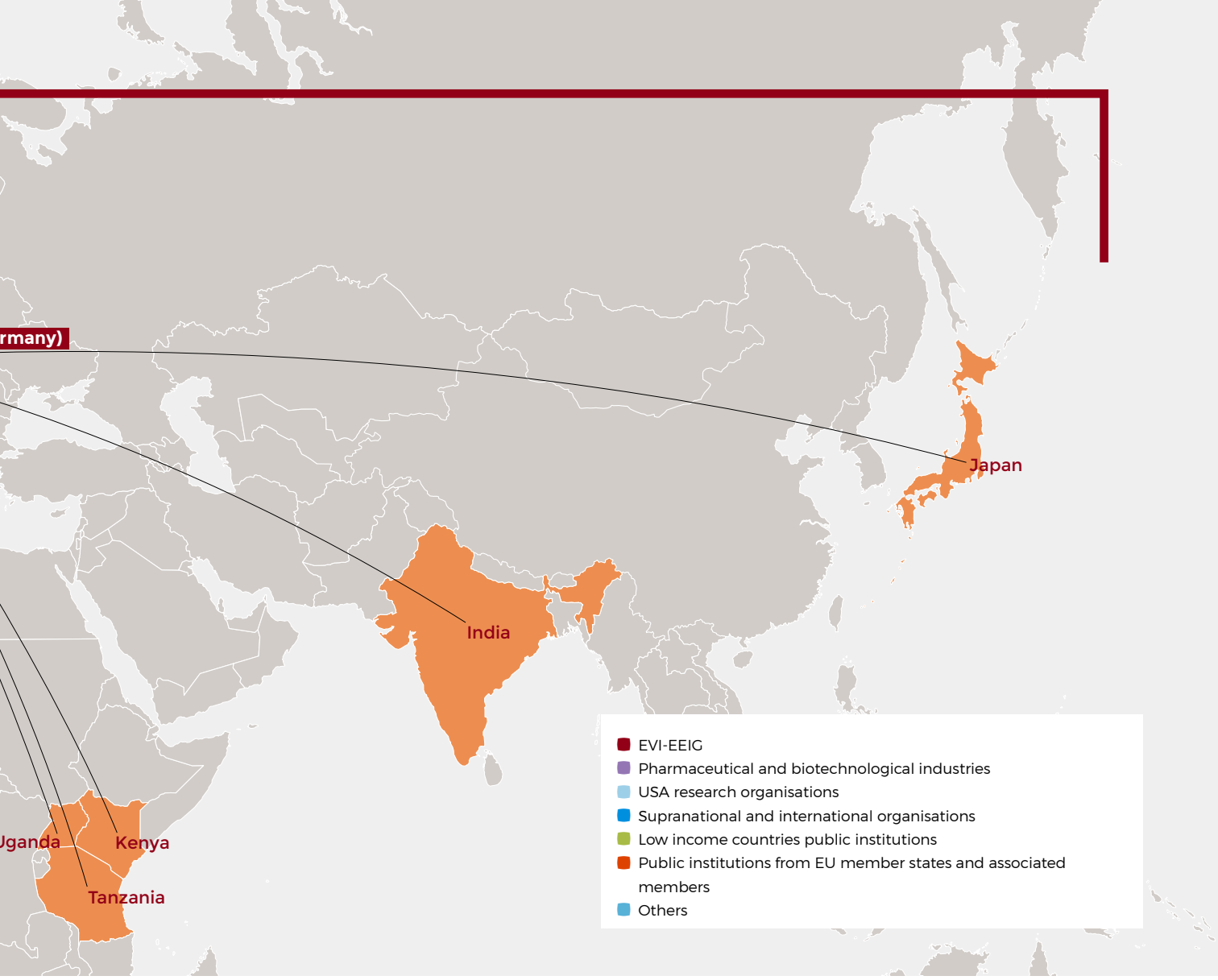
Italy
- ETNA Biotech s.r.l.
- Novartis
- Novartis Vaccines Institute for Global Health
- ReiThera s.r.l. (formerly Okairòs s.r.l.)
- Sclavo Foundation
- Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico
- Instituto Nazionale Malattie Infettive L. Spallanzani-IRCCS
- Istituto Superiore di Sanità
- University of Siena

Japan
- Nobelpharma
- Institute of Tropical Medicine Nagasaki University
- Institute of Tropical Medicine (NEKKEN), Nagasaki University
- Research Institute for Microbial Diseases

Kenya
- Kenya Medical Research Institute

Nigeria
- University of Ibadan

Portugal
- Instituto de Biologia Experimental e Tecnológica



Senegal
- Pharmalys
- Université Cheikh Anta Diop

Sweden
- Stockolm University
- AstraZeneca AB
- Novavax (formerly ISCONOVA)

Switzerland
- Preclin Biosystems AG
- Redbiotec AG
- Developping Countries Vaccine Manufacturers Network
- Malaria Vaccine Funders Group
- Roll Back Malaria Foundation
- World Health Organization
- Centre hospitalier universitaire Vaudois
- École polytechnique fédérale de Lausanne
- Swiss Tropical and Public Health Institute
- University of Lausanne

Tanzania
- Ifakara Health Institute
- National Institute for Medical Research – Mbeya Medical Research Program

The Gambia
- Medical Research Council Gambia

The Netherlands
- Biomedical Primate Research Centre
- Institute for Translational Vaccinology
- Abbott
- Artemis One Health Research BV
- Janssen
- WIL Research
- European Advanced Translational Research Infrastructure in Medicine
- EuroVacc Foundation
- Academisch Medisch Centrum bij de Universiteit van Amsterdam
- Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum
- Central Veterinary Institute
- Erasmus University Medical Centre Rotterdam

Uganda
- Medical Research Council Uganda on behalf of its MRC/UVRI Uganda Research Unit on AIDS
- Unganda Virus Institute

United Kingdom
- Jenner Vaccine Foundation
- ALMAC Sciences
- Nova Laboratories Ltd
- Malaria Consortium LBG
- European Medicines Agency
- Jenner Institute
- London School of Hygiene and Tropical Medicine
- MHRA-Department of Health
- National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency
- The Chancellor, Masters and Scholars of the University of Oxford
- University of Oxford
- Wellcome Trust Sanger Institute
- Gregory Fryer Associates Ltd
- Pharmalys

USA
- Pfenex Inc.
- Infectious Diseases Research Institute
- National Institute of Health / National Institute of Allergy and Infectious Diseases / Laboratory of Malaria Immunology and Vaccination
- Vaccine and Gene Therapy Institute Florida
- PATH Malaria Vaccine Initiative

2015 EVI VACCINE PROJECTS

Strengthening the portfolio

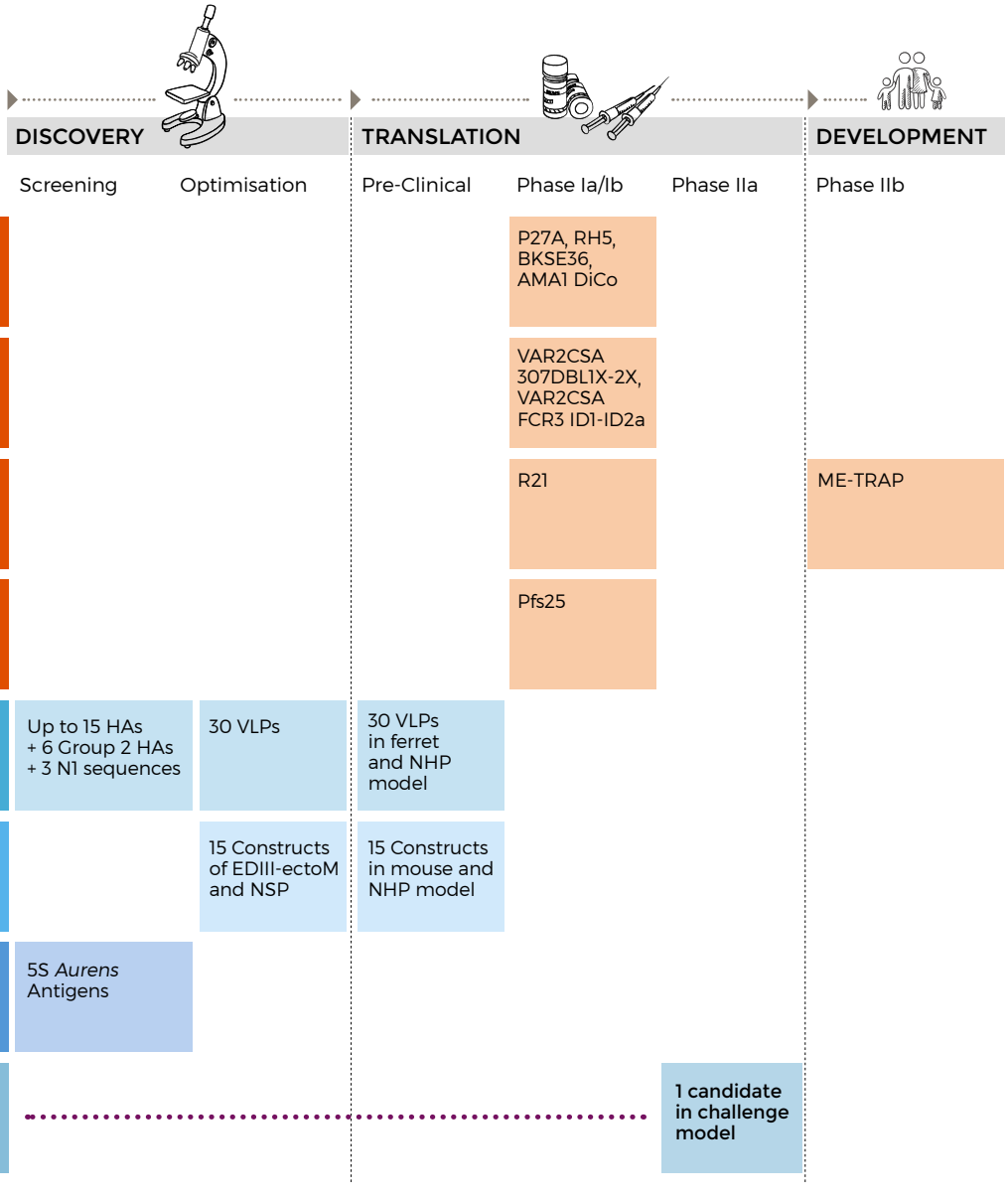
Malaria vaccines

Other vaccines

Cross-cutting activities

Strengthening the portfolio

The EVI portfolio is targeting several EVI's annual project portfolio review took place at Institut Pasteur, Paris, on 9 December 2015. The meeting was as lively as ever, and was attended by approximately 90 participants. The review of the portfolio by the scientific community supported the recommendations made by the EVI SAC for the continuation or termination of specific projects. The EVI Scientific Advisory Committee (SAC) welcomed two new members, Chetan Chitnis from Institut Pasteur, Paris, and Nancy Le Cam Bouveret, an independent clinical development and regulatory consultant.



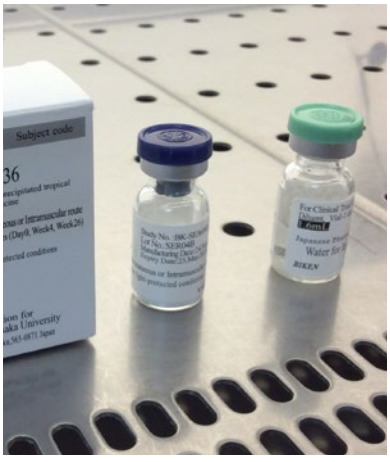
Malaria vaccines remain the core components of the EVI portfolio with 10 malaria antigens at different stages of development. However, EVI is extending to include other targets such as dengue, universal influenza and para-typhoid vaccines, and EVI will invest substantially in capacity strengthening and the harmonisation of vaccine development in Europe and in Africa.

MALARIA VACCINES

Blood-stage malaria vaccines: AMA1-DiCo, P27A, BK-SE36 and PfRH5

The EVI fast-track strategy for early clinical development in Europe and Africa was successful for both the AMA1-DiCo and P27A vaccines, and the phase Ia/b clinical trials were completed in France/Burkina Faso and Switzerland/Tanzania, respectively. The analysis of safety and immunogenicity data is underway.

The age-de-escalation phase Ib clinical trial of BK-SE36 vaccine started in June 2015 in Burkina-Faso, with the immunisation of two staggered cohorts of children (2-5 years old) followed by toddlers (1-2 years old) after clearance by the independent safety monitoring committee (ISMC). The last booster immunisations were scheduled in April 2016.



Process development for the PfRH5 vaccine candidate was completed in 2015 with the establishment of cell lines expressing different variants, and purified proteins were characterised and tested for functional antibody induction in rabbits. The PfRH5 antigen expressed in viral vectors was assessed using a heterologous prime-boost regime (ChAd63 followed by MVA) in a phase Ia clinical trial in the UK. The data have been analysed and the final report will be available in mid-2016. The vaccine candidate achieved a good safety and immunogenicity profile, including functional antibodies detected in *in vitro* assays.

Placental malaria vaccines

EVI continues to support the development of placental malaria vaccines by three major research groups led by Thor Theander in Denmark, Benoit Gamain in France, and Patrick Duffy in the USA. In France, the PRIMALVAC project completed the GMP production of its vaccine candidate and the clinical batch was released after passing toxicology studies and quality controls. The ANSM (French regulatory authority) and Ile-de-France III Hopital-Tarnier-Cochin, Paris CPP (competent research ethics committee) approved the clinical trial in France. The application for the clinical trial in Burkina Faso was submitted to the institutional and national ethics committees as well as the national regulatory authority. In Denmark, the PAMCPH project also completed GMP production of its vaccine candidate (PAMVAC), and the PlacMalVac consortium gained approval from independent ethics committees in Germany and Bénin, as well as the Paul Ehrlich Institute (German regulatory authority) to start the phase Ia/Ib clinical trial in Germany. To accelerate the decision process for assessment and the selection of placental malaria antigens, EVI is supporting the PlacID project for the development of a non-human primate model for placental malaria at NIH/NIAID in the USA.

Pre-erythrocytic malaria antigens: ME-TRAP, R21

Good safety and immunogenicity profiles were achieved for the viral-vectored ME-TRAP vaccine candidate co-administered with the Expanded Programme on Immunization (EPI) vaccines in the MVVC 2 phase Ib clinical trial in The Gambia.

The results of the MVVC phase IIb clinical trial were presented and discussed at the EVI Rendez-Vous 2015. The vaccine candidate demonstrated safety and immunogenicity, with a limited efficacy against severe malaria in Burkinabe infants aged 5-17 months. A manuscript is in preparation.

The main achievements of the MultiMalVax project included completing GMP production of R21, a circumsporozoite-based candidate pre-erythrocytic malaria vaccine, and the initiation of phase Ia clinical trials. The first will assess R21 with the AS01 adjuvant developed by GSK.

Transmission-blocking vaccine

The transmission-blocking vaccine candidate Pfs25 is expressed using the viral vectors ChAd63/MVA in which the antigen is fused to the IMX313 fusion tag. This has been produced and tested in preclinical studies, and it is ready to be assessed in a phase Ia clinical trial. IMX313 promotes the oligomerisation of the antigen and potentially increases both B cell and T cell immunogenicity. This strategy is therefore expected to improve the efficacy of the vaccine candidate.

OTHER VACCINES

Dengue vaccine

EVI supports the Institut Pasteur approach for dengue antigens expressed in attenuated measles virus vectors (MVDVax). After screening 15 constructs containing dengue virus EDIII-ectoM and NSP antigens, candidate vaccines were down-selected in mouse model and are now being assessed in a non-human primate model. If MVDVax achieves preclinical proof-of-concept, the vaccine will be tested in a phase Ia clinical trial in collaboration with Japanese partners from the Institute of Tropical Medicine, Nagasaki University (NEKKEN), Nagasaki, and the preparation of the site for a phase II clinical in South-Asia will be initiated.

Influenza vaccine

The EDUFLUVAC project successfully prepared all the intended virus-like particles for mouse immunisation studies, and organised a successful workshop on immunoassay standardisation for universal influenza vaccines that took place at the National Institute for Biological Standards and Control (NIBSC).

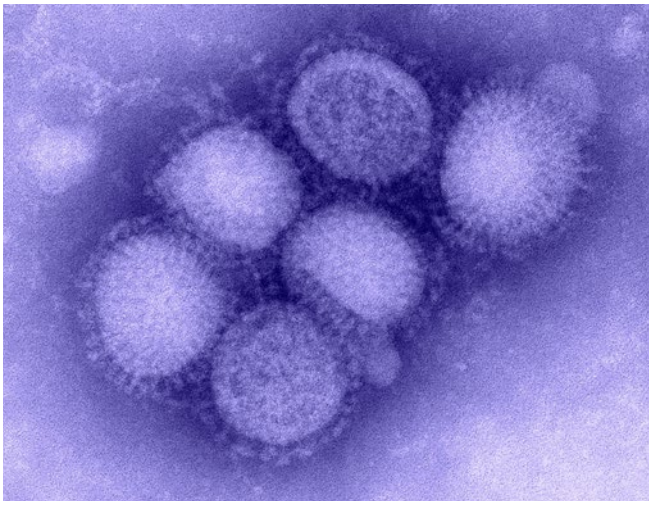
The FLUCOP project began in 2015, supported by the IMI with funding from the European Union FP7 program. The long-term objective of the FLUCOP project is to improve and standardise existing immunological assays for influenza (for the definition of correlates of protection in future efficacy trials) and, whenever feasible, to develop new assays that better evaluate influenza vaccine immunogenicity. In 2015, factors influencing the variability of the influenza haemagglutination inhibition assay were assessed, and an optimised and standardised assay protocol is now under development.

Para-typhoid project

The PIM project was completed in 2015 and successfully demonstrated the safety and practicality of the first ever human challenge study for *Salmonella paratyphi A*.

Staphylococcus aureus vaccine

To address the critical issue of antibiotic-resistant *Staphylococcus aureus* several constructs carrying different antigens were screened in 2015 in a range of preclinical animal models. A fusion of three antigens with the IMX313 tag was identified as a potential vaccine candidate.



H1N1 influenza virus

CROSS-CUTTING ACTIVITIES

Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth Infections

The main achievement in 2015 was the successful completion of the IDEA project and the submission of the final report to the European Commission. The clinical activities involving EVI included clinical trials assessing the effect of helminth infections on the performance of vaccines against HIV/AIDS and tuberculosis, revealing good safety profiles and initial immunogenicity data.

The development of the European vaccine research and innovation roadmap

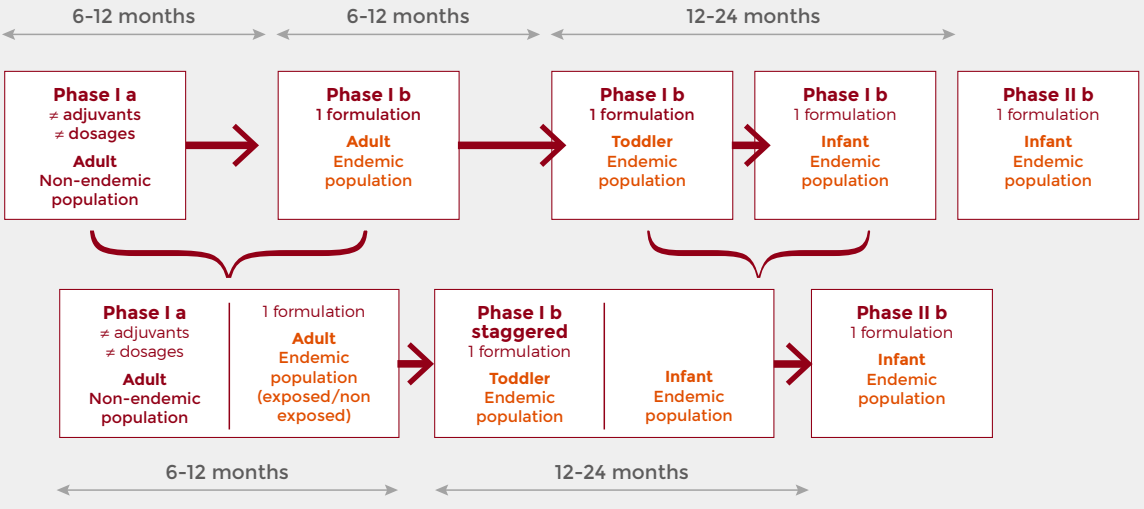
The IPROVE project (the innovation partnership on vaccines in Europe) aims to establish a clear vision of the priority innovations and technologies required to boost research in the field of vaccine and vaccinology in Europe and beyond. During 2015, the last two stakeholder consultation meetings were organised by the consortium, one on "Research & innovation and research infrastructures", and the final one on "Therapeutic vaccines". The consortium is currently finalising the roadmap launched in 2016.

Developing next generation vaccines

The EVI portfolio was consolidated and diversified over the last two years, and now includes malaria, dengue, para-typhoid, influenza, and *S. aureus* vaccines.

