EUROPEAN VACCINE INITIATIVE

ANNUAL REPORT 2016

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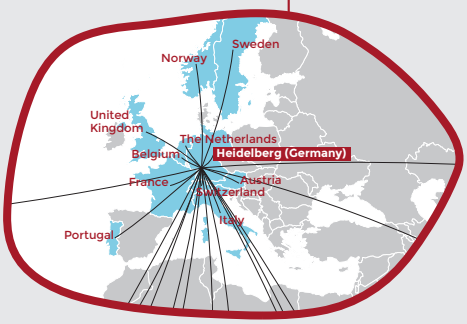


Profile

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.

Broadening EVI's scope

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

I am pleased to share with you the EVI Annual Report 2016. Great progress has been achieved during the last year, both by starting several new projects -some of which moved into new directions- as well as by successfully advancing the vaccine candidates that already formed part of EVI's portfolio.

One of the new and exciting areas EVI has ventured into is the development of a novel Zika vaccine. Zika virus infection called recently the attention of the international community due to a large outbreak that started in 2015 that affected more than 70 countries and territories. Although disease symptoms are generally mild, the possible complications to pregnancy, new-borns and neurologic complications in adults, highlight the need of effective measures to prevent this disease, even more so considering that currently no specific treatments or vaccines available exist against this virus. The ZIKAVAX project –funded under the EU´s Horizon2020 framework programme- aims to develop a safe, effective, and affordable preventive vaccine against Zika virus infection, using a delivery platform technology based on a measles vector with demonstrated proof of principle in humans and a preclinical track record of rapid adaptability and effectiveness for a variety of pathogens.

Another new initiative that started in 2016 is the VAC2VAC project, funded by the Innovative Medicines Initiative (IMI) 2 and coordinated by EVI. The main objective of this ambitious project involving many partners from the public and private sector is to demonstrate the proof-of-concept of the consistency approach for batch release testing of vaccines. If successful, the project is likely to have a major impact on how vaccines will be controlled in the future.

Concerning the progress made by vaccine candidates that were already in EVI's portfolio, in 2016 several of EVI's malaria candidates have achieved major milestones, of which I will mention here only a few. Both

the AMA1-DiCo and P27A blood stage vaccine candidates concluded their phase Ia/b clinical trials, and the safety and immunogenicity analysis indicate that both vaccine candidates are safe, well tolerated and immunogenic in malaria-naïve and exposed population. Another blood stage candidate - BK-SE36- commenced the phase Ib clinical trial and expanded to include the younger cohort. The trial follow-up phase Is expected to be completed in February 2017. Acknowledging the high potential of this project, the Japanese Global Health Innovative Technology (GHIT) Fund in 2016 awarded follow-up funding to EVI and partners for the further clinical development of the BK-SE36 blood stage malaria antigen. Also both placental malaria vaccine candidates supported by EVI commenced their phase Ia/b clinical trials to assess the safety and immunogenicity of these vaccine candidates.

Last but not least, significant progress has been made by EVI in the attempt to develop a universal influenza vaccine in the context of the EDUFLUVAC project. Mouse immunogenicity studies were successfully completed in 2016 and the proof of concept challenge studies in two animal models could be started. Also, a successful workshop on experimental animal models for universal influenza vaccines was organised at Biomedical Primate Research Centre (BPRC) in The Netherlands.

Finally, with great interest the EVI Board has followed the establishment of the Coalition for Epidemic Preparedness Innovations (CEPI), a new alliance that aims to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics. Establishment of CEPI and the commitment to this initiative shown by several leading investors is a rewarding confirmation to the EVI Board that by supporting and accelerating the development of vaccines for diseases of poverty EVI is on the right track.

GOVERNANCE

Members of EVI Board as of 31 December 2016

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

Corinne Kruiswijk
Institute for Translational Vaccinology, Bilthoven The Netherlands

Clemens Kocken
Biomedical Primate Research Centre, Rijswijk, The Netherlands

Claude Leclerc
Institut Pasteur, Paris, France

Samuel McConkey
Novartis Vaccines, Royal College of Surgeons in Ireland, 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 2016

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 2016

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

Dominique Mazier
University Pierre et Marie Curie, France

James Searl Robertson
Retired, United Kingdom

Mahamadou Aly Thera
Mali

Members of EVI Finance and Risk Management Committee (FRMC) as of 31 December 2016

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 2016

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

Eric Nébié
EDCTP/TDR fellow

Oliver A. Schraidt
Project Manager

Fabrice Somé
EDCTP/TDR fellow

Nicola Viebig
Leader, Strategic Research

2016 GOVERNANCE EVENTS

The EVI governing bodies were highly involved in the 2016 activities leading to a restructuring of EVI with the aim of increasing the overall efficiency of the organisation. The final strategic plan 2016-2020 that was approved by the Board in late 2016 was launched in August 2016[1].

EVI Scientific Advisory Committee (SAC)

The EVI SAC met face to face twice at the Institut Pasteur in Paris:

- For the review of vaccine development projects on **31 May**
- For the annual review of EVI portfolio on **14 December**.

Dominique Mazier joined the EVI SAC in January 2016. With the EVI SAC meeting in May, Aissatou Touré and Samuel McConkey completed their SAC membership terms according to the "Rules of Procedure of EVI SAC" after many years of dedicated contribution to EVI in the role of EVI SAC members.

EVI Board

The EVI Board met face-to-face on **31 May** and **15 December** at the Institut Pasteur in Paris.

The EVI Board also held two teleconferences on **1 July**, to approve the annual report and discuss the development of the new strategic plan, and on **23 September** for regular updates on EVI activities and decisions on EVI's strategic directions.

In May, Samuel McConkey switched his position from an EVI SAC to an EVI Board member, replacing Ruairi Brugha as the RCSI representative. Corine Kruiswijk took over the Intravacc seat on the EVI Board from Jan Hendriks in **December**.

EVI Board of Stakeholders (BoS)

The EVI BoS met jointly with the EVI Board on **15 December**.

EVI Rendez-Vous

For the third time and to follow the tradition, the **6th EVI Rendez-Vous** took place at Institut Pasteur in Paris. The meeting was attended by stakeholders from various European countries, North America, Asia and Africa, including members of EVI's governing bodies, funders, research partners, and the EVI Secretariat. The international experts participating in EVI's annual portfolio review were positively impressed by the expansion of EVI 'portfolio.

EVI Finance and Risk Management Committee (FRMC)

The FRMC held two teleconferences to review the annual financial audit report and the risk register.

1. http://www.euvaccine.eu/sites/default/files/uploads/Files/uploads/EVI_SP%201620_Final_160724.pdf

EDCTP/TDR CLINICAL RESEARCH AND DEVELOPMENT FELLOWSHIP

The strengthening of public health and vaccine research capacities in Low- and Middle-Income Countries (LMICs) is part of EVI's mission to combat diseases of poverty. The training of scientists is key in the empowerment of research institutions in LIMCs, to address public health challenges and develop and implement appropriate solutions. To this end, EVI joined the EDCTP/TDR Clinical Research and Development Fellowship Scheme in 2016 as a hosting institution providing training to researchers from LMICs who are involved in clinical research projects.

The purpose of this training is to provide support to researchers and key members of clinical trial research teams from LMICs to acquire essential skills in clinical research and development through placements in pharmaceutical companies and PDPs. The scheme targets early to mid-career researchers or clinical staff (clinicians, pharmacists, medical statisticians, data managers, other health researchers) who are employed by a legal entity in LMICs where they are currently working on activities in the scope of EDCTP or TDR. Fellows must be committed to return to their home organisation for a minimum of two years after completion of the fellowship. Then they will transfer the skills acquired to their home institution through a re-integration plan of 6 months.