Fast-track clinical trials strategy

Traditionally, vaccine against diseases of poverty early clinical development starts with a phase Ia clinical trial to assess safety and immunogenicity in a disease naïve population at a single centre in the USA or Europe. Once the phase Ia clinical trial is completed, safety and immunogenicity are then evaluated in a phase Ib clinical trial in a endemic population. To accelerate this early stage of vaccine development, EVI and partners have designed a fast-track strategy in which the first-in-human evaluation involves a staggered multi-centre phase Ia/b clinical trial. Following the positive safety assessment of the first vaccination dose in a limited number of adult subjects in Europe, this vaccination dose is immediately administered to adults in a disease endemic population, where dose escalation is then performed (Figure 1).
A single common protocol is prepared jointly by the European and African teams, and submitted concomitantly to both local ethics committees and regulatory authorities before the start of the clinical trial. Bilateral communication in this North-South collaboration achieves a deeper understanding of the needs and country-specific regulations, which are taken into consideration during the clinical trial design. Thus far, the EVI fast-track strategy has been successfully implemented in several projects: the AMA1-Dico and P27A clinical trials are completed and data analysis is underway, whereas clinical trials assessing the placental malaria vaccine candidates PRIMVAC and PAMVAC started in May 2016.



Delivery Platforms, Adjuvants and Viral Vectors

A number of delivery platforms are currently used for 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 pre-clinical and clinical trials. Please contact EVI at contact.evi@euvaccine.eu for further information.

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.

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 agreements on standardised laboratory procedures, preparations and reagents.

VACCINES THAT PREVENT MALARIA INFECTION: liver-stage malaria 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 or prevents the development of the parasite inside the hepatocytes. This is typically a vaccine for travellers because it would prevent the clinical disease if completely efficacious. A partially efficacious pre-erythrocytic vaccine would also be expected to reduce the incidence of new blood-stage infections.

In October 2015, the World Health Organization's Strategic Advisory Group of Experts on Immunization and the Malaria Policy Advisory Committee jointly recommended a pilot implementation of the RTS,S vaccine in Africa. The RTS,S vaccine was developed jointly by the Malaria Vaccine Initiative (MVI PATH) and GlaxoSmithKline (GSK) based on the repeat and T cell epitope in the pre-erythrocytic circumsporozoite protein (CSP) of *P. falciparum* and a Hepatitis B virus envelope protein (HBsAg), to which was added a chemical adjuvant (AS01).
The vaccine induces both humoral and cellular immune responses, with high antibody titres that block the parasite from infecting the liver. RTS,S/AS01 was reviewed by the European Medicines Agency (EMA) which issued a positive scientific opinion on the vaccine in July 2015. However, the efficacy of RTS,S is rather modest (39%), it achieves relatively short-term protection, and a series of four vaccinations is required outside of the standard Expanded Programme on Immunization (EPI) schedule, so a second-generation malaria vaccine is urgently needed.

MVVC

Malaria Vectored Vaccines Consortium (MVVC) was funded by European and Developing Countries' Clinical Trials Partnership (EDCTP) in response to the 2008 call "Malaria Vaccines Integrated Project – Clinical Trials / Capacity strengthening / Networking".

The total funding provided by EDCTP was €5,613,936, complemented by co-funding from Irish Aid (Ireland), Swedish Development Agency (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.

PARTNERS

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

(formerly Okairòs s.r.l.) remains a separate entity after the acquisition of Okairòs 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 strengthening 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 beyond the end of the project;

Delivery Platform, Adjuvants and Viral Vectors

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

Clinical Development

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 serious adverse events related to the vaccine candidates were reported. The safety and immunology data from the phase Ib adult clinical trials in Kenya and The Gambia were published in PLOS One[1] and Molecular Therapy[2], respectively. The safety and immunogenicity data from the phase Ib clinical trials in 138 children and infants in The Gambia and in Burkina Faso were published in Molecular Therapy[3]. The ChAd63-vectored vaccine and the ChAd63 prime/MVA boost regimens were used for the first time in children and infants. The findings demonstrated the ability of these vectors to induce high numbers of T cells and an acceptable safety profile in four cohorts of children of decreasing ages: 2–6 year olds in The Gambia; 5–17 month olds in Burkina Faso; 5–12 month olds and also 10 week olds in The Gambia. T cell responses to vaccination peaked seven days after boosting with MVA, with TRAP-specific T cell responses highest in 10-week-old infants. A manuscript describing further immunology results from the phase Ib clinical trial in children and infants is under review.

Phase IIb adult efficacy trials have been completed at KEMRI and UCAD. The KEMRI phase IIb clinical trial showed 67% efficacy against Polymerase Chain Reaction (PCR) positivity and the results were published in Science Translational Medicine[4]. However, the UCAD phase IIb clinical trial data did not reproduce the KEMRI results. A manuscript has been submitted.

A phase Ib lead-in/IIb clinical trial in the target age group (infants 5–17 months old 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 in 2014. The clinical trial ended in October 2014, data analysis was completed in 2015 and the results indicate potential efficacy against severe malaria. A manuscript is in preparation.

The follow up of subjects enrolled in the baseline epidemiological studies at UCAD and CNRFP 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[5].

Capacity strengthening

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.

Dr Muhammed Afolabi (MRC) successfully concluded his PhD studies at the London School of Hygiene & Tropical Medicine on 8 January 2015. The work of two other PhD students is progressing well – the major results of their studies were published in peer-reviewed journals [6] [7] [8] [9], and they are expected to graduate in 2016.

1. Ogwang C. et al. PLOS One 2013, doi:10.1371/journal.pone.0057726
2. Kimani D. et al. Molecular Therapy 2014, doi:10.1038/mt.2014.109
3. Afolabi M.O. et al. Molecular Therapy 2016, doi:10.1038/mt.2016.83
4. Ogwang C. et al. Science Translational Medicine 2015, doi:10.1126/scitranslmed.aaa2373
5. Nébié I et al. Clinical and Vaccine Immunology 2014, doi:10.1128/CVI.00723-13
6. Ndiath M et al. Malaria Journal 2014, doi:10.1186/1475-2875-13-453
7. Ndiath M et al. Malaria Journal 2015, doi:10.1186/s12936-015-0976-9
8. Kangoye DT et al. PlosOne 2014, doi:10.1371/journal.pone.010796
9. Kangoye DT et a. Vaccine 2016, doi:10.1016/j.vaccine.2015.10.058

- To develop the partners in the consortium into a well-established network using the 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 results of the phase IIb clinical trial to assess the efficacy of the ChAd63/MVA ME-TRAP vaccine candidates in Burkinabe children aged 5–17 months were presented at the EVI Rendez-Vous and indicate no significant efficacy against clinical malaria but potential efficacy against severe malaria. A manuscript is in preparation.

MVVC

Harmonisation

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 using standard controls with known antibody concentrations in each plate. The T-cell assays use an identical protocol, with identical standard 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 (www.optimalvac.eu) network to process shared samples, and an agreement was reached among the sites for specific responses and controls.

Outreach and Communication

Jean-Baptiste B. Yaro (CNRFP) presented "A phase I/IIb double blind randomised controlled trial of the efficacy, safety and immunogenicity of heterologous prime-boost immunisation with the candidate malaria vaccines ChAd63 ME-TRAP and MVA ME-TRAP in 5-17 month old Burkinabe infants and children" at the EVI Rendez-Vous, 9 December, Paris, France.

MVVC 2

MVVC 2 is an almost three-year project coordinated by EVI, building on the MVVC project which started to establish a strong network among four African partners and collaborators in Europe.

This network was enlarged to include two new partners, and capacity strengthening efforts were expanded during the course of MVVC 2.

MVVC 2 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 (MVVC 2)". The EDCTP grant is complemented by co-funding from European Union (EU) Member States, BMBF (Germany), Irish Aid (Ireland), MRC (UK), Sida (Sweden), and third-party contributions, with a total project budget of approximately €1,239,153. The MVVC 2 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 strengthening and networking activities were used to strengthen the clinical trial capabilities and laboratory facilities of the African sites, allowing them to conduct the proposed clinical trials and additional health research.

PARTNERS

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

The MVVC 2 consortium completed the clinical trial at MRC, The Gambia, with good safety and immunogenicity profiles when co-administered with EPI vaccines (complete data set expected mid-2016), and is preparing for the clinical trial at CNRFP, Burkina Faso. KHRC site also developed capacity in cellular immunology.

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigen ME-TRAP was 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-M1, provided by Novavax.

Clinical Development

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

The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines were 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 ended in November 2015, revealing good safety and immunogenicity profiles in all infant age groups. Analysis of EPI antibody responses is on-going. A manuscript is in preparation.

The clinical trial was prepared and, after an amendment, the safety and immunogenicity of the R21 CSP particle adjuvanted with Matrix-M will be assessed in African adults at the CNRFP, Burkina Faso. This clinical trial is expected to start in Q2 2016.

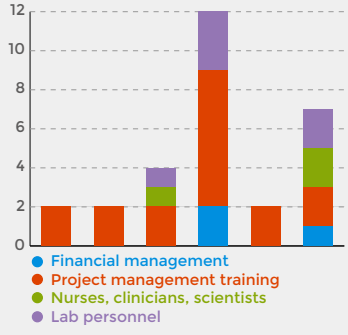
Capacity strengthening

As part of the MVVC 2 capacity strengthening activities, immunology facilities at the KHRC, Ghana, have been secured and made available. The laboratory facilities have been established and equipment has been sourced. An exchange visit between KHRC and CNRFP was organised to set up the immunology laboratory by sharing resources and expertise.

Exchange visits took place during the year to reinforce collaborations, especially between the African project partners. A true example of South-South collaboration was the exchange of expertise and laboratory personnel between the UCAD, Senegal and the MRC, The Gambia. The UCAD senior scientific staff gained experience by establishing and conducting paediatric malaria clinical trials while two UCAD laboratory technicians supported immunological analysis at the MRC.

The research clinician working on the clinical trial, Dr Ebrima Kanteh, won a competitive scholarship award to undertake Master's degree training in vaccinology at the University of Siena, Italy. Muhammed Afolabi received a travel grant to attend the 2015 Vaccines Bioprocess Development & Commercialization Workshop at Massachusetts Institute of Technology, Boston, USA, and an ASTMH Travel Award 2015 to attend the 64th ASTMH meeting, Philadelphia, USA.

FIGURE 1 TRAINING WITHIN MVVC 2



Additional training was provided in IT and statistics, financial management, project management and writing of scientific publications as well as training for nurses, clinicians, scientists and laboratory personnel at the various partner sites.

UOXF was responsible for the quality assurance of all immunoassays performed during MVVC 2. This enabled the young scientists at the Jenner Institute laboratories to gain valuable experience in the performance of these assays from samples obtained from clinical trials conducted in malaria endemic countries. In addition, this has counted towards their MSc and PhD programmes (e.g. for Carly Bliss and Georgina Bowyer).

Harmonisation

The MVVC 2 consortium has expanded the MVVC harmonisation efforts on immunoassays to include KHRC, and those concerning quantitative PCR to include CNRFP. This ensures that the sites generate comparable results in the MVVC 2 project and in future clinical trials.

Outreach and Communication

Muhammed Afolabi (MRC, The Gambia) presented "Heterologous prime-boost vaccination with candidate malaria vaccines ChAd63-MVA ME-TRAP is safe and highly immunogenic for effector T-cell induction when co-administered with EPI vaccines in healthy Gambian infants and neonates" at the 64th Annual Meeting of the American Society of Tropical Medicine & Hygiene, 25-29 October, Philadelphia, USA.

Victorine Mensah (UCAD) presented "Results of a phase Ib clinical trial in infants and neonates" at the EVI Rendez-Vous, 9 December, Paris, France.

MALARIA VACCINES THAT PREVENT MORTALITY AND MORBIDITY: blood-stage malaria vaccines

Clinical malaria occurs when malaria parasites from the genus *Plasmodium* invade and replicate within 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 either with pre-erythrocytic or other blood-stage antigens 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 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 include the development of recombinant antigens (AMA1-DiCo, Merozoite Surface Protein (PfMSP1) and Erythrocyte-Binding Antigen-175 (PfEBA175), SEmalvac), recombinant full-length proteins (PfRH5) and synthetic peptides (P27A).

AMA1-DiCo

AMA1 is a blood-stage antigen from *P. falciparum* which has been assessed by different research groups worldwide. 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*.

PARTNERS

- Biomedical Primate Research Centre (BPRC), NL
- Centre d'investigation clinique Cochin-Pasteur (CIC-Cochin), FR
- Centre national de recherche et de formation sur le paludisme (CNRFP), BF
- Confarma, FR
- European Vaccine Initiative (EVI), DE
- Fraunhofer Institute for Molecular Biology and Applied Ecology (Fraunhofer IME), DE
- Gregory Fryer Associates Ltd, UK
- Novasep (formerly Henogen), BE
- Infectious Diseases Research Institute (IDRI), USA
- Institut national de la santé et de la recherche médicale (Inserm), FR
- NNE Pharmaplan GmbH, DE
- Nova Laboratories, Ltd, UK
- Output Pharma, DE
- WIL Research, NL

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 conditions[10]. The product was evaluated in a phase I clinical trial with three different 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 doses were combined with AS02A and Montanide ISA720[11].

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 diversity coverage (DiCo) approach, recommended by the EVI SAC and approved by the Board in October 2008,

Preclinical, process development, production, IMPD

As per regulatory requirements, the long-term real-time stability analysis of the AMA1-Dico vaccine candidate at –20°C was completed after 36 months in storage at Fraunhofer IME.

Delivery Platform, Adjuvants and Viral Vectors

Glucopyranosyl Lipid A Adjuvant (GLA)-Stable Emulsion (SE) and aluminium hydroxide (Alhydrogel®) as a comparator are being used as adjuvants in the phase Ia/Ib clinical trial. Alhydrogel® was filled by EVI at Nova Laboratories Ltd. EVI has purchased GMP-grade GLA-SE and SE from the IDRI, under a clinical supply agreement involving EVI, Inserm and IDRI.

Clinical Development

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) conducted the clinical trial arm in the non-exposed population, and Dr Sodiomon Sirima (CNRFP, Balonghin, Burkina Faso) conducted the clinical trial arm in the exposed population.

The vaccination phase in France took place between January and September 2014 and the phase Ia subjects were followed until March 2015. In Burkina Faso, the vaccination phase was from July 2014 to February 2015 and the phase Ib subjects were followed until July 2015.

AMA1-DiCo formulated with aluminium hydroxide or GLA-SE was well tolerated and induced high titres of specific antibodies in malaria-exposed or non-exposed populations, although the titres were higher when the antigen was formulated with GLA-SE in the non-exposed population. Further exploratory analysis is underway to assess the functionality of the antibodies.

Capacity strengthening

EVI supported Inserm, the clinical trial sponsor, in providing the fast-track clinical trial design, in reviewing all clinical trial documentation, in supervising the vaccine accountability and overviewing of the clinical trial progress until its completion.

Harmonisation

Inserm, CIC Cochin, CNRFP and BPRC AMA1-DiCo team partners have continued harmonisation of the immunological assays of the AMA1-DiCo phase Ia/Ib clinical trial.

Outreach and Communication

Christine Durier (Inserm France) presented "AMA1-DiCo clinical trial phase Ia/Ib: Safety and preliminary immunogenicity results" at the EVI Rendez-Vous, 9 December, Paris, France.

10. Faber et al., Vaccine 2008, doi:10.1016/j vaccine.2008.08.055
11. Roestenberg, Plos One 2008, doi:10.1371/journal.pone.0003960.

Clinical development team of AMA1-DiCo

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 for the development of an AMA1-DiCo vaccine is €5,411,742.23, from the Directorate General for International Cooperation at Ministry of Foreign Affairs, The Netherlands (DGIS) and Irish Aid grants.

Following GMP production, the EVI-funded development of an AMA1-DiCo vaccine candidate moved into active clinical development in 2014 when a two-centre phase Ia/Ib clinical trial began at CIC-Cochin, France, in a malaria-naïve population, and was further transitioned to the malaria-exposed target population at CNRFP, Burkina Faso. In 2015, the active phase of the clinical trial was completed, and the safety and immunogenicity data are undergoing evaluation.

InnoMalVac

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

The project was successfully submitted to the EVI SAC for the "Innovation and Discovery" call of summer 2012, and was initiated in June 2013 with a duration of two years. InnoMalVac has a total budget of €175,000 and is funded by EVI from an Irish Aid grant. The project was successfully completed during 2015.

Polyclonal and monoclonal S2 cell lines expressing different variants of PfRH5 were established. The purified proteins have been characterised and tested for functional antibody induction in rabbits. Based on these studies, a full-length PfRH5 was selected for further clinical development. Funded by an MRC (UK) grant, GMP production of the protein was also completed in 2015. The clinical batch is currently undergoing stability and toxicology studies.

PARTNERS

- European Vaccine Initiative (EVI), DE
- ExpreS2ion Biotechnologies, DK
- University of Oxford (UOXF), UK

Preclinical, process development, production, IMPD

UOXF collaborated with ExpreS2ion Biotechnologies to produce polyclonal and monoclonal S2 cell lines expressing different variants of PfRH5. One variant was selected based on functional antibody assays after rabbit immunisation. The purified proteins have been characterised using different assays to select the best candidate. GIAs and Surface Plasmon Resonance analysis have been completed and based on these data the PfRH5 variant v2.0-Ctag (3D7 *P. falciparum* clone sequence) was selected.

The C-tag (the C-terminal four-amino-acid EPEA) based purification process was chosen because it achieved a better yield than the original His-tag (six histidine residues at the C-terminus) where a major contaminant co-purified with the PfRH5 protein.

The production and purification processes have been scaled-up to the 10 litre fermenter scale at the Clinical Biomanufacturing Facility (CBF), Oxford, and a pilot batch and a GMP batch have been produced. The pilot batch has been used for toxicology studies and both batches are undergoing stability studies. The final yield of pure product is 17 ml/L of fermenter broth.

Delivery Platform, Adjuvants and Viral Vectors

PfRH5 is expressed as a recombinant protein in *Drosophila* S2 cells and a version in viral vectors (ChAd63 and MVA) has also been produced during the MultiMalVax project.

Outreach and Communication

Simon Draper (UOXF) presented "Malaria, Ebola and Vaccines" at the Year 6 Talk at the Dragon School on 12 May, Oxford, UK, and at the Trinity College Scientific Society, 26 February, Dublin, Ireland.

Simon Draper gave an interview for the Nuffield Department of Medicine website on the WHO World Immunization Day, 24-30 April.

Simon Draper presented "PfRH5 blood-stage malaria vaccine candidate; antigen optimisation, production and phase I/II clinical trial" at the EVI Rendez-Vous, 9 December, Paris, France.

P27A

This vaccine candidate is an intrinsically unstructured, hydrophilic fragment of the *P. falciparum* protein PFF0165c, which is 104 amino acids in length[12], submitted in 2007 by Professor Giampietro Corradin, UNIL.

It was not originally recommended for funding by the 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, from an Irish Aid grant.

The inhibition of merozoite invasion and monocyte triggering by Antibody-Dependent Cellular Inhibition (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 Growth Inhibition Assay

PARTNERS

- ALMAC Sciences, UK
- Centre hospitalier universitaire vaudois (CHUV), CH
- CiToxLAB, FR
- European Vaccine Initiative (EVI), DE
- Gregory Fryer Associates Ltd, UK
- Ifakara Health Institute (IHI), TZ
- Infectious Diseases Research Institute (IDRI), USA
- Nova Laboratories Ltd, UK
- Output Pharma, DE
- Swiss Tropical and Public Health Institute (Swiss-TPH), CH
- University of Lausanne (UNIL), CH

12. Olugbile et al., Infection and Immunity 2009, doi:10.1128/IAI.00652-09

Preclinical, process development, production, IMPD

As per regulatory requirements the long-term real-time stability analysis of the drug product at -20°C was completed after 36 months in storage at Almac.

Delivery Platform, Adjuvants and Viral Vectors

Two adjuvants are being used in the clinical trial: aluminium hydroxide (Alhydrogel®) as a reference adjuvant as it has shown promising results in preclinical studies, and GLA-SE. Alhydrogel® was filled by EVI at Nova Laboratories Ltd. EVI has purchased GMP-grade GLA-SE and SE from IDRI, under a clinical trial agreement involving EVI, CHUV, IHI, IDRI and Swiss-TPH.

Clinical Development

The P27A phase Ia/Ib clinical trial is a staggered, randomised, single-blind, antigen and adjuvant dose-finding, multi-centre trial. It 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) conducted the evaluation of the vaccine in the non-exposed population, and Dr Seif Shekalaghe (IHI, Bagamoyo, Tanzania) conducted the clinical trial arm in the exposed population.

The vaccination phase in Switzerland took place from March to July 2014 and the phase Ia subjects were followed until January 2015. In Tanzania, the vaccination phase took place from July to December 2014 and the phase Ib subjects were followed until July 2015.

In both populations, the vaccine candidate was well tolerated and deemed safe. The humoral immune responses of all clinical trial subjects have been analysed in at CHUV whereas the cellular immune responses of the subjects were analysed at IHI, thus demonstrating a well-established North-South collaboration. The vaccine candidate elicited a high antibody titre although with a higher trend in the non-exposed population when formulated with GLA-SE. Exploratory studies are underway to assess the functionality of the antibodies. The cellular immune responses are also undergoing analysis, although preliminary data suggest a stronger response with GLA-SE adjuvanted vaccine.

Capacity strengthening

EVI supported the clinical trial sponsor CHUV in providing the fast-track clinical trial design, in reviewing all clinical trial documentation, in supervising the vaccine accountability and overviewing of the clinical trial management until its completion.

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

(GIAs) and ADCI assays, revealing that antibodies specific to 11 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[13].

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.

Following GMP production, the EVI-funded P27A vaccine candidate was moved into active clinical development in 2014 when a two-centre phase Ia/Ib clinical trial began at CHUV, Switzerland, in a malaria-naïve population, and was further transitioned to the malaria-exposed target population at IHI, Tanzania. In 2015, the active phase of the clinical trial was completed and the analysis of safety and immunogenicity data is underway.

Harmonisation

P27A CHUV and IHI P27A team partners have continued the harmonisation of immunological assays used during the P27A phase Ia/Ib clinical trial.

Outreach and Communication

Viviane Steiner-Monard (CHUV, Lausanne, Switzerland) presented "Safety and immunogenicity of the candidate malaria vaccine P27A with Alhydrogel® or GLA-SE as adjuvant in non-exposed European volunteers (Phase Ia)", Annual Congress of the Swiss Society for Allergology and Immunology, 12-13 March, Basel, Switzerland.

Said Jongo (IHI, Tanzania) presented "Safety and immunogenicity of P27A novel candidate blood-stage malaria vaccine P27A with Alhydrogel® or GLA-SE as adjuvant in healthy malaria non-exposed European and malaria exposed African adults aged 18-45 years", 9th European Congress on Tropical Medicine and International Health, 6-10 September, Basel, Switzerland.

François Spertini (CHUV, Lausanne, Switzerland), Salim Abdulla (IHI, Bagamoyo, Tanzania) and Claudia Daubenberger (Swiss TPH, Basel, Switzerland) presented "Safety and immunogenicity of novel candidate blood-stage malaria vaccine P27A with Alhydrogel® or GLA-SE as adjuvant in healthy malaria non-exposed European and malaria exposed African adults aged 18-45 years" at the EVI Rendez-Vous, 9 December, Paris, France.

SEmalvac

The *P. 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 NHP.

SE36 was produced 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

PARTNERS

- Centre national de recherche et de formation sur le paludisme (CNRFP), BF
- European Vaccine Initiative (EVI), DE
- Research Institute for Microbial Diseases (RIMD), JP
- Nobelpharma, JP
- Pharmalys, UK/SN
- London School of Hygiene and Tropical Medicine (LSHTM), UK

13. Villard et al., Plos One 2007, doi:10.1371/journal.pone.0000645

adults[14] and in a phase Ib clinical trial conducted in healthy subjects 6–32 years of age from a malaria-endemic area in Northern Uganda[15].

The main objective of the SEmalvac project supported by the GHIT Fund is to assess the safety and immunogenicity of the recombinant *Escherichia coli* (*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 age de-escalating clinical trial it will be possible to:

- Test the vaccine candidate in a younger age group (1–5 years old);
- Generate additional safety, immunogenicity and potential efficacy data; and
- 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 clinical 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.

The project started in August 2014 and the total budget is ¥99,999,999, from a GHIT Fund grant and US$400,000 from a Nobelpharma grant.

In 2015, the clinical trial commenced with the immunisation of children aged 2–5 years old, and following safety data review the clinical trial expanded to include the younger population aged 1–2 years old. The last boost immunisation is scheduled in April 2016.

SEmalvac

Preclinical, process development, production, IMPD

The BK-SE36 vaccine long-term stability analysis is underway at BIKEN. The current shelf life is 120 months when stored under light-protected conditions at +5 ± 3°C.

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigen SE36 is adsorbed onto aluminium hydroxide gel in the BK-SE36 vaccine manufactured at BIKEN.

Clinical Development

The age de-escalating phase Ib clinical trial was designed to assess the safety and immunogenicity of the recombinant *E. coli* BK-SE36 malaria vaccine candidate in healthy malaria-exposed African children aged 1–5 years living in Burkina Faso. The principal investigator is Dr Sodiomon Sirima (CNRFP, Ouagadougou, Burkina Faso) and the sponsor is Nobelpharma (Japan).

The clinical trial dossier including the clinical trial protocol, IMPD and IB received a favourable opinion from the institutional and national ethics committees in Burkina Faso in December 2014. The dossier was submitted to the regulatory authority in Burkina Faso and to the institutional ethics committees of Osaka University (directing the biological evaluation) and the London School of Hygiene and Tropical Medicine (directing the statistical analyses). Clearance to start the clinical trial was granted by all regulatory bodies in June 2015.

The vaccination of the children aged 2–5 years started in July 2015. After the second vaccination, a safety report was provided to an independent safety monitoring committee which recommended that vaccination could proceed in the younger population aged 1–2 years. The vaccination of the younger cohort started in October 2015. The vaccination phase should be completed by April 2016.

Outreach and Communication

Toshihiro Horii (RIMD, Japan) and Sodiomon Sirima (CNRFP, Burkina Faso) presented "An integrated approach to tackling malaria in Africa" at the Joint Egyptian - African - Japanese Scientific Symposium, International Symposium on Initiative for Promotion of Science and Technology Innovation: Cooperation between Africa and Japan, on 10-11 January, New Borg El-Arab City and Bibliotheca Alexandria, Egypt.

Toshihiro Horii (RIMD, Japan) presented "BK-SE36 malaria vaccine candidate for young children", Malaria R&D in a Time of Global Partnerships at University of Tokyo, 26 June, Tokyo, Japan.

Journalists from newspaper, radio and TV from Burkina Faso and Japan visited the CNRFP in August along with a representative of the GHIT Fund team. The meeting led to the preparation of several films by the different crews. Two of the films are available on the EVI SEmalvac website and the film prepared by the Japanese company "creative 21" was broadcast on TBS TV in a large audience program called "Door to the dream" on 13 September 2015.

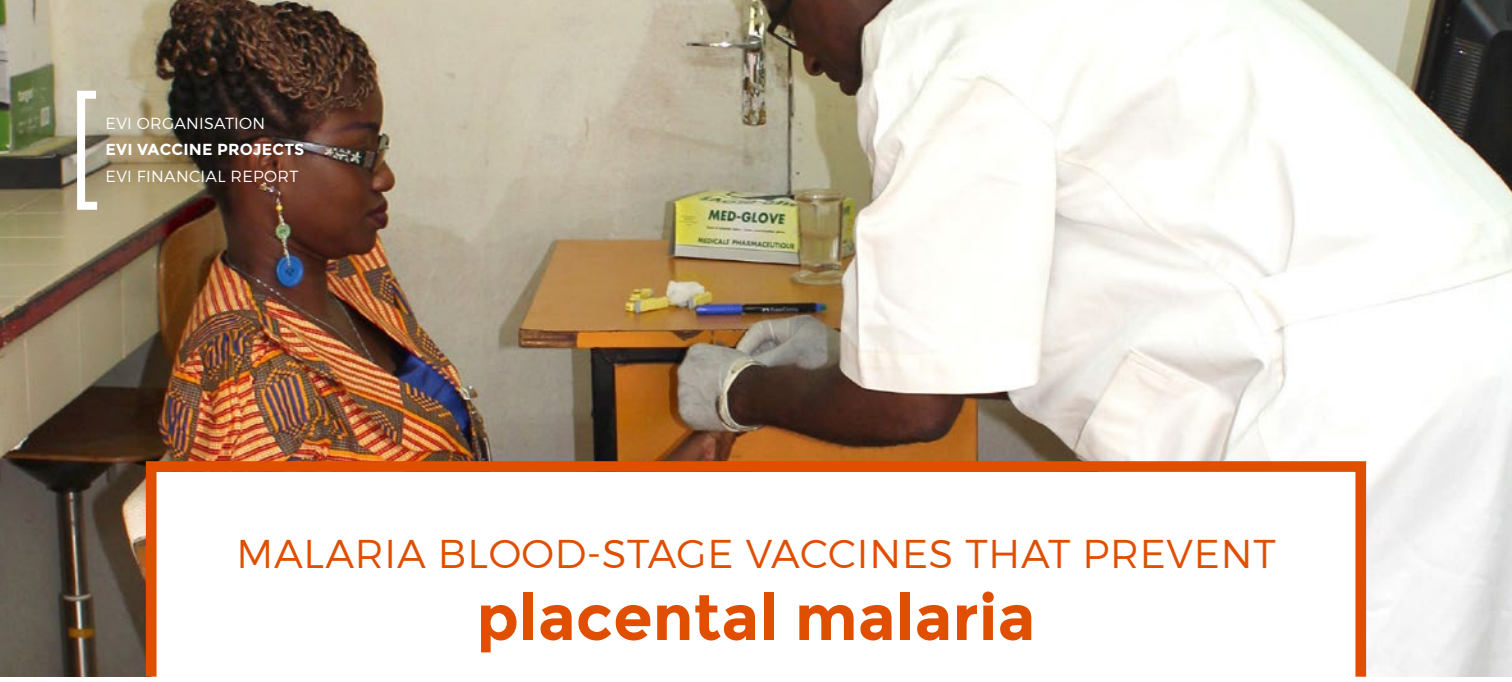
Toshihiro Horii (RIMD, Japan) presented "Clinical development of BK-SE36 malaria vaccine", at The 56th Annual Meeting for the Japanese Society of Tropical Medicine, 4-6 December, Osaka, Japan.

Toshihiro Horii (RIMD, Japan) presented "*P. falciparum* blood-stage vaccine BK-SE36" at the EVI Rendez-Vous, 9 December, Paris, France.

Toshihiro Horii (RIMD, Japan) presented "*P. falciparum* blood-stage vaccine BK-SE36" at Universal Health Coverage in the New Development Era Toward Building Resilient and Sustainable Health Systems, 16 December, Tokyo, Japan.

http://www.euvaccine.eu/portfolio/project-index/semalvac

14. Horii et al., Parasitology International 2010, doi:10.1016/j.parint.2010.05.002
15. Palacpac et al., Plos One 2013, doi:10.1371/journal.pone.0064073



MALARIA BLOOD-STAGE VACCINES THAT PREVENT **placental malaria**

Placental malaria is caused by parasite-infected blood cells binding to the placental receptor Chondroitin Sulfate A (CSA), and their subsequent accumulation in the placenta, from where they can cause disease and death for the mother and her offspring.

Pregnant women are particularly vulnerable to this type of malaria and even if they acquired immunity to malaria during childhood, they nevertheless become susceptible again during their first pregnancy. Parasites accumulate in the placenta, where a combination of altered blood flow and CSA expression provides a new niche for parasites to sequester. Every year, more than 100 million pregnant women are at risk of placental malaria, which causes the deaths of 80,000–200,000 children[16]. 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[17][18]. This relatively fast acquisition of protection has raised hope that a vaccine for placental malaria can be developed.

EVI has raised funds from BMBF, Institut national de la santé et de la recherche médicale (Inserm), the EU and the Danish National Advanced Technology Foundation (HTF) through University of Copenhagen (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 that the burden of malaria in pregnant women can be reduced, improving the health of mothers and newborns.

Blood spots for DNA extraction

16. Hartman et al., Annals of Tropical Paediatrics 2010, doi:10.1179/146532810X12858955921032
17. Brabin et al., Bull World Health 1983 PMC2536236
18 McGregor et al. Transactions of the Royal Society of Tropical Medicine and Hygiene 1983 doi: 10.1016/0035-9203(83)90081-0

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 human papilloma virus. Depending on the other malaria vaccines available on the market, a placental malaria vaccine could also be associated with a booster dose of a 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 the variant surface antigen that mediates adhesion of the infected erythrocyte to CSA (VAR2CSA) as a leading candidate for the placental malaria vaccine[19][20]. This is a *P. falciparum* Erythrocyte Membrane Protein-1 (PfEMP1) adhesin encoded by member of 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[21]. 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 trans-membrane protein has a 300-kDa extracellular region composed of six Duffy-Binding-Like (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[22][23]. Naturally-acquired antibodies, and those induced by vaccination against the domain between the N-terminal sequence and the DBL2X segment, target overlapping strain-transcendent anti-adhesion epitopes[24][25]. These data indicate that vaccines designed to block interactions between the parasite and CSA should be based on the N-terminal region of VAR2CSA.

Placental Malaria

Harmonisation

Harmonisation of the clinical trial design for a placental malaria vaccine has been implemented by the PlacMalVac and PRIMALVAC teams in order to compare the vaccine candidates.

To compare the efficacy of the vaccine candidates under development within the PAMCPH/PlacMalVac and PRIMALVAC projects, common immunoassays and standard control reagents have been discussed and agreed. Harmonisation has focused on the measurement of antibody titre by ELISA, antibody recognition of the surface of infected erythrocytes by flow cytometry and CSA-binding inhibition by antibodies using a Petri dish-based binding inhibition assay.

Harmonisation team for the development of placental malaria vaccines

19. Baruch et al., Cell 1995 doi:10.1016/0092-8674(95)90054-3
20. Su el al., Cell 1995 doi:10.1016/0092-8674(95)90055-1
21. Fried et al., Nature 1998, doi:10.1038/27570
22. Avril et al., Malaria Journal 2011; doi:10.1186/1475-2875-10-36
23. Dahlback et al., J Biol Chem 201, doi:10.1074/jbc.M110.1915101
24. Bordbar et al., Bioelectrochemistry 2011, doi:10.1016/j.bioelechem.2011
25. Bigey et al., J Inf Dis 2011, doi:10.1093/infdis/jir499

PAMCPH

The overall objective of PAMCPH is to manufacture a vaccine that protects both the foetus and the 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 Centre for Medical Parasitology at UCPH as the parasite protein which enables parasite accumulation in the placenta[26]. 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 project supports 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 €2,120,000 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 May 2016 after further funding and an extension of the project duration in mid-2015. The main achievements in 2015 were the completion of GMP manufacture of the vaccine candidate PAMVAC at CMC Biologics A/S including the release of PAMVAC based on supportive stability data and its evaluation in toxicology studies.

PARTNERS

- CMC Biologics A/S, DK
- European Vaccine Initiative (EVI), DE
- ExpreS2ion Biotechnologies, DK
- University of Copenhagen (UCPH), DK

Preclinical, process development, production, IMPD

The engineering batch was released for pharmacotoxicology studies performed by the CRO Huntingdon Life Sciences. GMP manufacture was completed at CMC Biologics and the PAMVAC drug product was released for the phase Ia/b clinical trial in Germany and Bénin. The IMPD and Investigator's Brochure (IB) were also completed.

Delivery Platform, Adjuvants and Viral Vectors

The selected adjuvants for the clinical trial are aluminium hydroxide (Alhydrogel®), the Monophosphoryl Lipid A (MPL) analogue GLA-SE and GLA- Liposome-QS21 formulation (LSQ). Alhydrogel® was filled by EVI at Nova Laboratories Ltd. Access to clinical-grade GLA-SE and GLA-LSQ has been negotiated by UCPH, with IDRI, Seattle, USA.

Outreach and Communication

Morten Nielsen, (UCPH, Denmark) presented "PAMVAC placental malaria vaccine candidate; production and adjuvants selection" at the EVI Rendez-Vous, 9 December, Paris, France.

26. Salanti A et al., Mol Microbiol 2003, doi: 10.1046/j.1365-2958.2003.03570.x

PlacMalVac

One objective of the PlacMalVac project is to conduct a phase I clinical trial with the placental malaria vaccine developed by PAMCPH. Another is the development of a phase II clinical trial centre.

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 2015 were the approval granted by the independent ethics committees in Germany and Bénin for the phase Ia/b clinical trial, and regulatory clearance granted by the Paul Ehrlich Institute (German regulatory authority) allowing the phase Ia/Ib clinical trial to be conducted in Germany.

PARTNERS

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

Delivery Platform, Adjuvants and Viral Vectors

The selected adjuvants for the clinical trial are aluminium hydroxide (Alhydrogel®), the Monophosphoryl Lipid A (MPL) analogue GLA-SE and GLA- Liposome-QS21 formulation (LSQ). Alhydrogel® was filled by EVI at Nova Laboratories Ltd. Access to clinical-grade GLA-SE and GLA-LSQ has been negotiated by UCPH, with IDRI, Seattle, USA.

Clinical Development

The phase Ia/Ib clinical trial is 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 in malaria-endemic areas in the target group (i.e. randomised, controlled, dose-finding at Institut de recherche clinique du Bénin (IRCB), Cotonou. The VAR2CSA antigen is formulated with aluminium hydroxide, GLA-SE or GLA-LSQ.

The sponsor is EKUT, the coordinating principal investigator is Dr Benjamin Mordmüller (EKUT) and the principal investigator in Bénin is Dr Saadou Issifou (IRCB).

The clinical trial protocol finalised with the results of the toxicology study was submitted along with the IMPD and IB to the ethics committee and to the regulatory authority in Germany in July 2015. Regulatory and ethical clearance was granted in November 2015. The clinical trial application was submitted to the ethics committee and to the regulatory authority in Bénin in November 2015.

The clinical trial is anticipated to start in Q2 2016 in Germany. Following a safety assessment of the vaccine in the non-exposed population by an independent safety monitoring board, the clinical trial will proceed in Bénin. EVI has appointed an independent auditor, who conducted an International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) audit of the investigational site in Bénin in November 2015 with a positive outcome with improvement needed.

Capacity strengthening

EVI supported the sponsor EKUT in providing the fast-track clinical trial design, reviewing the protocol and other clinical trial related documentation.

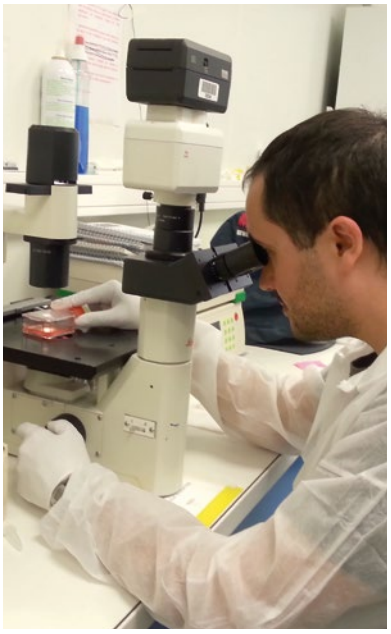
EVI also provided continued assistance in the setting of the quality assurance system of the sponsor as well as the phase Ia and Ib clinical trial sites.

Outreach and Communication

Morten Nielsen, (UCPH, Denmark) presented "PAMVAC placental malaria vaccine candidate; production and adjuvants selection" at the EVI Rendez-Vous, 9 December, Paris, France.

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 for 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 Institut national de la transfusion sanguine (INTS) and Irish Aid. The project started in December 2011 and will last four and a half years.

The highlights of 2015 included the completion of GMP production for the vaccine candidate PRIMVAC, successful toxicology studies, and preparations for the clinical trial. The ANSM (French regulatory authority) and Ile-de-France III Hopital-Tarnier-Cochin, Paris CPP (competent research ethics committee) gave authorisation for the clinical trial in France. The application for the clinical trial in Burkina Faso was submitted to the institutional and national ethics committees as well as the national regulatory authority.

Preclinical, process development, production, IMPD

Novasep manufactured the GMP batch of PRIMVAC in February 2015 and the PRIMVAC drug product was released in June 2016. Short-term and accelerated stability studies were performed and long-term stability studies are ongoing at Novasep. Toxicology studies were conducted by CiToxLAB in early 2015 and the final report is available. The IMPD and IB have been completed.

Delivery Platform, Adjuvants and Viral Vectors

The selected adjuvants are aluminium hydroxide (Alhydrogel®) and GLA-SE. A clinical supply agreement was signed by Inserm and IDRI. A new batch of GLA-SE produced in May 2015 will be used for the clinical trial. In the new batch, the phosphatidylcholine supply for the GLA has changed from egg-derived to non-animal derived. Alhydrogel® filled by EVI at Nova Laboratories Ltd. will be used for clinical trial.

Clinical Development

The PRIMALVAC project will carry out a phase Ia/Ib clinical trial in healthy adult subjects naïve to malaria and in exposed subjects in malaria-endemic regions of sub-Saharan Africa. The clinical trial is designed to assess the safety and immunogenicity of different doses of the VAR2CSA DBL1-2 vaccine candidate (PRIMVAC) in aluminium hydroxide and GLA-SE. The sponsor of the clinical trial is Inserm. The principal investigators of the clinical trial are Prof Odile Launay (CIC-Cochin, Paris, France) and Dr Sodiomon Sirima (CNRFP, Balonghin, Burkina Faso). The clinical trial protocol was finalised and the clinical trial dossier including the IMPD and IB was submitted to the ethics committee and to the regulatory authorities in France in August 2015 and September 2015 respectively. Authorisation for the clinical trial in France was obtained on 22 December 2015. The clinical trial dossier was submitted to the institutional and national ethics committees in Burkina Faso in December 2015. Following approval by the independent ethics committees the clinical trial application was submitted to the regulatory authorities. Regulatory clearance from Burkina authorities is expected by Q2 2016.

The site initiation of the clinical trial in France was planned for Q1 2016 and first vaccination of the first subject in May 2016.

Capacity strengthening

The personnel from the various collaborating French sites involved in the PRIMALVAC clinical trials were ICH-GCP trained on various occasions. All members of the CIC Cochin attended GCP training prior to the start of the clinical trial, and electronic training is performed regularly. Additionally, all investigators at the CIC Cochin attended GSK transcelerate training in 2015.

EVI also supported and mentored the clinical trial sponsor, Inserm, during the set-up and conduct of the pharmacotoxicological studies, during the preparation of the dossiers

PlacID

The overall objective of PlacID is to validate a novel NHP model to evaluate the placental malaria vaccine candidates and to assess this model as a platform for testing placental malaria vaccine candidates prior to human testing.