Two researchers from Burkina Faso with different educational background and working experiences were awarded with the EDCTP/TDR fellowship and spent one year at EVI in Heidelberg, Germany supporting EVI staff and acquiring key competencies in vaccine development and project management.

FELLOW'S PROFILES AND THEIR EXPERIENCE AT EVI

Fabrice Somé

Fabrice commenced his training at EVI on 8 January 2016. He obtained one MSc in Animal Biology at the faculty of Sciences Semlalia of the University of Marrakech in 2006, another MSc in Applied Biology at the University of Ouagadougou in 2009, and a PhD in Applied Biology in 2014 at the Polytechnic University of Bobo-Dioulasso. Since 2007 he is working at the Institut de Recherche en Sciences de la Santé (IRSS), Bobo-Dioulasso, and has been involved in several projects assessing antimalarial drug efficacy and *Plasmodium falciparum* drug resistance. After completion of his EDCTP-TDR Clinical Research and Development fellowship at EVI, Fabrice returned to IRSS as Assistant Professor.

"The training I received at EVI was a great opportunity to learn the practical aspects of managing vaccine development projects, on both pre-clinical and clinical stages and to address the financial, legal and intellectual property management of vaccine projects. My fellowship also allowed me to attend several international scientific meetings and benefit from visiting three different European laboratories."

Eric Nébié

Eric started his fellowship at EVI on 30 November 2015. Eric has a Medical Doctorate from the University of Ouagadougou in 2010, followed by several years of experience in vaccinology and clinical research. He has held various positions at hospitals/health centres in Burkina Faso, and most recently supervised immunisation campaigns (Polio campaigns, measles and rubella campaign) on behalf of the World Health Organization (WHO).

"The training at EVI was a good opportunity for an effective improvement of my capabilities in clinical research. I am now sharing the skills gained at EVI with the clinical team at the Centre de Recherche en Santé de Nouna (CRSN), Burkina Faso, through daily work experience and workshops. As part of my reintegration plan, I also proposed the implementation of a better quality management system at CRSN as it was one of the key goals of my training. I am still in contact with EVI which is giving me valuable assistance and I hope we will soon have the possibility to collaborate in future projects".

Training at EVI

The goal of the placement at EVI is to strengthen the fellow´s capabilities in clinical research implementation according to international guidelines particularly for early stage vaccines development. Following the spirit of the EDCTP-TDR calls, the training at EVI aims to facilitate critical decision-making in vaccinology by providing fellows with an overview of the field, from antigen discovery to vaccine development and clinical trials as well as the socio-economic, regulatory and ethical issues of vaccination.

The training methodology has two complementary approaches: a series of lectures combined with hands-on training. Topics covered include, among others, project management, antigen discovery, regulatory aspects, GMP and clinical development. An experienced EVI staff member is allocated as a mentor to the trainee, under supervision of the EVI Executive Director, Odile Leroy. The mentoring concept encourages the trainees to take personal responsibility of project tasks, offers assistance and stimulates individual creativity.

To strengthen the skills of the EDCTP/TDR fellows, EVI organised two workshops (on publication writing and project management) and monthly lectures that were presented by EVI internal staff or external experts. The lecture series addressed the main aspects of vaccine development from antigen discovery to preclinical and clinical development.

"We expect that after successful completion of this training programme, our fellows will contribute to promote high quality research in LMICs. One strategy for this is training of peers, as stated in the reintegration plan of both trainees, and the other is the strengthening of collaborative work and networking, which is facilitated by the network of EVI partners", says Odile Leroy.

Following the positive experience in 2016, EVI is happy to welcome two new trainees in 2017.

FUNDRAISING

The sustained efforts to mobilise and diversify resources in 2016 allowed EVI to raise the total of 15.6 M€. In addition to mobilising 7.85 M€ from the Innovative Medicines Initiative (IMI) 2, Japan's Global Health Innovation Technology (GHIT) Fund demonstrated its commitment to support EVI by awarding follow-up funding for the continuation of one of EVI´s malaria vaccine project. Moreover, a new project coordinated by EVI surrounding the development of a Zika vaccine was awarded by the EC.

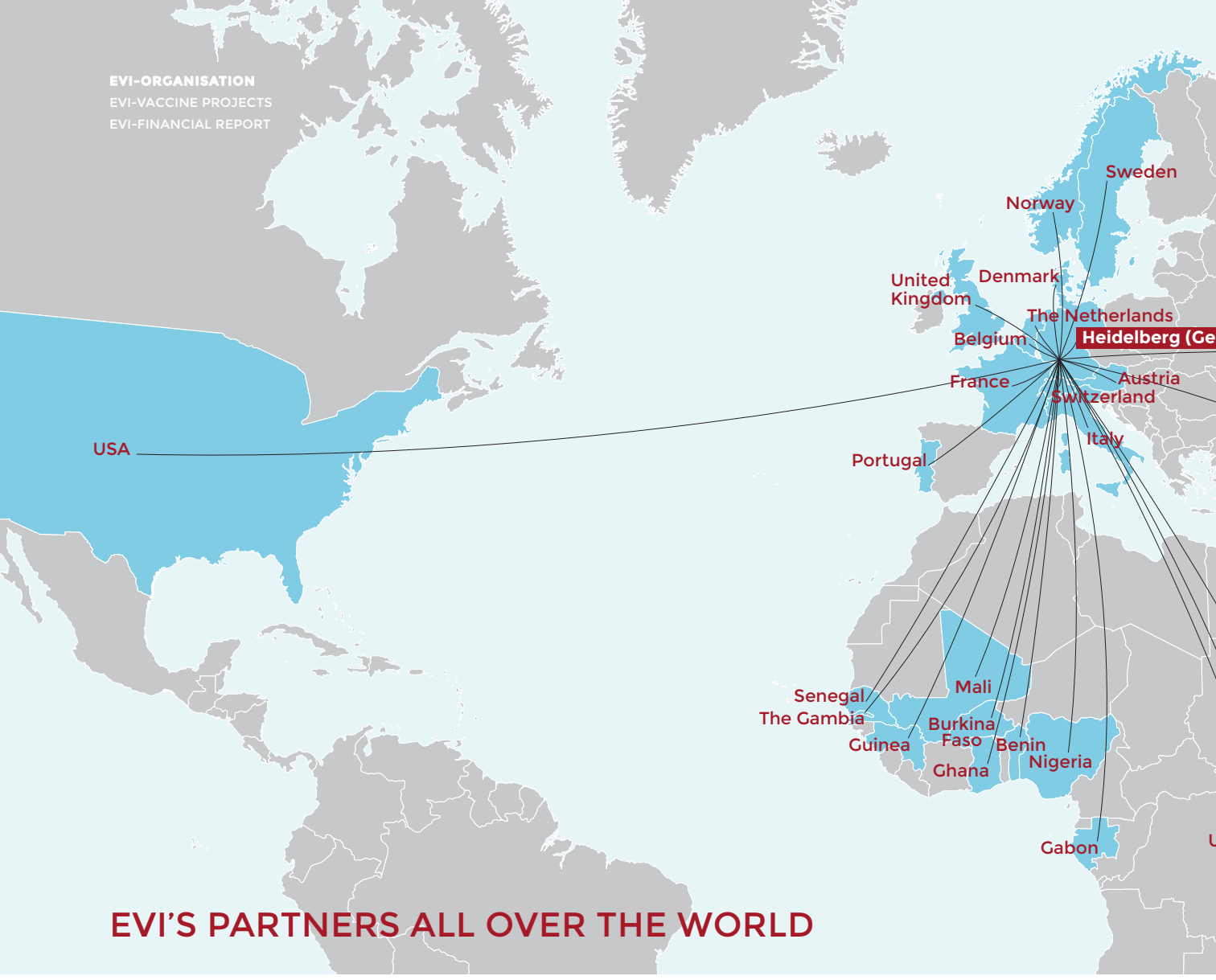
The VAC2VAC project, supported by IMI2 with additional €8,128,429 provided by the EFPIA partners, is a public-private partnership coordinated by EVI involving a total of 20 partners, including six leading pharmaceutical companies developing human and animal vaccines. Aims of the project are to develop and validate quality testing approaches using non-animal methods.