The lack of a reliable preclinical model for placental malaria in the past has significantly delayed the development of placental malaria vaccines.

The LMIV, NIH/NIAID has established a NHP model of placental malaria that for the first time reproduces all the features of *P. falciparum* malaria in pregnant women. Members of the genus *Aotus* are among the few species that are affected by *P. falciparum*, making them suitable for NHP experimental models in malaria research. Importantly, the animals in this model develop broadly neutralising antibodies over successive episodes of placental malaria, as do women, suggesting that this may be an appropriate model for preclinical qualification and the down-selection of vaccine candidates.

The specific objectives of PlacID are:

- To confirm that the passive transfer of purified immune IgG from multigravid African women will confer protection in pregnant *Aotus* monkeys when they are exposed to placental infection with *P. falciparum*.
- To conduct a vaccination study that assesses the leading placental malaria vaccine candidates, including the two candidates from the EVI portfolio, as well as appropriate controls.

The project started in July 2015 and will continue in 2016. The total budget is €816,400. Passive transfer and vaccination studies commenced in 2015.

PARTNERS

- European Vaccine Initiative (EVI), DE
- Institut national de la santé et de la recherche médicale (Inserm), FR
- National Institute of Allergy and Infectious Diseases (NIAID) - Laboratory of Malaria Immunology and Vaccinology (LMIV), USA
- University of Copenhagen (UCPH), DK

PlacID

Preclinical, process development, production, IMPD

Passive immunity studies using IgG from malaria-immune multigravid women and malaria-naïve individuals were initiated in the *Aotus* NHP model in November 2015. In the vaccination study, the animals received their first vaccinations with PRIMVAC, PAMVAC and the NIH/NIAID vaccine candidate in December 2015.

Harmonisation

The study procedures have been harmonised for the different vaccine candidates of the three leading groups working on placental malaria vaccine development.

Outreach and Communication

Patrick Duffy (NIH/NIAID) presented "Placental malaria animal model" at the EVI Rendez-Vous, 9 December, Paris, France.

PARTNERS

- BIOTEM, FR
- Centre national de recherche et de formation sur le paludisme (CNRFP), BF
- Centre d'investigation clinique en Cochin-Pasteur (CIC-Cochin), FR
- CiToxLAB, FR
- Creapharm, FR
- European Vaccine Initiative (EVI), DE
- GTP Technology, FR
- Infectious Diseases Research Institute (IDRI), USA
- Institut national de la santé et de la recherche médicale (Inserm), FR
- Nova Laboratories, UK
- Novasep (formerly Henogen), BE
- Novavax, USA (formerly ISCONOVA, SE)
- Pfenex Inc., USA
- Voisin Consulting Life Sciences, FR

PRIMALVAC

relevant for the clinical trial (e.g. IB, IMPD, clinical trial protocol), and during the manufacture and/or release of the drug product and adjuvants to the clinical trial.

Outreach and Communication

Benoit Gamain (Inserm) presented "Développement d'un vaccin contre le paludisme gestationnel" at the workshop CoReVac - PalSud, 2-3 December, Paris, France.

Benoit Gamain (Inserm) and Sophie Hallez (Novasep) presented "PRIMVAC preclinical activities and GMP production" at the EVI Rendez-Vous, 9 December, Paris, France.

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.

MultiMalVax

The aim of the EU FP7 MultiMalVax project, which started in October 2012 with a budget of €8,000,000, is to assess a multi-stage malaria vaccine to 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 vaccine candidates for the first time, with strong chances of success.

Participants of the annual meeting

These advances include:

- The availability of a new vectored prime-boost vaccination regime based on ChAd technology that induces exceptionally potent CD8+ T-cell responses and high titres of antibodies against multiple malaria antigens;
- The development of R21, an improved version of the leading partially-protective RTS,S sporozoite vaccine candidate, 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.

PARTNERS

- European Vaccine Initiative (EVI), DE
- GlaxoSmithKline (GSK), BE (formerly Novartis Vaccines and Diagnostics s.r.l., IT, acquired by GSK)
- ReiThera s.r.l., IT (formerly Okairòs s.r.l., IT)
- Université Pierre et Marie Curie (UPMC), FR
- University of Oxford (UOXF), UK

This collaboration includes one Small and Medium Enterprise (SME), two universities, one global pharmaceutical company and EVI, and will provide complementary abilities to facilitate the development of this promising vaccine product.

The main achievements of the MultiMalVax project thus far include the completion of GMP production of R21, the start of the phase Ia clinical trials assessing R21 adjuvanted with AS01 and the viral vectored (ChAd63/MVA) transmission-blocking vaccine candidate Pfs25-IMX313, and the completion the PfRH5 blood-stage clinical trial.

MultiMalVax

Preclinical, process development, production, IMPD

ChAd63 and MVA vectors expressing Pfs25-IMX313 were produced under GMP conditions at CBF UOXF and the ChAd63 vector was released for the clinical trial.

A R21 GMP batch was produced at CBF UOXF and released for the clinical trial. The corresponding IBs and IMPDs were also prepared.

Delivery Platform, Adjuvants and Viral Vectors

The malaria antigens ME-TRAP, PfRH5 and Pfs25 are designed to be delivered in a prime boost strategy using two different vectors: ChAd63 and MVA. The transmission-blocking Pfs25 antigen is fused to the IMAXIO IMX313 tag. Fusion to the IMX313 DNA sequence led to oligomerisation of the recombinant protein because the IMX313 tags spontaneously auto-assemble into a heptamer. The oligomerisation of the antigen is expected to significantly increase both B cell and T cell immunogenicity, therefore improving vaccine efficacy. R21 is administered with the AS01B adjuvant.

Clinical Development

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 regions.

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, with the long-term objective to provide a deployable high-efficacy product for use in malaria-endemic areas. The initial ambitious objective of developing a vaccine candidate targeting each stage of the parasite life cycle was modified to a multi-component vaccine, for which a combination vaccine trial will start in Mid-2016.

The Medicine and Healthcare Products Regulatory Agency (MHRA) approved the VAC056 clinical trial, which uses the RTS,S biosimilar R21 in combination with AS01 as a pre-erythrocytic vaccine and the clinical trial commenced in December 2015. The clinical trial is taking place at the Southampton National Institute for Health Research Wellcome Trust Clinical Research Facility and UOXF.

Approval for the mosquito-stage vaccine trial was granted by the research ethics committee in UOXF on 12 May and by the MHRA on 21 June. The first vaccination started in the Southampton trial site on 12 October with the ChAd63-Pfs25-IMX313 vector and the vaccine showed a good safety profile. The ChAd63-Pfs25-IMX313 / MVA Pfs25-IMX313 prime-boost group will commence in early 2016 following the release of the vector for the clinical trial.

The vectored PfRH5 blood-stage vaccine clinical trial started in August 2014 and ended in October 2015. No safety signals were observed and ChAd63/MVA PFRH5 showed good immunogenicity, inducing antigen-specific T cells and IgG. Induced antibodies showed activity in GIAs in correlation with the concentration of antibodies, and cross-strain GIA activity was observed. A manuscript is in preparation.

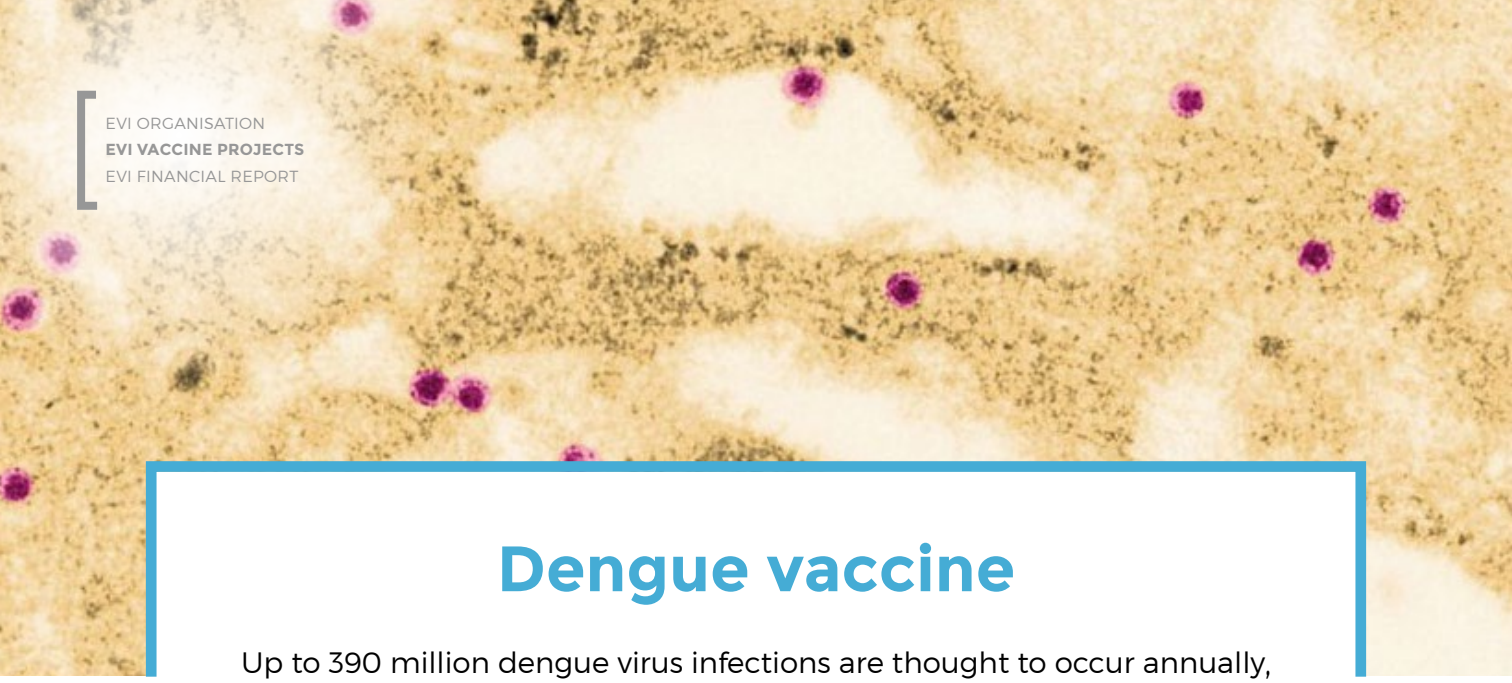
Harmonisation

UOXF is a member of the MVVC and MVVC 2 consortia and was part of the OPTIMALVAC (www.optimalvac.eu) network and was thus involved in antibody and T-cell assay harmonisation activities. In addition, phase I clinical trials assessing the transmission-blocking antigen Pfs25-IMX313 and the pre-erythrocytic R21 vaccine candidate are being conducted at the Centre for Clinical Vaccinology and Tropical Medicine, UOXF, and the Southampton National Institute for Health Research Wellcome Trust, and clinical activities are harmonised across these centres.

Outreach and Communication

Adrian Hill (UOXF, Oxford, UK) presented “Development of a multi-component multistage malaria vaccine” at the EVI Rendez-Vous, 9 December in Paris, France.

Simon Draper (UOXF, Oxford, UK) presented “PfRH5 blood stage malaria vaccine candidate; antigen optimisation, production and phase I/II clinical trial” at the EVI Rendez-Vous, 9 December in Paris, France.



Dengue vaccine

Up to 390 million dengue virus infections are thought to occur annually, 96 million of which have clinical manifestations.

Dengue is estimated to cause 20,000 deaths every year, mainly among children. Although mortality is lower compared to other tropical infectious diseases such as malaria, the scale of human suffering and the resources invested in the control of dengue make it a major global health problem.[27]

The several vaccine candidates for dengue currently in preclinical or clinical development do not achieve equal protection against all four known dengue serotypes. This poses the risk of limited protection against specific serotypes and of the so-called dengue viral interference problem: sequential infections with different dengue serotypes can increase the risk of developing a severe and potentially lethal disease.

PARTNERS

- European Vaccine Initiative (EVI), DE
- Institut Pasteur Paris (IPP), FR
- Institute of Tropical Medicine Nagasaki University (NEKKEN), JP

MVDVax

MVDVax is a GHIT-funded project with a budget of ¥61,290,240, which commenced in October 2015 and will last for one year.

The aim of the current project stage is to demonstrate the proof-of concept of a measles-virus-dengue vaccine candidate (MVDVax) in a NHP model, to produce all the data required for follow-up projects, and to ready for GMP production, toxicology studies and the phase I clinical trial.

MVDVax target populations are primarily young children in dengue-endemic regions and travellers to affected areas. MVDVax overcomes the lack of equal protection provided by current vaccine candidates against different serotypes by using a monovalent live dengue vaccine, allowing the more balanced and controlled expression of the antigens representing different serotypes. Furthermore, MVDVax focuses on T-cell responses by expressing a mixture of non-structured protein regions, which show stronger T-cell response compared to structured dengue proteins, but are missing from almost all dengue vaccines in development (except live attenuated dengue virus). In addition, MVDVax uses only part of the E-protein, avoiding regions suspected to induce antibody-enhancing phenotypes and allowing for a smaller vector insert. Because MVDVax uses the measles virus as a way to express the dengue antigens, it reduces the cost of production to that of the measles vaccine cost, which is appropriate for a disease of poverty.

The project was launched at the kick-off meeting on 4 November 2015. During 2015, the preclinical study and the corresponding immunoassays (sandwich ELISA) were optimised, the protocol for the NHP model was developed, and approvals were granted by the relevant scientific and ethics committees.

MVDVax

Preclinical, process development, production, IMPD

The preclinical study and the corresponding immunoassays to be used (sandwich ELISA) have been optimised.

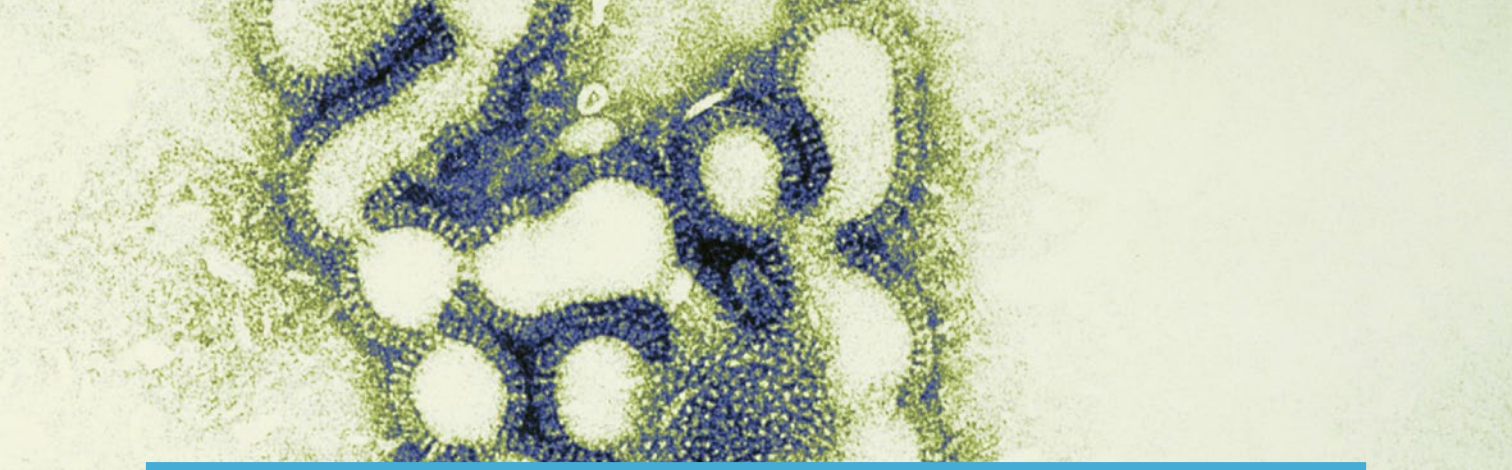
Delivery Platform, Adjuvants and Viral Vectors

Measles virus is used as a vector to express the immunogenic dengue antigens.

Outreach and Communication

The start of the project was announced at a press release from GHIT Fund on 5 November.

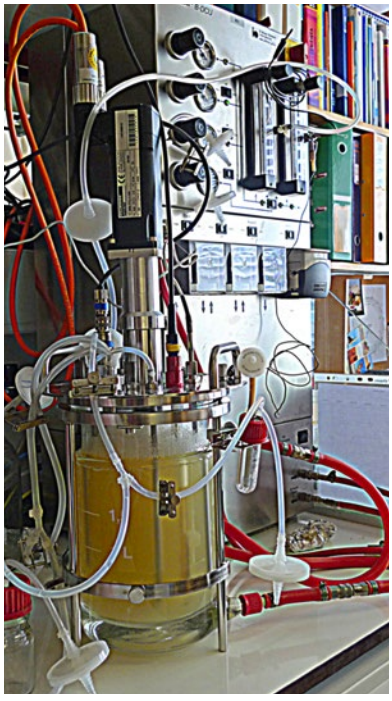
27. http://www.who.int/mediacentre/factsheets/fs117/en/



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 compositions 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.



EDUFLUVAC

In order to address the problem of antigenic drift and annual vaccine reformulation, the EU FP7 EDUcate inFLUenza VACcine (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 haemagglutinin (HA) and/or neuraminidase (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 to 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 NHP models. Furthermore, an optimised process suitable for the GMP-compliant manufacture of VLPs

PARTNERS

- Biomedical Primate Research Centre (BPRC), NL
- Central Veterinary Institute (CVI), NL
- ETNA BIOTECH s.r.l., IT
- European Vaccine Initiative (EVI), DE
- Instituto de Biologia Experimental e Tecnológica (iBET), PT
- National Institute for Biological Standards and Control (NIBSC), a centre of the Medicines and Healthcare Products Regulatory Agency, UK
- Redbiotec AG, CH

will be developed. The project will take note of new influenza vaccine regulatory guidance and will be geared towards the development of a complete Investigational Medicinal Product Dossier (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 in 2015 were the preparation of all intended VLPs, their use in mouse immunisation studies and the organisation of a successful workshop on immunoassay standardisation for universal influenza vaccines that took place at NIBSC.

Participants of the annual meeting

EDUFLUVAC

Preclinical, process development, production, IMPD

Redbiotec has generated all baculovirus vectors for the expression of the selected influenza HA and NA antigenic variants. Those vectors have been provided to iBET, which has generated all VLPs intended for the mouse studies. All mouse immunisation studies have been completed at ETNA BIOTECH and sera have been analysed by ELISA. The first results generated suggest that epitope dilution phenomena may also apply to influenza virus HA. The neutralisation capacity of the mouse sera is being tested at NIBSC. Supporting analytical activities for the characterisation of the VLPs have commenced at iBET and NIBSC.

Delivery Platform, Adjuvants and Viral Vectors

The EDUFLUVAC project will use VLPs to deliver multiple influenza HA and/or NA antigenic variants. Following careful selection of the antigen strains, assembly in baculovirus vectors and VLP production in insect cell lines has been completed at Redbiotec AG, Switzerland, and at iBET, Portugal, respectively.

Capacity strengthening

The iBET team attended the course on integrative structural biology tools for the study of protein-ligand interactions, in July 2015, Lisbon, Portugal.

In August, the Redbiotec team organised a workshop on intellectual property in the context of the EDUFLUVAC project, Zurich, Switzerland.

Harmonisation

The EDUFLUVAC consortium partners' iBET and NIBSC continued their cooperation to develop a method for the quantification of multiple HA in influenza VLPs by isotope dilution mass spectrometry.

Outreach and Communication

Ed Remarque and Gerrit Koopman (BPRC, NL) presented the EDUFLUVAC project at the UNISEC (EC FP7-funded project on universal influenza vaccines) meeting, 6 March 2015, Copenhagen, Denmark.

Ed Remarque (BPRC, NL) presented "The epitope dilution phenomenon: Lessons learnt from a polymorphic malaria vaccine candidate (AMA1) and applicability to polymorphic vaccine antigens" at the 5th Modern Vaccines and Adjuvants & Delivery Systems conference, 18-20 May, Leiden, Netherlands.

Sofia Carvalho (iBET, Portugal) presented "A click chemistry approach to monitor and improve influenza VLPs downstream processing" at the 21st Biennial Meeting of the International Society for Molecular Recognition, 27 September-1 October, Puerto Vallarta, Mexico.

Cristina Peixoto (iBET, Portugal) presented "Universal label-free in-process analytical tool for influenza VLPs quantification" at the 21st Biennial Meeting of the International Society for Molecular Recognition, 27 September-1 October, Puerto Vallarta, Mexico.

Ed Remarque (BPRC, NL) presented "EDUFLUVAC project introduction and overview" at the 5th Influenza Vaccine for the World, 6-9 October, Albufeira, Portugal.

Antonio Roldão (iBET, Portugal) presented "A click chemistry approach to monitor and improve influenza VLPs downstream processing" at the 5th Influenza Vaccine for the World, 6-9 October, Albufeira, Portugal.

Antonio Roldão (iBET, Portugal) presented "Combining stable insect cell lines with baculovirus-mediated expression for production of multi-HA influenza VLPs" at the 5th Influenza Vaccine for the World, 6-9 October, Albufeira, Portugal.

Ed Remarque (BPRC, NL) presented "Diversity covering approach for universal flu vaccines: updates from the EDUFLUVAC project" at the EVI Rendez-Vous, 9 December, Paris, France.

Othmar Engelhardt (NIBSC, UK) presented "Harmonisation of immunoassays for universal flu vaccines" at the EVI Rendez-Vous, 9 December, Paris, France.

EDUFLUVAC

workshop on immunoassay standardisation for universal flu vaccines

EDUFLUVAC – workshop on immunoassay standardisation for universal flu vaccines

Capacity strengthening

The first EDUFLUVAC workshop on immunoassay standardisation for universal flu vaccines took place on 18-19 June 2015 at NIBSC, UK. This workshop was co-organised and co-sponsored by the NIH/NIAID, USA.

More than 50 worldwide experts from the universal influenza vaccine R&D field met to discuss how the community should concentrate its efforts to define the path from immunoassay validation towards harmonisation and ultimately standardisation.

In summary, the workshop audience agreed that it is not possible to establish one universal immunoassay for universal flu vaccines because the approaches differ significantly according to the nature and immunogenicity of the vaccines.

Therefore, different scientific rationales are required for the choice of immunoassays during the development of different universal flu vaccines. In order to avoid the dilution of efforts, the choice of the primary evaluation criteria (e.g. serological assays such as HA or NA inhibition versus T cell assays, Enzyme-Linked ImmunoSpot Assay (ELISpot) etc.) should drive the effort of harmonisation. However, during the early phase of clinical development, exploratory assessments should be undertaken to better define the immune profile.

The workshop concluded that each laboratory will aim to validate the appropriate immunoassays used during the entire process of vaccine development from antigen discovery to the establishment of correlates of protection, including the different quality control steps (e.g. potency assays), animal studies and human clinical development. Standardisation of the immunoassays is the ultimate objective and there is a long way to go.

A manuscript describing the outcome of the workshop is being prepared and will be published in peer-reviewed journal. The presentations from the workshop are available on the EDULFUVAC website: http://www.edufluvac.eu/node/1117

A clear need for more collaboration on the harmonisation of immunoassays was identified by the first workshop and the EU partnership. The discussions during the first EDUFLUVAC workshop naturally lead to a decision on the topic of the next workshop: Experimental animal models for universal influenza vaccines.

Standardisation and development of assays for the assessment of influenza vaccine correlates of protection

PARTNERS

- Abbott,NL
- Artemis One Health Research BV, NL
- AstraZeneca AB, SE
- Erasmus Universitair Medisch Centrum Rotterdam (EUMCR), NL
- European Medicines Agency (EMA), UK
- European Vaccine Initiative (EVI), DE
- Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, IT
- Biomedical Primate Research Centre (BPRC), NL
- GlaxoSmithKline (GSK),BE
- Istituto Superiore di Sanità, IT
- Janssen, NL
- MHRA-Department of Health,UK
- Novartis, IT
- Paul-Ehrlich-Institut, Bundesinstitut Für Impfstoffe Und Biomedizinische Arzneimittel, DE
- QUINTEN, FR
- Sanofi Pasteur, France
- Sclavo Vaccines Association, IT
- The Chancellor, Masters and Scholars of the University of Oxford, UK
- Università degli Studi di Siena, IT
- Universiteit Gent, BE
- Universitetet i Bergen, NO
- University of Surrey, UK

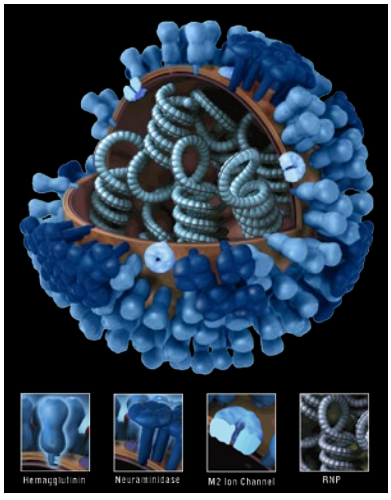
FLUCOP

Despite the development and licensing of influenza vaccines along with clinical evidence of their ability to protect against influenza, the potential correlates of protection induced by these vaccines are still not fully understood.

The availability of a toolbox of standardised, validated serological assays for human influenza vaccines, agreed and used by key parties in the public and private sectors, will have a tremendous impact on the research and development (R&D) process globally, and will pave the way for future investigations and the definition of correlates of protection for these vaccines.

The FLUCOP project is supported by the IMI, with funding from the EU FP7. The project commenced in March 2015 and will have a duration of five years, ending in February 2020. The total budget is €13,999,164 with equal contributions from IMI and European Federation of Pharmaceutical Industries and Associations (EFPIA). EVI is managing dissemination and communication in the project, and benefits from the harmonisation achievements and the consortium network.

The long-term objective of the FLUCOP project is to improve and standardise existing immunological assays for the definition of correlates of protection in future efficacy trials and, whenever feasible, to develop new assays to better evaluate influenza vaccine immunogenicity.



3D graphical representation of the biology and structure of a generic influenza virus, and are not specific to the 2009 H1N1 virus.

The ultimate objectives will be achieved through three intermediate objectives:

- Achieving the standardisation of haemagglutination inhibition and virus neutralisation assays as the primary objective;
- Advancing the understanding and application of cell-mediated immunity and NA assays as tools to evaluate the performance of influenza vaccines as a secondary objective;
- Consideration of new technologies that could be used to investigate correlates of protection and population-based evaluations of influenza vaccines as an exploratory objective.

FLUCOP

Harmonisation

The FLUCOP team assessed factors influencing the variability of the influenza haemagglutination inhibition assay. An optimised and standardised assay protocol is under development.

Outreach and Communication

The FLUCOP website was established and is updated regularly: (http://www.flucop.eu).

A FLUCOP flyer was generated and distributed: (www.flucop.eu/flyer).

The first FLUCOP newsletter was sent to an audience of more than 800 relevant people (www.flucop.eu/NL1).

The launch of FLUCOP was announced to EVI partners with a press release and published on the EVI webpage on 10 March 2015.

The scientific coordinator of FLUCOP, Emanuele Montomoli, presented "Standardisation and development of assays for assessment of influenza vaccine correlate of protection" at the EVI Rendez-Vous, 9 December, Paris, France.

Paratyphoid vaccine

Systemic enteric fever in humans is often caused by *Salmonella typhi* and *S. paratyphi* A, resulting in 27 million new cases worldwide and 200,000 deaths each year[28].

The highest number of cases occur in South and Southeast Asia. However, there are no vaccines against *S. paratyphi* A, which is emerging as a major cause of pandemic enteric fever and 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 translation of early vaccine concepts into expensive field trials needs new and innovative approaches. Furthermore, because *S. paratyphi* is a human-restricted pathogen, there is no animal model that allows the protective efficacy of vaccines to be evaluated. *S. paratyphi* is the Achilles heel in the global battle against enteric fever.

PIM

The Paratyphoid Infection Model (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 that are efficacious against *S. paratyphi*.

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 *S. paratyphi* A, identify potential correlates of protection and evaluate the efficacy of vaccine candidates by providing early proof of the vaccine concept.

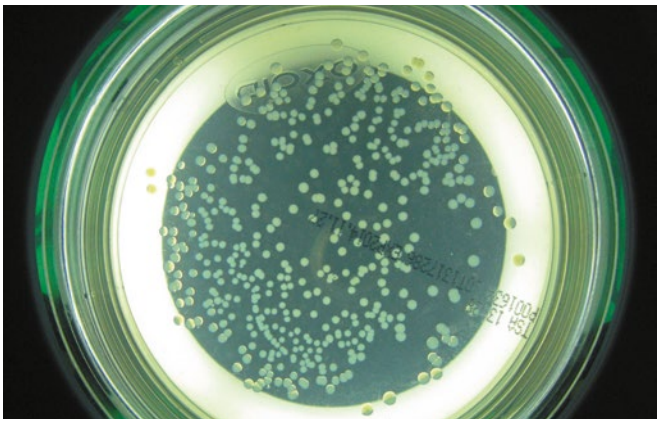
This two-year project has a total budget of €325,000 provided by EVI complemented by co-funding from the Bill and Melinda Gates Foundation (BMGF).

In 2015, the clinical trial was completed, and has demonstrated the safety and practicality of the first ever human challenge study for *S. paratyphi* A. A clinical/laboratory attack rate of 60% was achieved at a challenge dose of 1-5 x 103. The *S. paratyphi* A challenge model could therefore be used to test candidate vaccines against an important and neglected pathogen.

PARTNERS

- European Vaccine Initiative (EVI), DE
- Novartis Vaccines Institute for Global Health, IT
- University of Oxford (UOXF), UK
- Wellcome Trust Sanger Institute, UK

28. Buckle GC et al, J Glob Health, 2012, doi:10.7189/jogh.02.010401



Agar plates

Preclinical, process development, production, IMPD

The strain of *S. paratyphi* A (NVGH308) used for the development of the controlled human infection model was isolated from a case of human paratyphoid infection in Nepal and was grown under GMP conditions. Full microbiological characterisation and antibiotic sensitivity of the strain has been demonstrated and further characterisation, including genome sequencing, has been completed at the Sanger Institute, Cambridge, UK.

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

Clinical Development

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, to identify biomarkers and to evaluate the efficacy of vaccine candidates.

To determine the dose of *S. paratyphi* A required for the development of the human challenge model, healthy volunteers have been challenged with escalating doses of *S. paratyphi* A in order to give a clinical/laboratory attack rate of 60%. The clinical trial was completed in 2015. The Oxford vaccine group recruited 47 subjects, of which 40 were challenged. Half of them received 1–5 x 103 colony forming units (CFUs) *S. paratyphi* and the other half received 0.5–1 x 103 CFUs *S. paratyphi*. The safety and practicality of the first ever human challenge study for *S. paratyphi* A was demonstrated. The outpatient management of participants challenged with *S. paratyphi* A was shown to be safe and well-tolerated. When administered with bicarbonate solution, a target attack rate of 60% was achieved at a challenge dose of 1–5 x 103 CFUs. The early response indicates successful infection of all subjects although cytokine responses do not seem to predict subsequent diagnosis. However, transcriptional data may be able to predict the outcome.

The *S. paratyphi* A challenge model has the potential to be used to test vaccine candidates against an important and neglected pathogen.

Harmonisation

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.

Outreach and Communication

Hazel Dobinson (Oxford Vaccine Group, UOXF, UK) presented "Development of a human model of *Salmonella enterica* serovar paratyphi A challenge in healthy adult volunteers" at the 9th International Conference on Typhoid and Invasive Non-Typhoidal Salmonella (iNTS) Disease, 30 April-3 May, Bali, Indonesia.

Hazel Dobinson (Oxford Vaccine Group, UOXF, UK) presented PIM data at 2nd Annual Microbiology & Infectious Diseases Asia Congress, 23-24 June, Singapore.

Andrew Pollard (Oxford Vaccine Group, UOXF, UK) presented "Paratyphoid infection model, development of a human model of *Salmonella enterica* serovar paratyphi A challenge to accelerate vaccine development" at the EVI Rendez-Vous, 9 December in Paris, France.

New vaccine technologies and a vaccine against *S. aureus*

Potent immunogenic tags have the potential to increase the immunogenicity of vaccine antigens.

IMAXIO, a French biotechnology company, has developed IMX313, a small DNA sequence that can be fused to any antigen gene of interest. Recombinant proteins fused to IMX313 spontaneously auto-assemble into heptamers and thus present the antigen seven times to the immune system. Antigen oligomerisation significantly increases both B cell and T cell immunogenicity, therefore improving the efficacy of corresponding vaccine candidates. IMX313 is compatible with subunit, DNA and viral-vectored vaccines, but is also synergistic with conventional adjuvant technologies. This technology has been tested since 2013 in a phase I clinical trial of a tuberculosis (TB) vaccine candidate and it is undergoing preclinical development for malaria and *S. aureus* vaccine candidates.

S. aureus, including Methicillin-Resistant *S. aureus* (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 *S. aureus* strains such as MRSA has created a serious global public health threat and a growing economic burden. Because recent vaccine candidates against *S. aureus* have not proven effective and therefore have not been licensed by the Food and Drug Administration agency or the European Medicines Agency, there is an urgent need to develop new vaccine strategies against this pathogen. Furthermore, a major phase III clinical trial of a *S. aureus* vaccine developed by Merck (V710) in more than 8000 subjects showed an unexpected increase in the mortality in vaccinated individuals. This phenomenon, which was not observed previously, caused the termination of this Merck vaccine development program, and emphasised the uncertainty surrounding naturally-occurring immune responses to *S. aureus* in pre-clinical models. Subsequent analysis suggested that the greater mortality might be associated with a particular profile of cytokine responses (low IL-17A and IL-2 concentrations)[29].

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 *S. aureus* vaccine candidate targeting both the cellular and humoral immune responses. It is designed to protect against both MRSA and more sensitive *S. aureus* strains.

The BELLEROPHON project comprises four European institutions involved in vaccine development, each contributing specialist expertise

PARTNERS

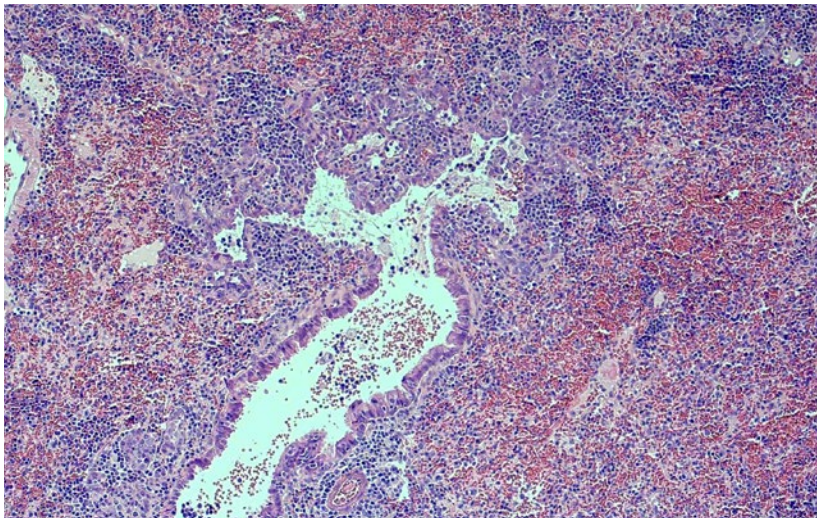
- European Vaccine Initiative (EVI), DE
- IMAXIO SA, FR
- Preclin Biosystems AG, CH
- University of Oxford (UOXF), UK

29. McNeely et al., Human vaccines & immunotherapeutics, 2014. doi: 10.4161/hv.34407

and technology. IMAXIO, the French biotechnology company focusing on immunology, was the leader of the project application. The Jenner Institute (UOXF, UK) is an academic institution with key expertise in *S. 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.

The fourth member is Preclin Biosystems, a Swiss Contract Research Organisation (CRO) with strong expertise in preclinical efficacy models for infectious diseases.

The main achievements during 2015 were the assessment of the vaccine candidate in different preclinical animal models and progress towards the discovery of new potential vaccine antigens.



Pneumonia histopathology

Preclinical, process development, production, IMPD

The BELLEROPHON team has worked on the optimisation and validation of the vaccine candidate. Preclinical batches of the selected antigen combination have been produced in two delivery systems: recombinant proteins and viral vectors (ChAdOx/MVA) with and without the IMX313-tag. The vaccine candidates have been assessed in three different animal models: pneumonia, kidney abscess formation and sepsis intraperitoneal models in mice. The preclinical evaluation of the vaccine candidate did not support further clinical development within the BELLEROPHON project timelines. Additional antigen discovery is underway at UOXF and the results are promising.

Delivery Platform, Adjuvants and Viral Vectors

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 and thus enhances its presentation to the immune system.

Additionally, the vaccine antigens are being assessed using a prime boost regime with viral vectors ChAdOx and MVA developed at UOXF.

Capacity strengthening

Amy Flaxman, UOXF, has attended following training courses:

- Statistics: Designing clinical research and biostatistics, University of Oxford (28-29 October 2015)
- Introduction to Phlebotomy, Geopace Training (22 January 2015)
- Flow Cytometry Course, University of York (27-30 January 2015)

Claudia Lindemann, has attended following training courses:

- Designing Clinical Research and Biostatistics, IT Services, University of Oxford (3-4 June 2015)
- Introduction to Statistical Package for the Social Sciences, Medical Science Skills Division, University of Oxford (1-5 June 2015)
- Good Clinical Practice, Online Tutorial, University of Oxford (7 April 2015)

Outreach and Communication

Amy Flaxman (UOXF, UK) presented poster "Microenvironment-specific changes in microflora and immune parameters identified during a study of murine *S. aureus* carriage" on the Staphylococcal Diseases - Gordon Research Conference & Seminar, 12-17 July in Lucca (Barga), Italy and at the Second Annual Florey Symposium, University of Sheffield 11 September, Sheffield, UK.

David Wyllie (UOXF, UK) presented "*S. aureus* - antigen discovery" at the EVI Rendez-Vous, 9 December, Paris, France.

Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth Infections

Neglected infectious diseases (NIDs) are 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[30]. Indeed, there is growing epidemiological evidence for 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 the World Health Organization (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[31]. 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.

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.

30 Eziefula AC et Brown M, Curr Opin Infect Dis, 2008, doi:10.1097/QCO.0b013e32830f97fd
31. 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 (CHUV), CH
- Centre de Recherches Medicales de Lambarene (CERMEL), GA
- Eberhard Karls Universitaet Tübingen (EKUT), DE
- Ecole Polytechnique Federale de Lausanne, CH
- European Vaccine Initiative (EVI), DE
- EuroVacc Foundation, NL
- Fondation international de l'Hopital de Dr. Albert Schweitzer de Lambarene, GB
- Ifakara Health Institute (IHI), TZ
- Institut national de la santé et de la recherche médicale (Inserm), FR
- Istituto Nazionale Malattie Infettive L.Spallanzani - IRCCS, IT
- Kenya Medical Research Institute (KEMRI), 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 (Swiss-TPH), CH
- University of Ibadan, NI
- University of Oxford (UOXF), UK
- Vaccine and Gene Therapy Institute Florida, USA

Clinical Development

The IDEA work package measuring 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 a malaria vaccine controlled, double-blind, multi-centre study to evaluate the efficacy, safety, and immunogenicity of three doses of GMZ2 candidate malaria in Lambaréné, Gabon, were completed early 2013. Samples were analysed by PCR and microscopy to detect parasites. Immunogenicity studies are ongoing. Unblinding of the data has been postponed until 2016. Pilot studies were carried out on samples from phase I clinical trials of GMZ2 to assess the effect of helminth infection on the natural antibody responses to mature gametocyte surface and intracellular antigens in vaccinated individuals. The data proved that children infected with *T. trichiura* have a lower antibodies production when compared to none infected children. Basically, intestinal parasites modulate antibody response to mature gametocytes of *P. falciparum*.

The TB clinical 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 Bacillus Calmette-Guérin (BCG). The recruitment for the clinical trial was successfully accomplished without loss to follow up. Immunisation and sampling are complete, and good safety and initial immunogenicity data have been demonstrated. Additional analysis is ongoing and a manuscript will be prepared later.

The HIV clinical trial aims to evaluate the safety and immunogenicity of HIV vaccine candidates, including a DNA prime followed by an AIDSVAX B/E protein boost, in HIV-1-free adult participants with or without underlying schistosomiasis infections. The clinical trial took place in two sites (Entebbe and Masaka) in Uganda. Vaccination, sampling and follow-up have been completed. All clinical trial data have been collected and entered into the OpenClinica database. Preliminary immunogenicity data have been obtained, and unblinded preliminary analysis is anticipated in Q2 2016.

Capacity strengthening

In 2015, IDEA continued capacity strengthening activities in sub-Saharan Africa. In total, IDEA has now supported nine Masters students at UVRI (Uganda), CERMEL (Gabon) and IHI (Tanzania) and 16 PhD students at UVRI, IHI, Mbeya (Tanzania), CERMEL, University of Ibadan (Nigeria), and KEMRI (Kenya). IDEA has also contributed to the establishment of a Masters course in immunology and clinical microbiology at the Makerere University, Uganda. IDEA has provided opportunities for post-graduate research and has contributed to the development of emerging African centres of excellence in both parasitological and immunological techniques. In addition, IDEA has supported multiple North-South and South-South exchanges with the primary objective of strengthening capacity in immunology.

IDEA has funded and co-funded multiple cutting-edge technique workshops and immunology short courses:

- Immunology in the tropics (details can be found in previous annual reports)
- Molecular techniques workshop
- Parasite PCR
- Multiplex Ligation-dependent Probe Amplification
- Bioinformatics shop
- R programming
- Viral genomics
- Functional genomics
- Luminex analysis

In response to the tremendous interest in immunology generated by the short courses in Uganda (to which IDEA contributed) and by the establishment of a laboratory at Makerere University College of Health Sciences (MU-CHS), the department of microbiology at MU-CHS has established a Masters course in immunology and clinical microbiology which has entered its fifth year.

•••

Harmonisation

The IDEA project continued to encourage the harmonisation and implementation of novel immunological and diagnostic assays, and data management for clinical trials in African settings, led by African principal investigators thus building African skills. IDEA also leverages parallel research programs funded by the EC and international initiatives for sustained development, involving the further exchange of immunological assays and diagnostic methods across the study sites. Standard operating procedures for functional polychromatic flow cytometry, Luminex and gene profiling were unified and the reagents were standardised.