The new grant from the EC in the amount of €4,918,137.50 will provide support for the further preclinical and clinical testing of a novel Zika vaccine based on a measles vector. Apart from EVI, Institute Pasteur, CEA and Themis Bioscience are partners in the project.

The award secured by EVI and its partners from the GHIT Fund is supporting the further clinical development of the BK-SE36 blood stage malaria antigen in the context of the SEmalvac2 project. Apart from coordinator EVI, the other partners in this project are Osaka University, Osaka University Hospital, CNRFP and Nobelpharma. Nobelpharma provides M€0.7 of co-funding to EVI and other partners of this project.

EVI has received private direct funding and support from several companies, including All4cloud and SAP.

Thanks to the fresh funding secured during 2016 on addition to the Irish Aid and BMBF grants, EVI continues to achieve a significant return on investment for our funders whose – sustained – commitment to support EVI we gratefully acknowledge.



EVI'S PARTNERS ALL OVER THE WORLD

Austria
- Themis Bio
- Austrian Agency for Health and Food Safety
- Vienna School of Clinical Research

Belgium
- GlaxoSmithKline
- Novasep (formerly Henogen)
- Vaccines Europe / European Federation of Pharmaceutical Industries and Associations
- Gent University
- Zoetis Belgium SA
- European Commission, Joint Research Centre
- Scientific Institute of Public Health

Benin
- Institut de recherche clinique du Bénin
- 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
- Sanofi Pasteur
- Institut Pasteur, Paris
- BIOTEM
- CiToxLAB
- Confarma
- GTP Technology
- Imaxio SA
- 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
- Merial SAS
- Association Internationale de Standardisation Biologique pour l'Europe
- Institut Pasteur, Lille

Gabon
- Centre de recherches médicales de Lambaréné
- Fondation internationale de l'hôpital du Dr Albert Schweitzer de Lambaréné
- Albert Schweitzer Hospital

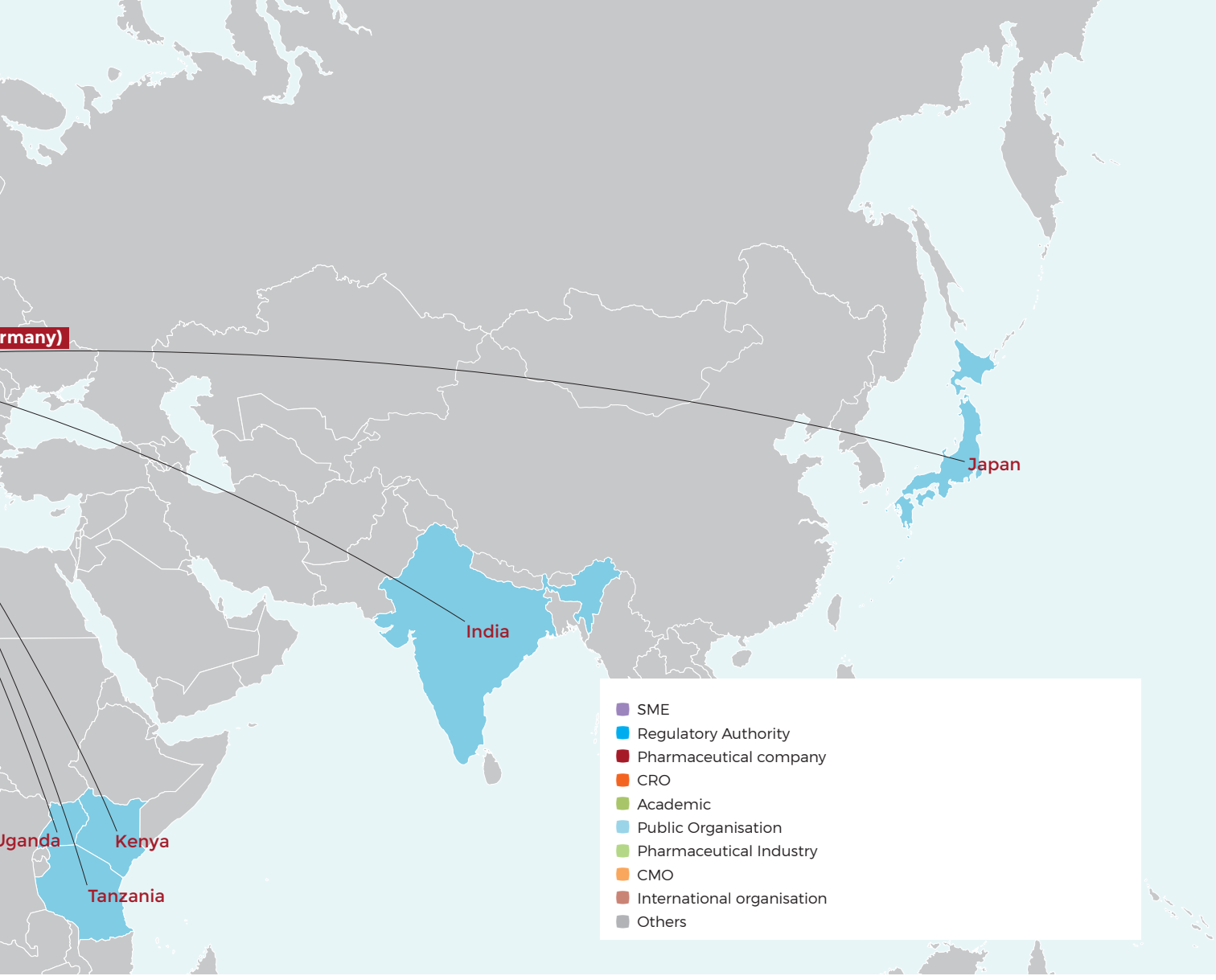
Germany
- Paul-Ehrlich-Institut
- IDT Biologika
- NNE Pharmaplan GmbH
- Output Pharma
- Eberhard-Karls Universität Tübingen
- Fraunhofer IME
- Ludwig-Maximilians-Universitaet München
- Boehringer Ingelheim Vetmedica GmbH

Ghana
- Kintampo Health Research Centre

India
- Zydus Cadilla
- DiagnoSearch Life Sciences Pvt. Ltd.
- International Centre for Genetic Engineering and Biotechnology

Italy
- Istituto Superiore di Sanità
- ETNA Biotech s.r.l.
- Novartis
- Novartis Vaccines Institute for Global Health
- ReiThera s.r.l. (formerly Okairòs s.r.l.)
- Sclavo Foundation
- University of Siena
- Novartis Vaccines and Diagnostics s.r.l.