In addition, IDEA has also established a central database. Demographic, epidemiological and clinical data from the main IDEA studies have been cleaned, quality controlled and imported. The database will be instrumental for future cross-study analysis beyond the life span of the IDEA project.

Outreach and Communication

Alison Elliott presented "IDEA research initiative on poverty related neglected diseases and helminth infections" during a visit of European MPs on 10 April at UVRI, Uganda, organized by Deutsche Stiftung Weltbevoelkerung.

Odile Leroy presented "A world free of the intolerable burden of diseases of poverty" during a visit of German MPs on 28 May at UVRI, Uganda, organised by Deutsche Stiftung Weltbevölkerung (DSW) for product development partnerships (PDP) funded by the German government.

Alison Elliott presented "IDEA: dissecting the immunological interplay between poverty related diseases and helminth infections: An African-European research initiative" during a visit of German MPs on 28 May at UVRI, Uganda, organised by DSW for PDP funded by the German government.

IDEA presented a project lab and a stand at the 2015 European Development Day, 3-4 June, Brussels, Belgium. The central theme for both the project lab and the stand is the building of sustainable research in sub-Saharan Africa. Scientists from both Europe and sub-Saharan Africa presented their research and concluded that sustainable development can only be achieved through an integrated approach and international cooperation between policymakers, funding agencies and research communities.

Matthieu Perreau (CHUV, Switzerland) gave a keynote presentation "Helminths and poverty related diseases vaccines: Scientific hypothesis generated by IDEA" at the EVI Rendez-Vous, 9 December, Paris, France.

Anne Wajja (UVRI, Uganda) presented "Helminths and TB vaccine candidate" at the EVI Rendez-Vous, 9 December, Paris, France.

IDEA was a five-year EU-funded project with 20 consortium members coordinated by CHUV and had a total budget of €10,300,000. The primary objective 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 achievement in 2015 was the successful termination of the project and submission of the final report to the EC. EVI was involved in clinical trials assessing the effect of helminth infections on vaccination against HIV and TB. These trials were successfully completed showing good the safety and initial immunogenicity data. Further analysis is currently underway.

Samples collection for TB vaccine trial in Uganda

Vaccine research and development policy

EVI continued to engage with several EU member states and other governments to advocate for sustained funding for global health R&D.

Activities with EVI involvement included a meeting at the German Chancellery with the Sherpa team of the G7 summit that took place in June 2015, a visit with several German members of parliament (MPs) to a clinical trial site in Uganda, the participation in discussions with British MPs over dinner, and the participation in a parliamentary event in Berlin relating to the R&D product pipeline for global neglected diseases.

PARTNERS

- European Advanced Translational Research Infrastructure in Medicine (EATRIM), NL
- European Vaccine Initiative (EVI), 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 2015, the two final stakeholder consultation meetings were organised, focusing respectively on Research & innovation/ research infrastructures, and on Therapeutic vaccines.

Outreach and Communication

A stakeholder consultation on "Research & Innovation and Research Infrastructures" was organised in Brussels on 12-13 March, with participation from research, academia, industry, policy bodies, scientific societies and IPROVE project partners. Its objective was to identify key gaps and needs to be addressed jointly and at the EU level to bolster vaccine innovation.

A stakeholder consultation on "Therapeutic Vaccines" was organised on 26 May in Brussels, focussing on vaccine R&D issues linked to both infectious and non-infectious diseases.

International Fora and Advocacy

International Fora

EVI members attended several scientific conferences and events to sustain fruitful networking and communication with the research community. The events and conferences attended by EVI members are listed in Annex 1.

Advocacy

EVI has been actively involved in several political events, including parliamentary events in London, UK and Berlin, Germany, and the visit of four members of the German parliament in Uganda, amongst other activities. Moreover, representatives from EVI and two other PDPs met with the German G7 sherpa in the German Chancellery in Berlin to advocate for a sustained support by the G7 countries to global health R&D.

A major impact of EVI´s advocacy activities in 2015 has been the renewed commitment of the German government to support product development for neglected and poverty related diseases, and the commitment by the G7 countries to more support for global health R&D. Continued EVI advocacy work at EU and Member States level resulted in the publication of a call by the EC in 2015 to support the further development of a European vaccine R&D infrastructure with up to €10 million.

GLOBVAC Annual Meeting, 17-18 March, Oslo, Norway

The title of the 9th Conference on Global Health and Vaccination Research "How can research inform the post-2015 agenda for women's and children's health and rights?" The meeting agenda was very much influenced by the post- Millennium Development Goal – Sustainable Development Goals discussion and the impact on global health. EVI was represented at this meeting by Stefan Jungbluth.

Telephone interview with Norwegian MFA/Norad, 29 April

EVI participated in an interview with representatives from the Norwegian MFA/Norad in the context of their review of the Norwegian support to product development funding in global health. Conclusions from this process were published by NORAD in a report end 2015. Sustained commitment by funders and policy and decision makers to global health R&D.

Meeting at the German Chancellery, 8 May, Berlin, Germany

Meeting with German G7 sherpas ministers responsible for preparing the G7 Summit in Germany, June 2015. Representatives from several leading PDPs met with representatives from the German Chancellery and the BMBF to offer input and support regarding health-related items on the G7 agenda (antimicrobial resistance, Ebola, and neglected tropical diseases). EVI was presented by Stefan Jungbluth.

German MP study tour to Uganda, 26-30 May, Entebbe, Uganda

The visit of the German MPs to Uganda was organised by Deutsche Stiftung Weltbelvolkerung (DSW), a very influential non-governmental organisation in Germany working on global health. The aim of the tour was to give the MPs an impression of health research sites and facilities in countries where neglected tropical diseases are endemic and the role of the PDP

GIHT on the ground

model on the R&D in the region. Odile Leroy accompanied the delegation and presented EVI as an example of a successful PDP.

Kooperationsstelle EU der Wissenschaftsorganisationen (KoWi) annual meeting for EU research support, 16-18 June, Berlin, Germany

This annual meeting, organised by KoWi, an initiative that supports German research organisations in their quest for EU funding, serves as an information and discussion platform for all fields of EU research funding: strategic, topic-related, and administrative. The meeting was attended by Stefan Jungbluth from EVI.

Second meeting of the WHO Product Development for Vaccines Advisory Committee, 7-9 September, Geneva, Switzerland

WHO convened the second meeting of the Product Development for Vaccines Advisory Committee to review current vaccine development status for each of 25 different diseases or pathogens. EVI was represented by Odile Leroy.

Communicating research under pressure from public relations, 5-6 October, Hannover, Germany

The meeting was organised by the Volkswagen Foundation and focused on the interface between science communication and public relations, and the conflict very often generated when these two worlds meet. Various speakers presented their own experience and the lessons learned. EVI was represented by Stefan Jungbluth.

Parliamentary evening "The unrecognised revolution in global health", 13 October, Berlin, Germany

A parliamentary event organised by DSW and PolicyCures hosted by the Hon. Stephan Albani, member of parliament. The meeting provided a short overview of the state of the neglected disease R&D product pipeline, where issues surrounding current disease product pipelines, potential transformative technologies and others were discussed. EVI was represented by Stefan Jungbluth who gave a short statement on some of the critical issues identified.

PDP UK parliamentary dinner event, 14 October, London, UK

A dinner discussion with British MPs was organised by the EU PDP coalition to discuss with experts on the contribution that research and development investments in global health is making to the lives of those most affected by poverty-related neglected diseases. EVI was represented by Odile Leroy.

Publications

EVI

Nicola K. Viebig, Flavia D'Alessio, Simon J. Draper, B. Kim Lee Sim, Benjamin Mordmüller, Paul W. Bowyer, Adrian J.F. Luty, Stefan Jungbluth, Chetan E. Chitnis, Adrian V.S. Hill, Peter Kremsner, Alister G. Craig, Clemens H.M. Kocken, Odile Leroy. Malaria vaccine development in Europe - preparing for the future. *Vaccine*, 2015 33(46).

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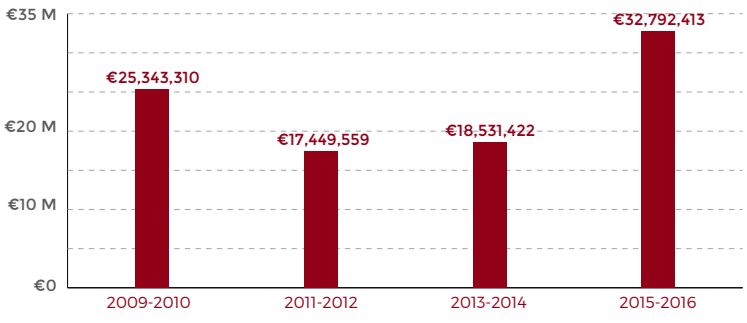
Financial performance report

EVI receives funding from national and international governmental agencies, as well as private organisations. EVI uses those funds to finance a broad portfolio of projects which help to accelerate the development and clinical assessment of vaccine candidates for diseases of poverty, to promote the affordability and accessibility of those vaccines, and to act as a focal point to enhance the alignment of all major stakeholders in the area of vaccine development for diseases of poverty. The strategic objective is to improve the worldwide access of people in need to adequate and affordable medicines.

The EVI Secretariat consists of 16 staff members, working mainly from the EVI headquarters in Heidelberg, Germany, and partly from local offices in Denmark and Belgium. EVI is led by its Executive Director, Odile Leroy, and is governed and advised by its governing bodies, the Board, the SAC and the BoS. The EVI governing bodies receive no remuneration except the reimbursement of travel costs and subsistence costs according to EVI statutes. The SAC members receive €200 per day for their time spent reviewing the project files.

Portfolio funding

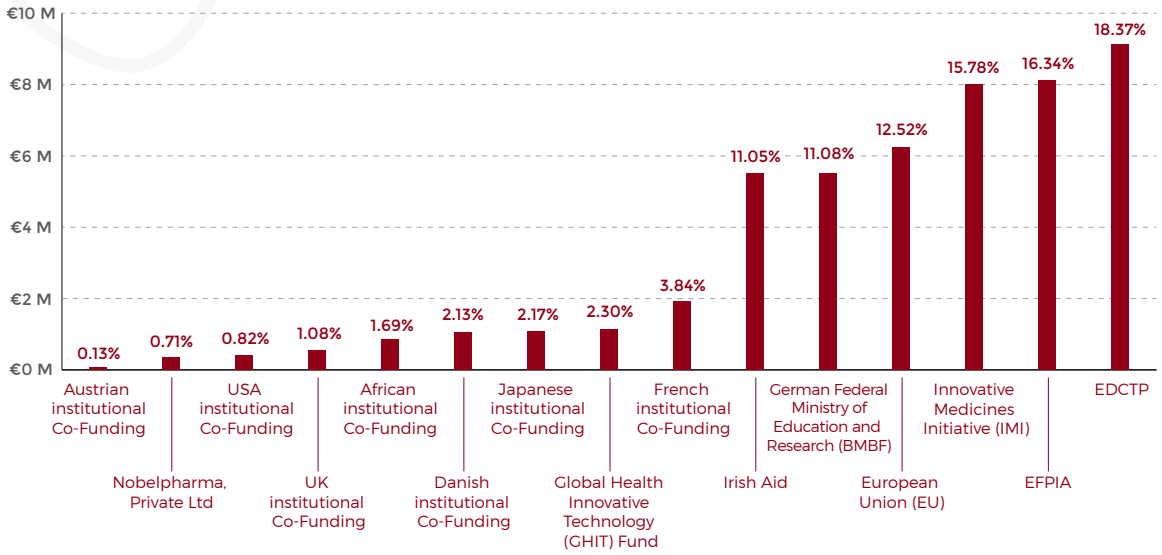
FIGURE 2 SIGNED AND PROJECTED EVI GRANTS 2009 – 2016 (INCLUDING CO-FUNDING)



EVI's project portfolio as of 31 December 2015 comprises 13 different active projects in the broad field of R&D, capacity strengthening and process development. In terms of portfolio funding, and despite the negative impact of the global economic turmoil in 2014, EVI succeeded in raising almost €15 million in new funds in 2015 through continued funding efforts, the establishment of new partnerships, and much appreciated continued support by its long-term partners. Therefore, the total funding in 2015 came close to the level achieved before 2014, and further activities with additional funding are anticipated in 2016.

Since its move from Denmark and the establishment at new premises at Heidelberg University, Germany, in 2009, EVI has raised in total more than €94 million, which has been used to fund its projects and Secretariat. Furthermore, since its foundation in 2009, EVI has successfully diversified its funding sources in order to reduce its connected financial risks.

FIGURE 3 DISTRIBUTION OF FUNDS RECEIVED BY OR PLEDGED TO EVI SINCE 2009 (AS OF 31/12/2015) (BY DONORS IN %)



EVI has likewise managed to diversify its collaborations and fundraising efforts in Europe to include partner organisations from the USA, Africa and Japan. The project portfolio includes plans for further expansion in Asia, Australia and South America, which will make new collaborations and fundraising efforts relevant in those areas.

Although EVI is a European organisation, it understands the importance of global cooperation in order to achieve scientific objectives and to coordinate fundraising efforts with our numerous partners.

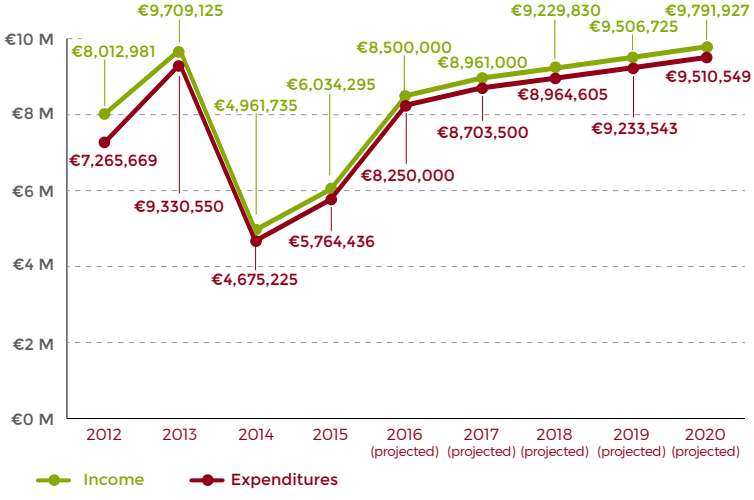
Diseases know no boundaries, and although some diseases are linked to poverty, the EVI mission is not restricted to offering poverty-stricken populations a safer life and stronger opportunities and economies of scale and scope. Indeed, the impact of global migration and global warming brings an unprecedented challenge to combat diseases of poverty before they spread and affect even more people. Global cooperation and fundraising is therefore essential.

Financial efficiency

Between 2009 and 2015, every euro of EVI funds invested through matched co-funding and in- kind contributions has leveraged approximately €5.50 of R&D value, which in comparison with other PDPs and non-profit organisations is an extraordinary achievement.

Following a significant drop in income and expenses in 2014 due to the more limited fundraising opportunities especially in Europe, EVI's revenues and investments have substantially recovered in 2015 and are expected to approach and exceed the 2013 level by 2020 at the latest through the anticipated coordination of larger research and infrastructure projects and the

FIGURE 4 REALISED AND PROJECTED EVI INCOME AND EXPENSES



further diversification of its funding portfolio in the near future.

With regards to the deployment of funds and activities in 2015, EVI has focused on streamlining and improving its processes to maximise the funds in its portfolio of projects and to minimise administrative expenses. Taking extraordinary effects into consideration, this has resulted in a reduction in management costs to less than 1% of total costs (3.44% excluding extraordinary effects).

During the limited income period in 2014, EVI trimmed its management costs to the absolute minimum. Although both the budget and the threshold increased in 2015, EVI has chosen to keep management costs at the lowest possible level because donations and funding in general should be used to achieve the EVI vision and mission, and not to support costs that do not generate added value for the true stakeholders – the people.

Though its scientific excellence and financial prudence and productivity, EVI aims to serve the people that will ultimately benefit from the work delivered by our projects.

By focusing its funds on operational activities while striving to keep administrative costs to a minimum, EVI has for the fourth consecutive year limited its management costs to below 7% of total costs per calendar year, thus investing a minimum of 93% of funds into its projects, despite the slight increase in the Secretariat headcount in 2015 from 15 to 16 members.

TABLE 1 DEVELOPMENT OF MANAGEMENT COSTS (IN % OF TOTAL COSTS)

Management percentage			
Year	Upper threshold	Result	Direct investment percentage of each euro donated
2012	7%	2.2%	97.8%
2013	7%	3.7%	96.3%
2014	7%	7.0%	93.0%
2015	7%	0.6%	99.4%

Portfolio management

FIGURE 5 EVI TOTAL ACTIVITIES IN 2015

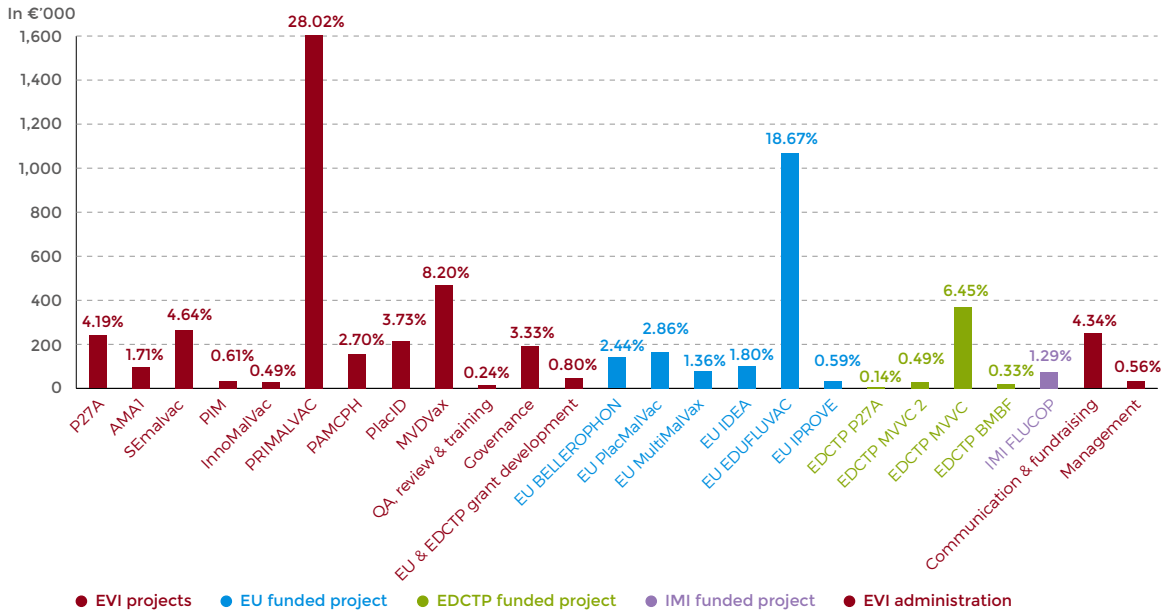
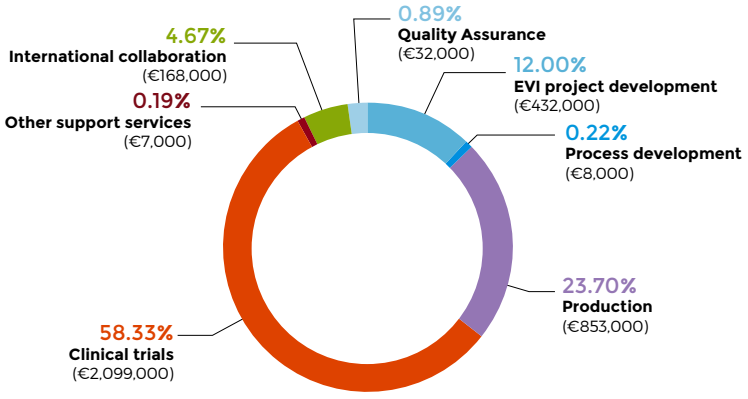


Figure 7 shows EVI's cost activity over the current reporting period, during which expenditure covering the broad portfolio of EVI, EDCTP, IMI, GHIT and EU projects has produced major achievements given the level of funding. The financial conclusion of the current reporting period is that the performance of EVI has been continuously resilient, and that funds are properly utilised to accelerate the global development of vaccines against diseases of poverty.

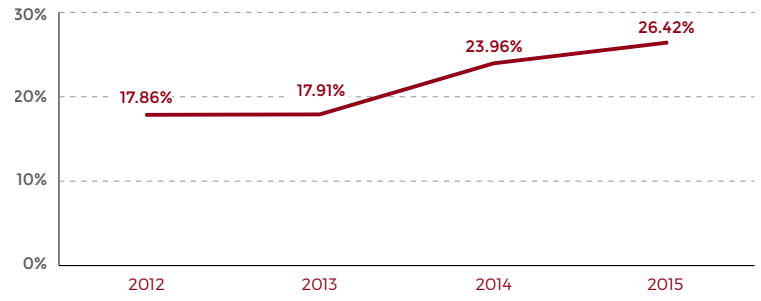
FIGURE 6 AREAS OF INVESTMENT WITHIN EVI PROJECTS 2015



Regarding the different activities funded under EVI projects, Figure 8 shows that most funds have been spent on GMP production and clinical trials, making up more than 80% of total expenditure. This highlights the core business of EVI: moving efficiently towards projects that focus on safety, and making proper use of public funding by allocating funds to the appropriate projects and processes to make them cost effective.

Key ratios

FIGURE 7 EVI EQUITY RATIO 2012-2015



Regarding the EVI's capital structure, prudent financial budget, income and cost management has enabled EVI to continuously improve its equity base as another safety buffer for the sustainable financing of its operations. The EVI's enhanced equity base is reflected in the recent continuous increase of its equity ratio.[32]

32. Equity Ratio=Total Equity Capital / Total Capital

EVI's current EU status in terms of key ratios is "good", which is the highest achievable grade in terms of sustainability, solvency, liquidity and profitability. EVI is backed by major organisations in Europe and is a fiscally strong organisation that takes its risks and liabilities into account in its financial planning. EVI clearly shows a high level of responsibility toward its donors and stakeholders as shown by the strong ongoing ratios and equity forecasting. EVI understands the requirements of both the public and private investors, which focus on sound financial management and fiscal awareness. Thus, year by year, EVI takes its responsibility to the highest level of financial management (Figure 9).

TABLE 2 EVI LIQUIDITY RATIOS 2015

Cash ratio ((Cash + Cash equivalents) / Current liabilities)	2.82
Quick ratio ((Cash + Cash equivalents + Accounts receivables) / Current liabilities)	2.84
Current ratio (Current assets / Current liabilities)	2.84

Liquidity management is required to maintain a safe liquidity position and to ensure, after taking all applicable risks into consideration, the ability to fulfil current liabilities and obligations. In 2015, EVI retained sufficient liquid funds and also met the required qualifications by donors and other public and private parties with an interest in EVI and its important work. This is reflected by the EVI's liquidity measurement ratios in 2015 (Table 2).

Management and auditing

EVI has taken further measures of to reduce risks caused by changes in its business environment, legal changes, currency risks, volatile financial markets, and uncertainties regarding new funding sources. In addition to the obligatory annual project and company audits conducted by Falk & Co (Germany), these include annual voluntary financial audits of EVI's internal processes, risks and potential contingency measures by the external auditing company Prentis & Co. LLP (UK). The outcome of the audits is under review by EVI and is incorporated annually into EVI's processes and policies in order to optimise its protection against adverse effects. EVI also maintains relationships with major banks in Germany, Denmark and the UK in order to perform global banking transactions at minimum cost, to move investments of temporary surplus funds into non-risk bearing assets, and to diversify banking risks. The current negative interest rate at the European Central Bank has not affected EVI in terms of potential loss.

In accordance with its accounting and reporting obligations, EVI's 2015 financial statements were prepared in compliance with German general accepted accounting principles (GAAP). In order to enhance the comparability of its financial statements with other international entities, EVI has also provided its financial statements according to international accounting standards / international financial reporting standards (IAS/IFRS) on a voluntary basis since 2013. The following financial tables are extracted from the EVI statements according to IAS/IFRS.

Financial presentation 2015

TABLE 3 STATEMENT OF FINANCIAL POSITION AS OF 31 DECEMBER 2015

In EUR	Notes	2015	2014
CURRENT ASSETS			
Cash and cash equivalents:			
Cash and banks - key accounts		3,552,935.73	1,830,384.37
Time deposits		2,750,000.00	4,000,000.00
Total cash and cash equivalents		**6,302,935.73**	**5,830,384.37**
Current accounts and receivables:			
Other receivables		19,799.85	29,627.05
Prepaid expenses		17,704.73	9,451.17
Total current accounts and receivables		**37,504.58**	**39,078.22**
Total current assets		**6,340,440.31**	**5,869,462.59**
Non-current assets			
Tangible fixed assets, net	**2**	25,834.70	26,184.85
Total non-current assets		**25,834.70**	**26,184.85**
Total assets		**6,366,275.01**	**5,895,647.44**
CURRENT LIABILITIES			
Creditors	**3**	1,318,008.30	660,101.24
Accrued expenses	**4**	890,363.26	1,023,423.23
Other liabilities	**5**	24,842.64	29,454.55
Deferred income	**6**	2,450,804.36	2,770,271.39
Total current liabilities		**4,684,018.56**	**4,483,250.41**
Equity of organisation			
Operating result		269,859.42	286,510.11
Unrestricted operating funds		1,412,397.03	1,125,886.92
Total equity of the organisation		**1,682,256.45**	**1,412,397.03**
Total equity and liabilities		**6,366,275.01**	**5,895,647.44**

TABLE 4 STATEMENT OF COMPREHENSIVE INCOME FOR THE YEAR AS OF 31 DECEMBER 2015

In EUR	Notes	2015	2014
INCOME	**7**		
Turnover from sales		(4,239.95)	35,522.95
Public institutional funding:	**7**		
Governmental & public international organisations		3,694,707.83	3,119,175.65
EU & IMI grants		1,662,418.00	1,457,325.00
EDCTP		405,267.41	411,461.52
Total public institutional funding	**7**	**5,762,393.24**	**4,987,962.17**
Other income net		272,525.74	(74,446.94)
Total income		**6,030,679.03**	**4,949,038.18**
SOCIAL MISSION EXPENDITURE			
Research & vaccine development expenditure:	**8**		
EVI vaccine development projects		3,144,689.89	1,905,722.94
EU-funded research and vaccine development projects		1,588,550.79	1,457,063.89
IMI funded research and vaccine development projects		73,867.21	0.00
EDCTP-funded research and vaccine development projects		424,663.67	411,461.52
Advocacy & communications expenses		118,068.29	205,857.66
Total social mission expenditure		**5,349,839.85**	**3,980,106.01**
Supportive social mission expenditure	**8**		
Training, quality assurance and project development		14,853.13	59,292.85
Fundraising		177,236.91	114,802.27
Governance		190,846.90	191,965.08
Total supportive social mission expenditure		**382,936.94**	**366,060.20**
Non-social mission expenditure	**8**		
General executive administration		31,658.83	329,058.37
Total non-social mission expenditure		**31,658.83**	**329,058.37**
Total expenditure		**5,764,435.62**	**4,675,224.58**
Operating surplus / (loss)		266,243.41	273,813.60
OTHER INCOME (EXPENSES)			
Financial income, net	7	3,616.01	12,696.51
Total other income (expenses), net		**3,616.01**	**12,696.51**
Net surplus for the year prior to allocations		269,859.42	286,510.11
Allocation / (release) to restricted operating funds in equity		0.00	0.00
Allocation / (release) to unrestricted operating funds in equity		269,859.42	286,510.11
Net surplus for the year after allocations		**0.00**	**0.00**

TABLE 5 FUNDS FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2015 (WITH 2014 COMPARATIVE FIGURES)

Funds flow from operations (In EUR)	2015	2014
Net surplus for the year	269,859.42	286,510.11
Depreciation of fixed assets	14,485.06	14,599.04
Increase (decrease) in provisions	(4,611.91)	(4,748.36)
(Increase) Decrease in other receivables	9,827.20	(23,842.22)
(Increase) Decrease in prepaid expenses	(8,253.56)	4,103.31
Increase (decrease) in creditors	657,907.06	159,069.61
Increase (decrease) in accrued expenses	(133,059.97)	486,259.96
Increase (decrease) in deferred income	(319,467.03)	(1,319,370.86)
Funds flow from operations	**486,686.27**	**(397,419.41)**

Funds flow from investing activities (In EUR)	2015	2014
(Increase) Decrease of investments in tangible fixed assets	(350.15)	(7,884.86)
Funds flow from investing activities	**(350.15)**	**(7,884.86)**

Funds flow from financing activities (In EUR)	2015	2014
Cash increase (decrease)	472,551.36	(405,304.27)
Cash and cash equivalents – beginning of year	5,830,384.37	6,235,688.64
Cash and cash equivalents – end of year	**6,302,935.73**	**5,830,384.37**

Statement of changes in equity for the year ended 31 December 2015 (EUR)

	Opening balance	Allocation	Internal fund transfers	Closing balance
Internally generated funds as of 31 December 2014				
Paid-in capital	0.00	0.00	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	0.00
Unrestricted operating funds	1,125,886.92	0.00	286,510.11	1,412,397.03
Capital of the organisation	**1,125,886.92**	**286,510.11**	**0.00**	**1,412,397.03**
Internally generated funds as of 31 December 2015				
Paid-in capital	0.00	0.00	0.00	0.00
Surplus for the year	0.00	269,859.42	(269,859.42)	0.00
Restricted operating funds	0.00	0.00	0.00	0.00
Unrestricted operating funds	1,412,397.03	0.00	269,859.42	1,682,256.45
Capital of the organisation	**1,412,397.03**	**269,859.42**	**0.00**	**1,682,256.45**

Notes to the financial statement for the year 2015

Note 1 - Significant Accounting Policies

(a) General comment

EVI fully complies with the demands of German GAAP and continuously empowers its staff working on projects to participate in budget control and the control of spending. For an organisation 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's accounting method is accrual based, with consideration for projects governed by external guidelines.

One major basis of accounting that should be mentioned is that EVI retains the accounting treatment prescribed by IAS 20, namely recognise income up to the amount of expenditure allocated by government, the difference being recognised as deferred income.

The financial presentation in this report is based on the IFRS as endorsed by the EU and is prepared in addition to the German 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:

1. Statement of financial position;
2. Statement of comprehensive income (activity based method);
3. Funds flow statement;
4. Statement of changes in equity;
5. Notes and additional performance report.

Negative amounts are shown within brackets as required by standard.

(c) Basis of preparation

The financial statements are presented in euros (€) because the majority of EVI's activities are conducted in this currency (group functional and presentation currency). Fair value is the amount for which a financial asset, liability or instrument could be exchanged between knowledgeable and willing parties in an arm's length transaction.

The preparation of financial statements conforming to German GAAP requires management to make judgements, estimates and assumptions that affect the application of policies and reported amounts of assets and liabilities, income and expenditure.

The estimates and associated assumptions are based on historical experience and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis of making the judgements about carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates. If in the future such estimates and assumptions, which are based on management's best judgement at the date of the consolidated financial statements, deviate from the actual circumstances, the original estimates and assumptions will be modified as appropriate in the year in which the circumstances change.

(d) Funding parties

EVI is currently funded by Governmental agencies (Irish Aid, GHIT Fund, BMBF) and the EU in addition to the EDCTP and privately by Nobelpharma.

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.

(e) 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.

An unconditional grant is recognised as revenue in the statement of comprehensive income when the grant becomes receivable. Any other grant which has performance, timing or other conditions is recognised in the statement of financial position as revenue once EVI has complied with the stipulated conditions. If the conditions have not yet been fully complied with, then this grant component is reported as a contingent asset as disclosed. They are considered as unrestricted funds, unless the donor stipulates a specific restriction. A reconciliation between donations received in cash and income recognised in the consolidated statement of comprehensive income is shown in note 6. Government grants are recognised as income for the allowable expenses incurred in the current year. At year end, the difference between the income recognised and the cumulative expenses incurred is accounted for as deferred income. When the donor wishes to see a donation allocated to a specific cause, the donation is considered to be an allocated fund. Allocated funds that have not been used at the end of the year are presented in a separate section of the statement of financial position.

(f) Contributions in kind

Occasionally EVI receives donations in kind, primarily in the form of free use of goods or services or preferential discounts and funds used at the premises of the lead investigator. These contributions in kind are not stated in the statement of comprehensive income as this type of contribution is difficult to valorise.

(g) 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 posts them accordingly to the respective accounts.

(h) Social mission expenditure

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

Expenditure and grants allocated for R&D activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on the basis of contracts with grantees. In the event that a portion of a grant is unpaid at the year end, it is included under current liabilities. Expenses paid before year end for the following period are recorded as prepaid R&D commitments in current assets.

Regulatory and other uncertainties inherent in the development of new products in this sector preclude EVI from capitalising development costs.

(i) Investment income and interest receivable

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

(j) Primary and secondary commerce

EVI's primary focus is to develop vaccines against diseases of poverty. As a secondary activity, EVI may offer 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.

(k) 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

(l) 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.

(m) 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.

(n) 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: seven years
- IT equipment: four years

(o) 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

(p) 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.

(q) Equity

Funds held by EVI as equity:
Equity are utilised as a strategic reserve for R&D for the organisation. EVI does not pay out any dividends or similar benefits to its shareholders as stipulated by the statutes of the organisation.

(r) Foreign currencies

Transactions in foreign currencies are translated into euros 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. Monetary assets and liabilities denominated in foreign currencies at the consolidated statement of financial position date are translated to US$ at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognised in the consolidated statement of comprehensive income. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction. EVI has, for the year 2015, made use of the following currencies: EUR, DKK, INR, USD, GBP and XOF.

(s) Financial auditors

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

The auditor issues an annual financial 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 31/12/2014	
Cost at beginning of the period 01/01/2014	32,899.03
Additions	8,020.79
Disposals	0.00
Cost at end of the period 31/12/2014	40,919.82
Accumulated amortisation 01/01/2014	135.93
Depreciation / amortisation expense 2014	14,599.04
Net carrying amount end of the period 31/12/2014	**26,184.85**
Net carrying amount 31/12/2015	
Cost at beginning of the period 01/01/2015	26,184.85
Additions	16,105.01
Disposals	(202.99)
Cost at end of the period 31/12/2015	42,086.87
Accumulated amortisation 01/01/2015	1,767.11
Depreciation / amortisation expense 2015	14,485.06
Net carrying amount end of the period 31/12/2015	**25,834.70**

Note 3

Creditors (EUR)	2015	2014
Creditors for grant linked payments	1,236,342.49	607,156.13
Other creditors	81,665.81	52,945.11
Total	**1,318,008.30**	**660,101.24**

Note 4

Accrued expenses (EUR)	2015	2014
Accrued paid leave	76,260.02	101,016.61
Accrued payables (grants linked)	693,692.80	812,750.50
Accrued direct costs	55,118.75	22,513.96
Accrued indirect costs	65,291.69	65,504.08
Accrued other expenses	0.00	21,638.08
Total	**890,363.26**	**1,023,423.23**

Note 5

Other liabilities (EUR)

Carrying period as per 31/12/2014	
Wage tax liability	19,149.35
Social charges	6,463.70
Other liabilities	3,841.50
Total other liabilities 31/12/2014	**29,454.55**

Carrying period as per 31/12/2015	
Wage tax liability	17,654.71
Social charges	4,757.75
Other liabilities	2,430.18
Total other liabilities 31/12/2015	**24,842.64**

Note 6

Deferred income

Cumulative donations committed to EVI as of 31 December 2015 and current deferred income

Donors	Contract currency	Total commitment in currency	Total commitment in euro	Deferred income 31-12-2014	Payments received as per statement of operations	Costs/ income realisation as per statement of operations	Deferred income 31-12-2015
Irish Aid - IE	EUR	5,000,000.00	5,000,000.00	**(964,478.86)**	1,000,000.00	35,521.1	**0.00**
BMBF - DE	EUR	5,512,025.00	5,512,025.00	**237,588.99**	1,543,591.07	2,128,028.16	**(346,848.10)**
GHIT - JP	JPY	69,290,235.00	1,144,721.39	**291,887.69**	460,102.39	739,787.13	**12,202.95**
FP7 - EU	EUR	16,229,077.00	20,729,077.00	**174,008.03**	1,469,342.55	1,532,679.63	**110,670.95**
EDCTP	EUR	9,137,281.00	9,137,281.00	**(352,969.74)**	961,187.38	405,267.41	**202,950.23**
IMI	EUR	150,000.00	150,000.00	**0.00**	48,000.00	73,867.21	**(25,867.21)**
Nobelpharma	USD	200,000.00	177,357.38	**0.00**	177,357.38	0.00	**177,357.38**
EVI reserve funds	EUR	3,321,642.18	3,321,642.18	**3,384,235.28**	203,929.19	1,267,826.31	**2,320,338.16**
Total			**45,172,103.95**	**2,770,271.39**	**5,863,509.96**	**6,182,976.99**	**2,450,804.36**

Deferred income

(b) Balance overview of grants and reserves (EUR)

Donator/Grant	Type	Balance 31/12/2014	Payments Received 2015	Cost allocated 2015	Balance 31/12/2015
IE - Irish Aid	Core	**(964,478.86)**	1,000,000.00	35,521.14	**0.00**
EVI Board funds	Core	**3,076,441.85**	0.00	783,109.97	**2,293,331.88**
DE – BMBF	Restricted	**236,645.51**	1,529,930.85	2,113,424.46	**(346,848.10)**
DE – BMBF	Restricted	**943.48**	13,660.22	14,603.70	**0.00**
JP - GHIT SEmalvac	Restricted	**291,887.69**	0.00	269,366.27	**22,521.42**
JP - GHIT MVDVax	Restricted	**0.00**	460,102.39	470,420.86	**(10,318.47)**
EU/FP7 TRANSVAC	Restricted	**(55,871.16)**	0.00	(55,871.16)	**0.00**
EU/FP7 EDUFLUVAC	Restricted	**104,920.85**	1,164,877.22	1,070,095.09	**199,702.98**
EU/FP7 BELLEROPHON	Restricted	**123,143.17**	176,124.08	139,697.26	**159,569.99**
EU/FP7 PlacMalVac	Restricted	**39,524.47**	128,341.25	164,135.41	**3,730.31**
EU/FP7 IDEA	Restricted	**(20,768.28)**	0.00	102,511.27	**(123,279.55)**
EU/FP7 MultiMalVax	Restricted	**(5,657.51)**	0.00	78,389.05	**(84,046.56)**
EU/FP7 IPROVE	Restricted	**(11,283.51)**	0.00	33,722.71	**(45,006.22)**
IMI/IMI1 FLUCOP	Restricted	**0.00**	48,000.00	73,867.21	**(25,867.21)**
EDCTP MVVC	Restricted	**(254,499.33)**	687,540.17	433,040.84	**0.00**
EDCTP MVVC2	Restricted	**(83,158.16)**	273,647.21	(35,289.65)	**225,778.70**
EDCTP P27A	Restricted	**(15,312.25)**	0.00	7,516.22	**(22,828.47)**
Nobelpharma/ SEmalvac	Core	**0.00**	177,357.38	0.00	**177,357.38**
EVI Administration	Core	**307,793.43**	203,929.19	484,716.34	**27,006.28**
EVI Equity reserves	Core	**1,412,397.03**	269,859.42	0.00	**1,682,256.45**
Total core		**3,832,153.45**	**1,651,145.99**	**1,303,347.45**	**4,179,951.99**
Total restricted		**350,514.97**	**4,482,223.39**	**4,879,629.54**	**(46,891.18)**
Total EVI funds		**4,182,668.42**	**6,133,369.38**	**6,182,976.99**	**4,133,060.81**

Note 7: Income / realised (In EUR)

Funding used per project (restricted and unrestricted)

	Irish Aid	BMBF	GHIT	EU	IMI
EVI vaccine development projects	10,505.91	1,975,106.66	736,389.30	0.00	0.00
Supportive EVI development costs	94,983.67	0.00	0.00	0.00	0.00
EU R&D projects	0.00	0.00	0.00	1,588,550.79	0.00
Supportive EU development costs	8,188.86	0.00	0.00	0.00	0.00
IMI R&D projects	0.00	0.00	0.00	0.00	73,867.21
Supportive IMI development costs	0.00	0.00	0.00	0.00	0.00
EDCTP R&D projects	0.00	19,396.26	0.00	0.00	0.00
Supportive EDCTP development costs	5,480.84	0.00	0.00	0.00	0.00
Executive administration	33,093.96	138,317.80	3,397.83	0.00	0.00
Internal allocations	0.00	0.00	0.00	0.00	0.00
Total income	**152,253.24**	**2,132,820.72**	**739,787.13**	**1,588,550.79**	**73,867.21**

	EDCTP	Utilisation of reserves	Total income per activity	Overheads and interest	Total income
EVI vaccine development projects	0.00	422,688.02	3,144,689.89	0.00	3,144,689.89
Supportive EVI development costs	0.00	360,165.06	455,148.73	0.00	455,148.73
EU R&D projects	0.00	0.00	1,588,550.79	0.00	1,588,550.79
Supportive EU development costs	0.00	24,131.89	32,320.75	0.00	32,320.75
IMI R&D projects	0.00	0.00	73,867.21	0.00	73,867.21
Supportive IMI development costs	0.00	0.00	0.00	0.00	0.00
EDCTP R&D projects	405,267.41	0.00	424,663.67	0.00	424,663.67
Supportive EDCTP development costs	0.00	8,054.91	13,535.75	0.00	13,535.75
Executive administration	0.00	(143,150.76)	31,658.83	0.00	31,658.83
Internal allocations	0.00	0.00	0.00	269,859.42	269,859.42
Total income	**405,267.41**	**671,889.12**	**5,764,435.62**	**269,859.42**	**6,034,295.04**