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



Kenya
- Kenya Medical Research Institute

Mali
- Malaria Research and Training Centre

Nigeria
- University of Ibadan

Norway
- University of Bergen

Portugal
- Instituto de Biologia Experimental e Tecnológica

Senegal
- Pharmalys
- Université Cheikh Anta Diop

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

Switzerland
- Preclin Biosystems AG
- Redbiotec AG
- Developing Countries Vaccine Manufacturers Network
- Malaria Vaccine Funders Group
- Roll Back Malaria
- 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
- Erasmus University Medical Centre Rotterdam
- Biomedical Primate Research Centre
- Institute for Translational Vaccinology
- Abbott
- Artemis One Health Research BV
- Janssen
- European Advanced Translational Research Infrastructure in Medicine
- Academisch Medisch Centrum bij de Universiteit van Amsterdam
- Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum
- Wageningen Bioveterinary Research
- Intervet International BV (MSD)
- National Institute for Public Health and the Environment/ Rijksinstituut voor Volksgezondheid en Milieu
- University Medical Center Groningen
- University of Applied Sciences Utrecht
- University of Utrecht
- Wageningen University and Research Centre

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

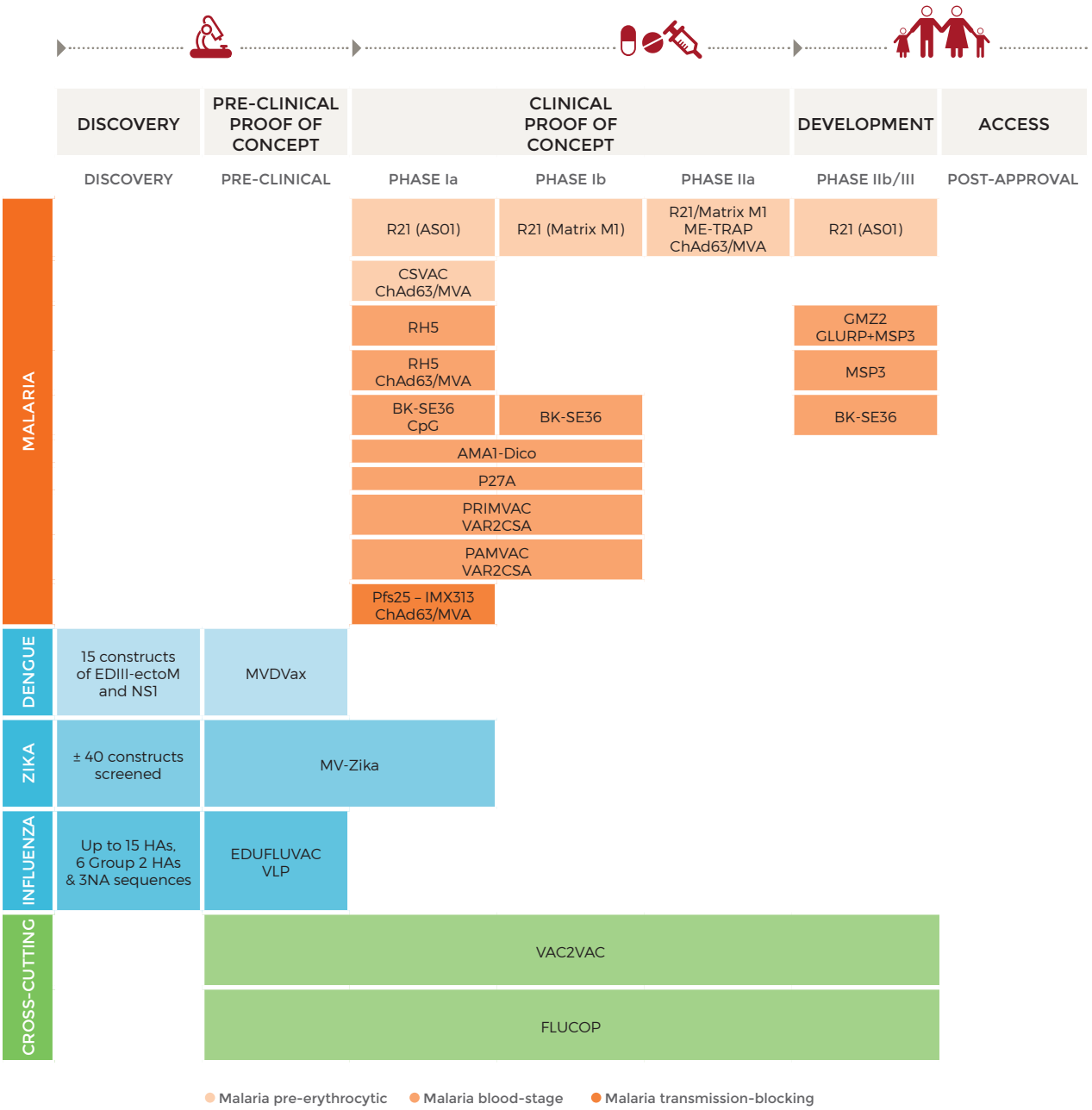
United Kingdom
- Pharmalys
- National Institute for Biological Standards and Control, a centre of the Medicines and Healthcare Products Regulatory Agency
- Jenner Vaccine Foundation
- ALMAC Sciences
- Nova Laboratories Ltd
- European Medicines Agency
- Jenner Institute
- London School of Hygiene and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

USA
- Pfenex Inc.
- Infectious Diseases Research Institute
- National Institute of Health / National Institute of Allergy and Infectious Diseases
- PATH Malaria Vaccine Initiative

2016 EVI-VACCINE PROJECTS

STRENGTHENING THE PORTFOLIO

Malaria vaccines remain the core components of the EVI portfolio with 10 malaria antigens at different stages of development. However, EVI is extending its portfolio to include other targets such as dengue, zika, universal influenza and paratyphoid vaccines. Furthermore, EVI will invest substantially in capacity strengthening and the harmonisation of vaccine development in Europe and 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 safety and immunogenicity analysis indicate that both vaccine candidates are safe, well tolerated and immunogenic in malaria-naïve and exposed population.

The age-de-escalation phase Ib clinical trial of BK-SE36 vaccine candidate commenced with the immunisation of children aged 2-5 years old and, following safety data review, it expanded to include the younger population aged 1-2 years old. The last boost immunisation was administered in April 2016 and the trial follow-up phase Is expected to be completed in February 2017.

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 pre-clinical work funded by EVI from the Irish Aid grant has been pivotal to mobilise additional funding that allowed GMP manufacturing of the vaccine candidate (funded by MRC) and the conduct of a phase I/IIa clinical trial to assess the safety, immunogenicity and efficacy of RH5.1/AS01 (funded by Liedos). 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 vaccine candidate achieved a good safety and immunogenicity profile, including functional antibodies detected in *in vitro* assays.

Placental malaria vaccines:

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 remains a major focus of EVI.

In Denmark, the PAMCPH/PlacMalvac project commenced a phase Ia/b clinical trial assessing the safety and immunogenicity of the placental malaria vaccine candidate PAMVAC adjuvanted with Alhydrogel, GLA-SE and GLA-LSQ in Germany and Benin. The PRIMALVAC phase Ia/b clinical trial assesses the vaccine candidate PRIMVAC adjuvanted with Alhydrogel or GLA-SE in France and Burkina Faso. The two clinical trials are operating according to similar timelines and the vaccinations of the first subjects in both clinical trials were performed the exact same day. 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

Within MVVC 2, good safety and immunogenicity profiles were achieved for Matrix-M1 adjuvanted R21 in a phase Ib clinical trial in healthy African adults at the CNRFP, Burkina Faso. Further analyses confirmed the good safety and immunogenicity results of 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 main achievements of the MultiMalVax project included the completion of the phase I clinical trial assessing the safety and immunogenicity of R21 with the AS01 adjuvant developed by GSK. Based on previous clinical trial results, a phase I/IIa clinical trial using Matrix-M1 adjuvanted R21 alone or in a combination trial with viral-vectored ME-TRAP has been initiated. The results are expected in early 2017.