Note 8

Social & non-social mission expenditure (EUR)	Notes	2015	2014
EVI vaccine development projects			
P27A	(a)	239,918.21	283,442.26
AMA1-DiCo	(a)	97,967.98	87,286.35
PlacID	(a)	214,476.13	0.00
PAMCPH	(a)	154,802.81	479,988.29
PRIMALVAC	(a)	1,605,827.72	843,689.30
SPOROVAC	(a)	0.00	7,047.82
InnoMalVac	(a)	27,993.91	5,818.00
PIM	(a)	35,040.59	6,140.93
MVDVax	(a)	470,420.86	0.00
SEmalvac	(a)	298,241.68	132,206.24
Supportive vaccine development costs	(a)	455,148.73	525,098.84
Total EVI vaccine development projects		**3,599,838.62**	**2,370,718.03**
EU-funded R&D projects			
MultiMalVax		78,389.05	62,172.33
TRANSVAC		0.00	763,333.09
IDEA		102,511.27	59,746.67
PlacMalVac		164,135.41	103,225.50
BELLEROPHON		139,697.26	117,990.97
EDUFLUVAC		1,070,095.09	292,216.47
IPROVE		33,722.71	58,378.86
Supportive project development costs		32,320.75	39,764.86
Total EU-funded R&D projects		**1,620,871.54**	**1,496,828.75**
IMI funded R&D projects			
FLUCOP		73,867.21	0.00
Supportive project development costs		0.00	0.00
Total IMI funded R&D projects		**73,867.21**	**0.00**
EDCTP funded R&D projects			
MVVC		369,895.63	129,921.02
P27A-EDCTP		7,516.22	139,280.05
MVVC 2		27,855.56	142,260.45
BMBF-EDCTP		19,396.26	60,103.75
Supportive project development costs		13,535.75	7,054.16
Total EDCTP funded R&D projects		**438,199.42**	**478,619.43**
Executive administration			
Executive administrative management cost		**31,658.83**	**329,058.37**
Total executive administration		**31,658.83**	**329,058.37**
Total of all projects related expenditure	**(b)**	**5,764,435.62**	**4,675,224.58**

(a) Breakdown of R&D

	2015	2014
1 - Project development	431,737.80	409,965.43
2 - Process development	8,023.93	35,002.68
3 – Pre-clinical	853,091.74	795,811.88
4 - Clinical trials	2,099,112.74	748,577.99
5 - Other support services	7,286.74	41,039.01
6 - International collaboration	168,458.02	289,348.63
7 - Quality Assurance	32,127.65	50,972.41
Total	**3,599,838.62**	**2,370,718.03**

(b) Breakdown R&D coordination expenditure for preclinical and clinical activities costs per purpose in 2015 – value of above €5,000

Category 3 – Preclinical

Projects	Partners	Expenditure 2015
AMA1-DiCo	Nova Laboratories Ltd	6,092.78
AMA1-DiCo	Inserm	8,335.00
AMA1-DiCo	Confarma	12,480.00
InnoMalVac	University of Oxford	25,000.00
P27A	Output Pharma Services	20,000.00
P27A	Nova Laboratories Ltd	25,000.00
P27A	ALMAC	28,362.00
PAMCPH	University of Copenhagen	65,000.00
PRIMALVAC	Inserm	295,541.68
PIM	University of Oxford	32,500.00
SEmalvac	LSTHM	16,003.00

Category 4 – Clinical trial

Projects	Partners	Expenditure 2015
AMA1-DiCo	Inserm	79,365.00
MVDVax	NEKKA	53,937.12
MVDVax	Institut Pasteur, Paris	371,193.68
P27A	University of Lausanne	154,500.00
PAMCPH	Nova Laboratories Ltd	18,289.10
PAMCPH	University of Copenhagen	45,000.00
PRIMALVAC	Nova Laboratories Ltd	21,198.10
PRIMALVAC	Inserm	1,203,547.75
PlacID	NIH/NIAID	204,100.00
SEmalvac	Pharmalys	21,000.00
SEmalvac	CNRFP	117,750.00

(c) Presentation of EVI expenditures per nature of expenses (EUR)

	2015	2014
6010 Payables - EVI program related	2,751,281.64	1,691,666.82
6060 Payables - EDCTP program related	366,258.74	122,973.72
6070 Payables – EU & IMI program related	926,054.88	854,921.62
7099 Salary costs (also includes in-house consultants)	1,141,839.07	1,199,423.13
7100 Contract service expenses	149,699.46	117,861.74
7200 Facility & equipment maintenance expenses:	89,651.81	70,085.69
7300 Equipment, hardware & software	15,125.93	15,179.99
7400 Travel & meetings expenses:	214,867.22	296,961.45
7500 Other direct expenses:	19,536.24	34,774.34
8000 Indirect business expenses:	71,885.86	248,256.72
9000 Board, BoS and SAC expenses:	15,480.76	18,764.24
9100 EU ISAC, SAC and SC expenses:	2,754.01	4,355.12
9299 Total expenses	**5,764,435.62**	**4,675,224.58**

Note 9

EVI stock of vaccine and adjuvant vials (non-accounted stock value)

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/15	Changes 2015	Quantity 31/12/15
NOVALABS	ALMy001	P27A vaccine	P27A Line A	ALMy001	703	(0)	703
NOVALABS	ALMy001	P27A vaccine	P27A Line B	ALMY001	822	(0)	822
NOVALABS	EVIy002	AMA1 - DiCo vaccine	pfAMa1 DiCo 60 µg lyophilised	EVIy002	904	(0)	904
NOVALABS	EVIy003	Adjuvant	Alhydrogel Line A	EVIy003	1490	(112)	1378
NOVALABS	EVIy003	Adjuvant	Alhydrogel Line B	EVIy003	1557	(147)	1410
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line A	EVIc001	0	1878	1878
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line B	EVIc001	0	1849	1849

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 31 December 2015.

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 31 December 2015 of European Vaccine Initiative EEIG, Heidelberg dated March 21 2016.

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 31 December 2015 in accordance with IFRS as endorsed by the EU relevant to preparing such financial presentation.

Heidelberg, March 21, 2016

FALK GmbH & Co KG
Wirtschaftsprüfungsgesellschaft
Steuerberatungsgesellschaft

(Meyer)
Wirtschaftsprüfer

(Ahrens)
Wirtschaftsprüfer

List of abbreviations

	3D7	*Plasmodium falciparum* clone 3D7
A	**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
B	**BCG**	Bacillus Calmette-Guérin
	BE	Belgium
	BELLEROPHON	A project combining cellular and humoral immune responses as a vaccine strategy against the pathogen *S. aureus*
	BF	Burkina Faso
	BK-SE36	*Plasmodium falciparum* serine repeat antigen-5 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
C	**CBF**	Clinical Biomanufacturing Facility
	CERMEL	Centre de Recherches Medicales de Lambarene
	CFU	Colony Forming Units
	CH	Switzerland
	ChAd	Chimpanzee Adenovirus
	CHUV	Centre hospitalier universitaire vaudois
	CIC	Centre d'investigation clinique
	CNRFP	Centre national de recherche et de formation sur le paludisme
	CRO	Contract Research Organisation
	CSA	Chondroitin Sulfate A
	CSP	Circumsporozoite Protein
	CVI	Central Veterinary Institute
D	**DBL**	Duffy-Binding-Like
	DE	Germany
	DGIS	Directorate General for International Cooperation at Ministry of Foreign Affairs, The Netherlands
	DiCo	Diversity Covering
	DK	Denmark
	DNA	Deoxyribonucleic Acid
	DSW	Deutsche Stiftung Weltbevölkerung
E	***E. coli***	*Escherichia coli*
	EATRIM	Infrastructure in Medicine
	EC	European Commission
	EDCTP	European and Developing Countries' Clinical Trials Partnership

	EDUFLUVAC	Educate Influenza Vaccine
	EEIG	European Economic Interest Grouping
	EKUT	Eberhard Karls Universität Tübingen
	ELISA	Enzyme-Linked Immunosorbent Assay
	ELISpot	Enzyme-Linked ImmunoSpot Assay
	EMA	European Medicines Agency
	EPI	Expanded Programme on Immunization
	ESWI	European Scientific Working Group on Influenza
	EU	European Union
	EVI	European Vaccine Initiative
F	**FP7**	Framework Program Seven
	FR	France
	Fraunhofer IME	Fraunhofer Institute for Molecular Biology and Applied Ecology
	FRMC	Financial Risk Management Committee
G	**GAAP**	General Accepted Accounting Principles
	GB	Gabon
	GH	Ghana
	GHIT	Global Health Innovation Technology
	GIA	Growth Inhibition Assay
	GLA	Glucopyranosyl Lipid A Adjuvant-Stable Emulsion
	GM	The Gambia
	GMP	Good Manufacturing Practice
	GMZ2	Recombinant *Lactococcus lactis* hybrid glutamate-rich protein and merozoite surface protein 3
	GSK	GlaxoSmithKline
H	**HA**	Haemagglutinin
	HIV	Human Immunodeficiency Virus
	HTF	Danish National Advanced Technology Foundation
I	**IAS**	International Accounting Standard
	IB	Investigator's Brochure
	iBET	Instituto de Biologia Experimental e Tecnológica
	IDEA	Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth Infections: An African-European Research Initiative
	IDRI	Infectious Disease Research Institute
	IE	Republic of Ireland
	IFRS	International Financial Reporting Standard
	IHI	Ifakara Health Institute
	IMI	Innovative Medicines Initiative
	IMPD	Investigational Medicinal Product Dossier
	IMX	Tag developed by IMAXIO
	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	Invasive Non-Typhoidal *Salmonella*
	INTS	Institut national de transfusion sanguine
	IPP	Institut Pasteur Paris
	IPROVE	Innovation Partnership for a Roadmap on Vaccines in Europe
	IRCB	Institut de recherche clinique du Bénin
	IRD	Institut de recherche pour le développement
	IT	Italy

J	**JP**	Japan
K	**kDa**	Kilodalton
	KE	Kenya
	KEMRI	Kenya Medical Research Institute
	KfW	Kreditanstalt für Wiederaufbau
	KHRC	Kintampo Health Research Centre
L	**LMIV**	Laboratory of Malaria Immunology and Vaccinology
	LSHTM	London School of Hygiene & Tropical Medicine
	LSQ	Liposome-QS21 formulation
M	**Matrix M**	Adjuvant by Novavax, in which matrix complexes are formed by a specific mixture of Quillaja saponin, cholesterol and phospholipids
	ME-TRAP	Multiple Epitope Thrombospondin-Related Adhesion Protein
	MHRA	Medicine and Healthcare Products Regulatory Agency
	MP	Member of Parliament
	MPL	Monophosphoryl Lipid A
	MRC	Medical Research Council
	MRSA	Methicillin-Resistant *S. aureus*
	MSc	Master of Science
	MSP	Merozoite Surface Protein
	MU-CHS	Makerere University College of Health Sciences
	MultiMalVax	Multi-stage Malaria Vaccine
	MVA	Modified Vaccinia Virus Ankara
	MVDVax	Measles Virus Dengue Vaccine
	MVI	Malaria Vaccine Initiative
	MVVC	Malaria Vectored Vaccines Consortium
	MVVC2	Malaria Vectored Vaccines Consortium 2
N	**NA**	Neuraminidase
	NEKKEN	Institute of Tropical Medicine Nagasaki University
	NHP	Non-Human Primates
	NI	Nigeria
	NIBSC	National Institute for Biological Standards and Control
	NID	Neglected Infectious Disease
	NIH/NIAID	National Institute of Health / National Institute of Allergy and Infectious Diseases
	NL	The Netherlands
	NO	Norway
O	**OPTIMALVAC**	Initiative on Optimising Malaria Vaccine laboratory assay evaluation
P	**P27A**	Fragment P27A of PFF0165c malaria protein
	PAMCPH	Recombinant VAR2CSA protein as a vaccine candidate for pregnancy-associated malaria
	PCR	Polymerase Chain Reaction
	PDP	Product Development Partnership
	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

	PlacID	Modelling Placental Infection and Disease
	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
R	**R**	Programming language and software environment for statistical computing and graphics
	R&D	Research and Development
	R21	Circumsporozoite protein particle
	RIMD	Research Institute for Microbial Diseases
	RTS,S	The RTS,S vaccine was engineered using genes from the repeat and Tcell epitope of Pf malaria CSP, a hepatitis B virus envelope protein (HBsAg) and a chemical adjuvant to boost the immune response
S	***S. aureus***	*Staphylococcus aureus*
	S. paratyphi A	*Salmonella enterica* serovar *paratyphi A*
	SAC	Scientific Advisory Committee
	SE	Stable Emulsion
	SE	Sweden
	SE36	*Plasmodium falciparum* serine repeat antigen 5 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
	Swiss TPH	Swiss Tropical and Public Health Institute
T	**TB**	Tuberculosis
	TBVI	Tuberculosis Vaccine Initiative
	TRANSVAC	European Network of Vaccine Research and Development
	TZ	Tanzania
U	**UAC**	Université d'Abomey-Calavi
	UCAD	Université Cheikh Anta Diop
	UCPH	University of Copenhagen
	UG	Uganda
	UK	United Kingdom
	UNIL	University of Lausanne
	UOXF	University of Oxford
	UPMC	Université Pierre et Marie Curie
	US	United States
	USA	United States of America
	UVRI	Uganda Vaccine Research Institute
V	**VAC2VAC**	Vaccine batch to vaccine batch comparison by consistency testing
	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
W	**WHO**	World Health Organization

Acknowledgments

The EVI Secretariat thanks the following people, who have contributed significantly to the success of EVI, especially all the participants in the clinical trials funded by EVI.

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On a sad note, EVI brings news of the death of Dr Egeruan Babatunde Imoukhuede. Tunde, as he was known to his friends, joined EVI in 2005 as Clinical and Regulatory Affairs Director. He left in 2013 to work for the Jenner Institute at University of Oxford. Babatunde was a brilliant advocate for the battle against diseases of poverty. During all the years he was fighting for his life, he was an example of resilience and professionalism. He will be remembered at EVI for his persistent commitment to research and development of malaria vaccines.

Partners

Abbott	NL
Academisch Medisch Centrum bij de Universiteit van Amsterdam	NL
Academisch Ziekenhuis Leiden – Leids Universitair Medisch Centrum	NL
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ALMAC Sciences	UK
Artemis One Health Research BV	NL
AstraZeneca AB	SE
Biomedical Primate Research Centre	NL
BIOTEM	FR
Central Veterinary Institute	NL
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Centre de recherches médicale de Lambaréné	GB
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Kenya Medical Research Institute	KE
Kintampo Health Research Centre	GH
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Malaria Consortium LBG	UK
Medical Research Council	GM
Medical Research Council on behalf of its MRC/UVRI Uganda Research Unit on AIDS	UK
MHRA-Department of Health	UK
National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency	UK
National Institute for Medical Research – Mbeya Medical Research Program	TZ
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NNE Pharmaplan GmbH	DE
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Nova Laboratories Ltd	UK
Novartis	IT
Novartis Vaccines and Diagnostics s.r.l.	IT
Novartis Vaccines Institute for Global Health	IT
Novasep (formerly Henogen)	BE
Novavax (formerly ISCONOVA)	SE
Output Pharma	DE
Paul-Ehrlich-Institut, Bundesinstitut Für Impfstoffe Und Biomedizinische Arzneimittel	DE
Pfenex Inc.	USA
Pharmalys	UK
Pharmalys	UK/SN
Preclin Biosystems AG	CH
QUINTEN	FR
Redbiotec AG	CH
ReiThera s.r.l. (formerly Okairòs s.r.l.)	IT
Research Institute for Microbial Diseases	JP
Royal College of Surgeons in Ireland	IE
Ruprecht-Karls-Universität Heidelberg	DE
Sanofi Pasteur	FR
Sclavo Vaccines Association	IT
Swiss Tropical and Public Health Institute	CH
The Chancellor, Masters and Scholars of the University of Oxford	UK
Uganda Virus Research Institute	UG
Università degli Studi di Siena	IT
Université Cheikh Anta Diop	SN
Université d'Abomey-Calavi	BN
Université Pierre et Marie Curie	FR
Universiteit Gent	BE
Universitetet i Bergen	NO
University of Copenhagen	DK
University of Ibadan	NI
University of Lausanne	CH
University of Oxford	UK
University of Surrey	UK
Vaccine and Gene Therapy Institute Florida	USA
Vaccines Europe / European Federation of Pharmaceutical Industries and Associations	BE
Vakzine Projekt Management GmbH	DE
Vienna School of Clinical Research	AT
Voisin Consulting Life Sciences	FR
Wellcome Trust Sanger Institute	UK
WIL Research	NL
World Health Organization	CH

Annex

"Club de Vaccinologie" meeting, 21-23 January 2015, Paris , France

The annual meeting organised by the French society of immunology took place at Institut Pasteur and highlighted some of the main issues and challenges in basic immunology, ongoing clinical trials, and the development of new vaccines. The French Society of Immunology promotes meetings and facilitates exchanges between scientists, not only in France but also at the international level. EVI was presented by Odile Leroy and Nathalie Imbault.

Advancing novel and promising TB vaccine candidates from discovery to preclinical and early clinical development, 11-12 February, Ijmuiden, Netherlands

Kick off meeting of the TBVAC2020 project funded by the EC under Horizon 2020. The project work packages and work programme were presented by the partners. Odile Leroy presented the plans for TRANSVAC2.

25th Annual meeting of the Society for Virology, 18-21 March, Bochum, Germany

The Society for Virology is the largest scientific society in Austria, Switzerland and Germany, and is an excellent example of the strong scientific links between these three German-speaking countries and their integration into the international scientific community. The meeting brings together leading experts in basic and translational virology, and provides an opportunity for extensive and fruitful networking. EVI was represented by Sophia Hundt.

BIOVISION Workshop: Vaccin/ Immunothérapie active, 16-17 April, Lyon, France

The workshop with CoReVac took place in connection with the 10th edition of BIOVISION, which is organised by an independent non-profit organisation, and brings together key decision makers from the academic, private, policy-making and civil society sectors, to translate innovative ideas into actionable solutions for the benefit of citizens. Odile Leroy participated in a workshop "Connecting the actors of innovation in vaccinology".

BioMalPar conference, 1-13 May, Heidelberg, Germany

Every year the BioMalPar conference brings together scientists involved in basic malaria research. The meeting offers excellent opportunities to discuss new advances in malaria biology. EVI was represented by Nicola Viebig.

9th European Congress on Tropical Medicine and International Health, 6-10 September 2015, Basel, Switzerland

The 9th European Congress on Tropical Medicine and International Health brings together 2000 of the most distinguished scientists and experts in the field of tropical medicine and international health. It is the premier European congress in this field. EVI was represented by Nathalie Imbault and Sophie Houard.

Vaccine Science Portfolio Advisory Council (VSPAC), 21 September, Washington, USA

Annual MVI PATH portfolio review meeting with presentations and discussions of projects open to funders, select partners and colleagues. EVI was represented by Stefan Jungbluth who attended as an observer.

VaxInEU 2015 Symposium, 30 September - 2 October, Barcelona, Spain

VaxInEu is a symposium on Vaccinology and Infection concerning the preparation of the Leading International Vaccinology Education proposal for a joint Erasmus Master's degree program involving the Universities of Lyon, St Etienne, Antwerp, Barcelona and Autònoma de Barcelona. EVI, represented by Odile Leroy, is one of many institutions in this exciting programme.

Developing Countries Vaccine Manufacturers Network (DCVMN), 5-7 October, Bangkok, Thailand

Odile Leroy served as moderator on an executive panel discussion on the challenges and opportunities of multicentre clinical trials.

Influenza Vaccines for the World, 6–9 October 2015, Albufeira, Portugal

Influenza Vaccines for the World 2015 was the fifth international conference and exhibition in this important series of influenza vaccine meetings, which focuses on 'Influenza Vaccination Issues', and is designed to complement the two other major influenza meetings in the conference calendar: European Scientific Working group on Influenza (ESWI) and the Options for Control of Influenza. EVI was represented by Sophie Houard.

ASTMH 64th Annual Meeting, 25–29 October, Philadelphia, USA

The American Society of Tropical Medicine and Hygiene (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. The meeting is designed for researchers, professors, government and public health officials, military personnel, travel clinic physicians, physicians practicing tropical medicine, students and all health care providers working in the fields of tropical medicine, hygiene and global health. EVI was represented by Nicola Viebig and Sophia Hundt.

EURIPRED Symposium, 2nd Annual Meeting and Mid Term Review Meeting; 9–12 November 2015, Grand Connaught Rooms, London

EURIPRED is an infrastructure project aiming at strengthening partnerships between European scientists and international research teams from disease endemic countries, for the development of reference standards and reagents, harmonization of biological assays for potency of vaccines and therapeutics and training provision to facilitate the R&D in poverty related diseases (mainly HIV, TB and malaria, also including hepatitis). Odile Leroy participated in the EURIPRED scientific symposium, and gave a presentation on the current status of new malaria vaccine development.

Workshop CoReVac – PalSud: Défis scientifiques et économiques du développement de vaccins pour les pays du Sud, 2–3 December, Paris, France

The workshop was organised to meet the needs of the CoReVac network identified during a survey within the scientific community launched earlier in 2015. CoReVac is a French nationwide multidisciplinary network of vaccine researchers, involved in basic, pre-clinical, translational, clinical, epidemiological and societal research, as well as industries, stakeholders funding the R&D efforts, and public health bodies involved in vaccine deployment. Odile Leroy gave a presentation entitled "Portofolio candidats vaccins EVI". Nathalie Imbault attended the meeting which was an opportunity to meet with the PlacMalVac partners.

Annual meeting of the Japanese Society of Tropical Medicine, 4–6 Dec 2015, Osaka, Japan

The major get-together of the Japanese tropical medicine research community. Presentations covered the major infectious diseases (HIV/AIDS, TB, and malaria) as well as several Neglected Tropical Disease. The meeting was attended by Stefan Jungbluth from EVI.


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