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. 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. The viral vectors have been produced and tested in preclinical studies, and a phase Ia clinical trial has started and is fully enrolled. The results are expected in Mid-2017.

OTHER VACCINES

Dengue vaccine

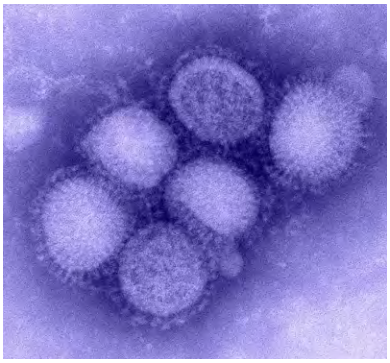
EVI supports the Institut Pasteur approach for dengue antigens expressed in attenuated measles virus vectors (MVDVax), showing promising preliminary results in a non-human primate model. Activities are underway to ensure funding to further test MVDVax in clinical trials.

ZIKAVAX

With the recent outbreak of Zika virus infections, EVI and partners embarked in October 2016 on the development of a safe and effected preventive vaccine against Zika virus infection. The vaccine concept is based on the use of the measles vector as a delivery platform technology for the Zika antigen(s). Preclinical studies are ongoing in order to first select the most promising vaccine candidate(s) and then perform immunogenicity and efficacy studies in mice and in a non-human primate challenge model that is to be developed by the consortium.

Influenza vaccine

The EDUFLUVAC project successfully completed the mouse immunogenicity studies and proceeded with the proof of concept challenge studies in ferrets and non-human primates. A successful workshop on experimental animal models for universal influenza vaccines was organised at Biomedical Primate Research Centre (BPRC).



H1N1 influenza virus

The FLUCOP project began in 2015, supported by the IMI with funding from the European Union (EU) 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 2016, several pilot studies commenced, including a study to assess the most influential variables of the haemagglutination inhibition assay in order to optimise a standardised assay protocol.

Paratyphoid project

The Paratyphoid Infection Model (PIM) project was officially concluded in 2016 and successfully demonstrated the safety and practicality of the first ever human challenge study for *Salmonella paratyphi A*. A paper describing the safe establishment of a paratyphoid challenge model was accepted for publication on Clinical Infectious Disease in December 2016.

Staphylococcus aureus vaccine

In 2016 the most important step towards addressing the critical issue of antibiotic-resistant *Staphylococcus aureus* was the discovery of a new promising vaccine antigen that showed protective efficacy in relevant animal models.

CROSS-CUTTING ACTIVITIES

Vaccine batch to vaccine batch comparison by consistency testing

The overall objective of the VAC2VAC project is demonstrated proof of concept of the consistency approach for batch release testing of established vaccines, using sets (toolbox) of *in vitro* assays ensuring that each vaccine batch from an individual manufacturer is consistent with a batch proven to be safe and efficacious in registration studies to ensure consistent quality of product released to market. The project was started in 2016 and the main achievements are finalising the mutual transfer agreements and sample shipments between research and industry partners. The development of the new *in vitro* tests is currently ongoing. At the same time the consortium is focussing on establishment of a roadmap to facilitate regulatory approval of these innovative testing.

Dissecting the Immunological Interplay between Poverty Related Diseases and Helminth Infections

The IDEA project was successfully completed in 2015 with the submission of the final report to the European Commission. Dissemination activities are still ongoing to have the project results published in peer-review articles and maximise the spread of the knowledge generated.

The development of the European vaccine research and innovation roadmap

The work of the IPROVE project (Innovation Partnership on Vaccines in Europe) culminated in 2016 with the official launch of the IPROVE Roadmap at a special summit at the European Parliament held in March 2016 that was co-hosted by several Members of European Parliament. The presentation of the roadmap was attended by a large number of participants from different stakeholders from the public and private sector.

DEVELOPING NEXT GENERATION VACCINES

Delivery Platform, Adjuvants and Viral Vectors

A number of delivery platforms are currently used at EVI for vaccine development and several adjuvants are being assessed for their ability to increase the antigens' immunogenicity.

EVI has filled vials of aluminium hydroxide under GMP conditions at Nova Laboratories Ltd. for use in preclinical and clinical studies.

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 seeks to develop a level of standardisation for several key assays through agreements on standardised laboratory procedures, preparations and reagents.

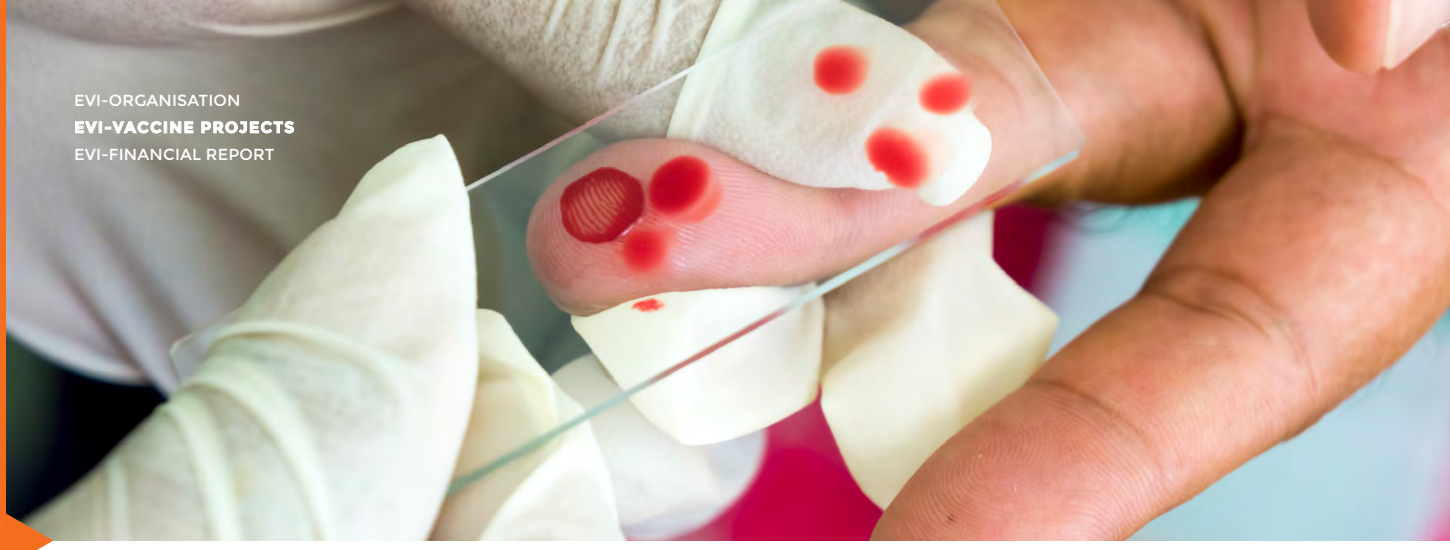
Malaria vaccines

Despite intensive control efforts over the past decade, malaria remains one of the most significant global public health problems. Malaria is caused by *Plasmodium* parasites that are transmitted by Anopheles mosquitoes. There were 212 million (range 148-304 million malaria cases) reported in 2015, leading to 429,000 (range 235,000-639,000) deaths[2]. From the *Plasmodium* species, *P. falciparum* is responsible for the majority of severe malaria cases and deaths. Mortality occurs primarily in infants and young children in sub-Saharan Africa, although pregnant women are also affected, which can severely impact the developing foetus.

Current efforts to control malaria rely on the use of insecticide treated bed nets and indoor residual spraying of houses to limit human contact with vectors, combined with early detection and treatment of malaria patients, currently with artemisinin combination therapy. Intensive implementation of these malaria control measures over the past couple of decades has led to significant reduction in transmission rates and malaria incidence. However, these measures are resource-intensive and need to be applied continuously, which raises questions of long-term sustainability, especially in resource-poor countries where malaria is endemic. Moreover, the rise and spread of artemisinin resistant *P. falciparum* strains threatens the efficacy of the current mainstay of malaria therapy[3]. While other antimalarial drugs are in development, *P. falciparum* parasites have become resistant to every drug put into widespread use so far, emphasising that drug treatment alone is not a viable elimination strategy.

Therefore, the development of vaccines targeting *P. falciparum* malaria would provide an extremely valuable, cost-effective tool complementary to current malaria control methods, and could add significantly to the drive the elimination and ultimately eradication of malaria.

2. World Health Organization, "World Malaria Report 2016," (2016).
3. F. Ariey *et al.*, A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature 505, 50-55 (2014).



VACCINES THAT PREVENT MALARIA INFECTION:

Pre-erythrocytic malaria vaccines

Malaria vaccines targeting the Pre-erythrocytic stages are designed to prevent sprorozoite invasion of hepatocytes and to impede the development of the parasite inside the hepatocytes, thereby preventing the development of the parasite into symptomatic blood-stages. Two main effector mechanisms are targeted to protect from malaria: antibodies that neutralise extracellular sporozoites by targeting surface exposed antigens, and T cells that eliminate intracellular liver stages after recognition of parasite-derived peptides presented to the immune cells on the hepatocyte surface.

Vaccine development has been a focus of malaria research for decades, but the majority of efforts have focussed on only a handful of pre-erythrocytic candidates. The RTS,S vaccine (Mosquirix™) developed jointly by the Malaria Vaccine Initiative (MVI PATH) and GSK is the only recombinant malaria vaccine to reach phase III clinical trials. However, the efficacy of RTS,S adjuvanted with AS01 is rather modest (39%)[4], it achieves relatively short-term protection, and a series of four vaccinations is required. To assess the vaccine's protective effect in real-life settings, the RTS,S vaccine will be rolled out in pilot implementation projects in three (3) in sub-Saharan Africa countries with start of vaccinations in 2018. Another approach, which has provided some evidence for significant efficacy is immunisation with irradiated sporozoites. Although this approach elicits significant protective efficacy against challenge with the homologous *P. falciparum* strain[5], attempts to increase the efficacy against heterologous strains and the duration of protection are underway. New approaches leading to a second-generation malaria vaccine are urgently needed.
The EVI portfolio currently includes leading pre-erythrocytic malaria vaccine programs. The first program is based on the RTS,S biosimilar R21 that is expected to elicit an improved malaria-specific immune response. The second approach uses the viral vectored prime-boost strategy where the modified vaccinia Ankara virus (MVA) is used for priming and a chimpanzee adenovirus (ChAd63) is used for boosting immune responses against the ME-TRAP antigen.

MVVC

The overall aim of the Malaria Vectored Vaccines Consortium (MVVC) was to integrate capacity building and networking in the design and conduct of phase I and II clinical trials of viral vectored candidate malaria vaccines in sub-Saharan African children and infants.

While the project was funded for five years (2009-2014) by EDCTP in response to the 2008 call "Malaria Vaccines Integrated Project – Clinical Trials / Capacity strengthening, workshops, training / Networking", data analyses and PhD student training were still on-going in 2016. The total funding provided by EDCTP was €5,613,936, complemented by co-funding from Irish Aid, Department of Foreign Affairs and Trade (Ireland), Swedish Development Agency (Sida) (Sweden), MRC (UK), the Federal Ministry of Science and

4. The RTS,S Clinical Trials Partnership (2014). PLoS Medicine 2014, doi.org/10.1371/journal.pmed.1001685
5. R. A. Seder *et al.*,. Science 341, 1359-1365 (2013).

PARTNERS

- Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Kenya Medical Research Institute (KEMRI),
- Medical Research Council (MRC), Gambia
- ReiThera s.r.l., IT (formerly Okairòs s.r.l., Italy)
- Université Cheikh Anta Diop (UCAD), Senegal
- University of Oxford (UOXF), United Kingdom
- Vienna School of Clinical Research (VSCR), Austria (until 31 Jan 2013)

Research (Austria), and third-party contributions from all the project partners, making a total budget of €9,514,711.

The candidate vaccine antigen, Multiple Epitope-Thrombospondin-Related Adhesion Protein (ME-TRAP) acts at the malaria liver stage. The clinical trials utilised a prime-boost regime by priming with Simian Adenoviral vector 63 (ChAd63) and boosting with Modified Vaccina Ankara (MVA) encoding ME-TRAP. Pre-clinical studies as well as the completed and ongoing phase I and II clinical trials found recombinant adenoviruses to be the most effective means of inducing strong CD8 T cell responses that are known to be protective against liver-stage malaria. These immune responses are enhanced by a booster immunisation with the widely used MVA vector.

MAIN ACHIEVEMENTS The main MVVC 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

Delivery Platform, Adjuvants and Viral Vectors

The Pre-erythrocytic 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.

Safety and immunogenicity of the vaccine candidates were successfully shown in phase Ib clinical trials at KEMRI and MRC in male adults the results from the phase Ib adult clinical trials in Kenya and The Gambia were published in PLOS ONE[6] and Molecular Therapy[7]. The ChAd63-vectored vaccine and the ChAd63 prime/MVA boost regimens were then 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. 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[8],[9].

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[10].

Vaccine efficacy in Kenyan Adults

	ME-TRAP		Control		Unadjusted efficacy		Adjusted efficacy	
	N	n	N	n	Efficacy (95% CI)	P	Efficacy (95% CI)	P
Any PCR positivity	61	11	60	28	67% (33-83%)	0.002	66% (31-83%)	0.003
>10 parasites/ml	61	4	60	19	82% (46-94%)	0.002	81% (42-94%)	0.03
New genotype	61	5	60	14	67% (7-88%)	0.035	65% (2-87%)	0.046

N, number of participants; n, number of end points identified. Efficacy figures are estimated from Cox regression, where efficacy = (1 – HR) × 100%.

However, the UCAD phase IIb clinical trial data did not reproduce the KEMRI results as indicated in the PLOS ONE publication[11].

Vaccine efficacy in Senegalese Adults

	TRAP		Control		Unadjusted Efficacy		Adjusted Efficacy	
	N	n	N	n	Efficacy (95% CI)	p	Efficacy (95% CI)	p
Any PCR positivity	57	12	58	13	8% (-200-50%)	0.6	8% (-164-39%)	0.53
>10 parasites/ml	57	11	58	12	9% (-180-50%)	0.8	9% (-141-46%)	0.74

N, number of participants; n, number of end points identified. Efficacy figures are estimated from Cox regression, where efficacy = (1 – HR) × 100%.

A phase Ib lead-in/IIb clinical trial in the target age group (infants 5-17 months old and children) was completed at CNRFP in 2014. 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[12].

6. Ogwang C. *et al.* PLOS ONE 2013, doi:10.1371/journal.pone.0057726
7. Kimani D. *et al.* Molecular Therapy 2014, doi:10.1038/mt.2014.109
8. Afolabi M.O. *et al.* Molecular Therapy 2016, doi:10.1038/mt.2016.83
9. Bliss C.M. *et al.* Molecular Therapy 2017, doi:10.1016/j.ymthe.2016.11.003
10. Ogwang C. *et al.* Science Translational Medicine 2015, doi:10.1126/scitranslmed.aaa2373
11. Mensah V.A. *et al.* PLOS ONE 2016, doi:10.1371/journal.pone.0167951.
12. Nébié I. *et al.* Clinical and Vaccine Immunology 2014, doi:10.1128/CVI.00723-13.

adults, children, and infants. The prime-boost vaccine combination using ChAd63 ME-TRAP and MVA ME-TRAP was safe and immunogenic when administered to African adults, children and infants and has demonstrated 67% efficacy in Kenyan adults. Three MSc students, three PhD students and one postdoc were trained. A series of workshops was organised for the MVVC project members as part of the capacity strengthening activities. Clinical trial infrastructure was upgraded at UCAD, Senegal and CNRFP, Burkina Faso.

Capacity strengthening, Workshops, Training

Dr Mahamadou Mansour Ndiath (UCAD) was awarded with his "Diplôme de Doctorat" from the Université Cheikh Anta Diop in August 2016. David Kangoyé has successfully defended his PhD and is expecting to receive his certificate in early 2017. The major results of their PhD studies were published in peer-reviewed journals[13],[14],[15],[16]. All MVVC capacity strengthening activities were achieved. This includes the successful completion of the training of the three MSc students, the three PhD students as well as one postdoctoral fellow. Short-term trainings were organised as centralised workshops on various topics and several networking events and exchange visits took place to reinforce collaborations, especially between the African project partners. 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).

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

Muhammed Afolabi (MRC, The Gambia) presented "Development and evaluation of a multimedia tool for obtaining informed consent in The Gambia: a mixed method study" at the Eighth EDCTP Forum, 6-9 September, Lusaka, Zambia.

Adrian Hill (UOXF, UK) presented the MVVC clinical trial safety, immunogenicity and efficacy results at various occasions in 2016.

13. Ndiath M. *et al.* Malaria Journal 2014, doi:10.1186/1475-2875-13-453
14. Ndiath M. *et al.* Malaria Journal 2015, doi:10.1186/s12936-015-0976-9
15. Kangoye D.T. *et al.* PLOS ONE 2014, doi:10.1371/journal.pone.010796
16. Kangoye D.T. *et al.* Vaccine 2016, doi:10.1016/j.vaccine.2015.10.058

MVVC 2

The EVI coordinated MVVC 2 project built on the MVVC project which established 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. The three-year MVVC 2 project (2012-2015) was 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 EU Member States, BMBF (Germany), Irish Aid, Department of Foreign Affairs and Trade (Ireland), MRC (UK), Sida (Sweden), and third-party contributions, with a total project budget of approximately €1,2m.

MVVC 2 aimed to determine whether the virally vectored prime-boost malaria vaccines are compatible with the EPI vaccination schedule and whether an adjuvanted Circumsporozoite Protein (CSP) particle (R21) is safe and immunogenic. As part of the integrated strategy, workshops, training and networking activities as well as infrastructure upgrades were used to strengthen the clinical trial capabilities and laboratory facilities of the African sites, allowing the partners to conduct the proposed clinical trials and additional health research. The KHRC site also developed capacity in cellular immunology.

RECENT ACHIEVEMENTS The safety and immunogenicity of the vectored liver-stage malaria vaccine candidates co-administered with EPI vaccines were assessed in Gambian infants. The MVVC 2 consortium completed the clinical trial at MRC, The Gambia, with good safety and immunogenicity profiles when

co-administered with EPI vaccines. The safety and immunogenicity of the Matrix-M1 adjuvanted CSP particle was assessed in a phase Ib clinical trial at CNRFP, Burkina Faso in Burkinabe adults showing good safety and immunogenicity of this regimen.

PARTNERS

- Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Kenya Medical Research Institute (KEMRI), Kenya
- Kintampo Health Research Centre (KHRC), Ghana
- Medical Research Council (MRC), Gambia
- Novartis Vaccines and Diagnostics, Italy
- ReiThera s.r.l., IT (formerly Okairòs s.r.l.), Italy
- Université Cheikh Anta Diop (UCAD), Senegal
- University of Oxford (UOXF), United Kingdom
- Vienna School of Clinical Research, Austria (until 31 Jan 2013)

MVVC2

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 was Matrix-M1, provided by Novavax.

Clinical Development

This project aimed 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 revealed good safety and immunogenicity profiles in all infant age groups. Analyses of EPI antibody responses were completed. A manuscript is in preparation.

The second clinical trial assessed the safety and immunogenicity of the R21 CSP particle adjuvanted with Matrix-M in African adults at the CNRFP, Burkina Faso. This clinical trial started in August 2016. Preliminary results show a good safety and immunogenicity profile of R21 adjuvanted with Matrix-M1. A manuscript is in preparation.

Capacity strengthening, Workshops, Training

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, equipment has been sourced and personnel trained.

Exchange visits took place within the project duration 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 working platform offered by the MVVC 2 project has been a great opportunity for the professional growth of the staff involved in the project. Exchange visits, meetings and short-term training activities created a highly stimulating working environment and have been instrumental to the formation of very competent clinical researchers. 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.

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 generated comparable results in the MVVC 2 project and will generate in future clinical trials.

Outreach and Communication

Katie Ewer (UOXF, UK) presented "Viral vector malaria vaccines induce potent T cell and antibody responses in West African infants" at the Malaria Vaccines for the World 2016, 2-4 May 2016, Leiden, The Netherlands.

Muhammed Afolabi (MRC, The Gambia) presented "Immunogenicity of malaria-vectored vaccines is not affected by co-administration with routine EPI vaccines in a randomised controlled trial in Gambian infants and neonates" at the Eighth EDCTP Forum, 6-9 September 2016, Lusaka, Zambia.

Sophie Roetynck (MRC, The Gambia) presented "Immunogenicity of ChAd63/MVA ME-TRAP malaria vectored vaccine is not affected by co-administration with routine EPI vaccines in a randomized controlled trial in Gambian infants and neonates" at the ASTMH 65th Annual Meeting, 13-17 November 2016, Atlanta, USA.

Adrian Hill (UOXF, UK) presented the MVVC 2 clinical trial safety and immunogenicity results at various occasions in 2016.

MALARIA VACCINES THAT PREVENT MORTALITY AND MORBIDITY:

blood-stage malaria vaccines

Clinical malaria occurs when *Plasmodium* parasites invade and replicate within red blood cells (the so called blood-stage infection). However, immunological studies in humans and animals have demonstrated that the immune response induced by blood-stage antigens can protect against the disease.

Blood-stage malaria vaccines aim to prevent mortality, reduce clinical disease and transmission, whilst potentially allowing for natural boosting of vaccine-induced responses as well as the acquisition of natural immunity[17]. Neutralising antibodies are most often sought that (i) prevent interactions between ligands of the invasive blood-stage merozoite and protein receptors present on the host red blood cell surface[18]; (ii) prevent the interaction of the parasite antigens displayed on the red blood cell surface with host cell receptors[19]; (iii) recognise antigens that get exposed upon parasite egress[20] and/or (iv) activate monocytes that inhibit parasite growth[21]. Indeed, passive transfer studies have shown that immunoglobulins from semi-immune individuals can confer clinical immunity to individuals exposed to geographically diverse parasite strains[22]. Studies in humans and animals have shown that controlling parasite density can reduce the generation of gametocytes in the bloodstream, thus also limiting transmission.

Blood-stage malaria vaccines represent an alternative and/or complementary approach to Pre-erythrocytic vaccines and will probably be an important component of a second-generation multi-antigen, multi-stage malaria vaccine. However, the development of an effective Blood-stage malaria vaccine has proven challenging. Most antigens currently used as vaccine candidates are merozoite antigens. Only the 3D7 based adjuvanted apical membrane antigen 1 (AMA1) antigen FMP2.1/AS02A has demonstrated protective efficacy against clinical malaria for the homologous parasite in phase II clinical trial so far[23].

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. To overcome antigenic diversity in the development of blood-stage vaccines, ideally, vaccine candidates should be based on less polymorphic and more conserved antigen domains or cover the diversity. EVI's current approaches include the development of recombinant antigens (AMA1-DiCo, SEmalvac), recombinant full-length proteins (PfRH5) and synthetic peptides (P27A) as well as virally vectored antigens (PfRH5).

17. Goodman A.L. *et al.* Ann Trop Med Parasitol 2010, doi:10.1179/136485910X12647085215534.
18. Wright G.J. and Rayner J.C. PloS Pathogens 2014, doi:10.1371/journal.ppat.1003943.
19. Chan J.A. *et al.* Cell Mol Life Sci. 2014, doi:10.1007/s00018-014-1614-3.
20. Kulangara C. *et al.* PLOS ONE 2012, doi:10.1371/journal.pone.0046112.
21. Olugbile S. *et al.* Infection and Immunity 2009, doi:10.1128/IAI.00652-09.
22. Sabchareon A. *et al.* Am J Trop Med Hyg. 1991, Sep;45(3):297-308.
23. Thera M.A. *et al.* N Engl J Med. 2011, doi:10.1056/NEJMoa1008115.

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), The Netherlands
- Centre d'investigation clinique Cochin-Pasteur (CIC-Cochin), France
- Centre national de recherche et de formation sur le paludisme (CNRFP), Burkina Faso
- Confarma, France
- European Vaccine Initiative (EVI), Germany
- Fraunhofer Institute for Molecular Biology and Applied Ecology (Fraunhofer IME), Germany
- Gregory Fryer Associates Ltd., United Kingdom
- Novasep (formerly Henogen), Belgium
- Infectious Diseases Research Institute (IDRI), United States of America
- Institut national de la santé et de la recherche médicale (Inserm), France
- NNE Pharmaplan GmbH, Germany
- Nova Laboratories, Ltd., United Kingdom
- Output Pharma, Germany
- WIL Research, The Netherlands

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[24]. 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[25].

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, 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

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

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.

RECENT ACHIEVEMENTS The active phase of the clinical trial was completed in 2015, and safety and secondary objective immunogenicity data were presented at the EVI Rendez-Vous 2016 and indicate that the AMA1-DiCo vaccine was safe, well tolerated and immunogenic in malaria-naïve and exposed population. The exploratory immunogenicity analyses are underway.

Preclinical, process development, production, IMPD

The preclinical, process development and production of the AMA1-DiCo have been published in 2016[26].

Delivery Platform, Adjuvants and Viral Vectors

Glucopyranosyl Lipid A Adjuvant (GLA)-Stable Emulsion (SE) and aluminium hydroxide (Alhydrogel®) as a comparator have been 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 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, Workshops, Training

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 have continued harmonisation of the immunological assays of the AMA1-DiCo phase Ia/Ib clinical trial.

Outreach and Communication

Sodiomon Sirima (CNRFP, Burkina Faso) presented "AMA1-DiCo clinical trial phase Ia/Ib: Safety and preliminary immunogenicity results" at the EVI Rendez-Vous, 14 December, Paris, France.

Edmond Remarque (BPRC, The Netherlands) presented "Blood-stage vaccine antigen discovery, identification, prioritisation & optimisation" at the 8th EDCTP forum, EVI symposium "Importance of blood-stage malaria vaccine candidates in the development of a next generation malaria vaccine", 7 November, Lusaka, Zambia.

26. Faber et al Plos One 2016, doi:10.1371/journal.pone.0164053.

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 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.

RECENT ACHIEVEMENTS The project was successfully completed during 2015 with the selection of a full-length PfRH5 that has now advanced into clinical development. Funded by an MRC (UK) grant, GMP production of the protein and toxicology studies were also completed in 2015 and a phase I/IIa clinical trial to assess the safety, immunogenicity and efficacy of RH5.1/AS01 started in the UK.

PARTNERS

- European Vaccine Initiative (EVI), Germany
- ExpreS2ion Biotechnologies, Denmark
- University of Oxford (UOXF), United Kingdom

InnoMalVac

Preclinical, process development, production, IMPD

UOXF collaborated with ExpreS2ion Biotechnologies to produce polyclonal and monoclonal S2 cell lines expressing different variants of PfRH5. The Growth Inhibition Assay (GIA) and Surface Plasmon Resonance assay were used to analyse the induction of functional antibodies following immunisation in rabbits.

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 were scaled-up to the 10 litre fermenter scale at the Clinical Biomanufacturing Facility (CBF), Oxford, and a pilot batch and a GMP batch were produced. 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.

P27A

This vaccine candidate is an intrinsically unstructured, hydrophilic fragment of the *P. falciparum* protein PFF0165c, which is 104 amino acids in length[27], 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 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[28].

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

27. Olugbile *et al.*, Infection and Immunity 2009, doi:10.1128/IAI.00652-09
28. Villard *et al.*, Plos One 2007, doi:10.1371/journal.pone.0000645

at CHUV, Switzerland, in a malaria-naïve population, and was further transitioned to the malaria-exposed target population at IHI, Tanzania.

RECENT ACHIEVEMENTS The active phase of the clinical trial was completed in 2015 and the analysis of safety and immunogenicity completed in 2016 and indicate that P27A is safe and induces a strong immunogenic response.

PARTNERS

- ALMAC Sciences, United Kingdom
- Centre hospitalier universitaire vaudois (CHUV), Switzerland
- CiToxLAB, France
- European Vaccine Initiative (EVI), Germany
- Gregory Fryer Associates Ltd., United Kingdom
- Ifakara Health Institute (IHI), Tanzania
- Infectious Diseases Research Institute (IDRI), United States of America
- Nova Laboratories, Ltd., United Kingdom
- Output Pharma, Germany
- Swiss Tropical and Public Health Institute (Swiss-TPH), Switzerland
- University of Lausanne (UNIL), Switzerland

P27A

Preclinical, process development, production, IMPD

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

Delivery Platform, Adjuvants and Viral Vectors

Two adjuvants have been 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 results indicate that cytophilic antibodies are induced which are able to recognize the P27A on the parasite and were inhibitory in *in vitro* antibody dependent cytotoxic inhibition assay.

Capacity strengthening, Workshops, Training

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 was partly supported by an EDCTP grant for the phase Ib arm of the phase I clinical trial.

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

Kristina M. Geiger (Institute of Biochemistry, University of Lausanne, Switzerland) presented "Epitope mapping and fine specificity of human antibody responses for novel Blood-stage malaria vaccine candidate P27A", Swiss Allergology and Immunology congress, 28-29 April, Montreux, Switzerland.

Said Jongo (IHI, Tanzania) presented "Safety and immunogenicity of P27A in healthy Swiss and Tanzanian Adults" at the 8th EDCTP forum, EVI symposium "Importance of Blood-stage malaria vaccine candidates in the development of a next generation malaria vaccine", 7 November, Lusaka, Zambia.

François Spertini (CHUV, 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, 14 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 non-human primates.

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 adults[29] and in a phase Ib clinical trial conducted in healthy subjects 6-32 years of age from a malaria-endemic area in Northern Uganda[30].

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

PARTNERS

- Centre national de recherche et de formation sur le paludisme (CNRFP), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Research Institute for Microbial Diseases (RIMD), Japan
- Nobelpharma, Japan
- Pharmalys, United Kingdom/ Senegal
- London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

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 was finished in April 2016, the 10 months follow-up period of the cohort of the older children was completed in November 2016 and the trial active phase will end in February 2017.

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

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.

RECENT ACHIEVEMENTS 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 was administered in April 2016 and the trial follow-up phase Is scheduled to be completed in February 2017.

SEmalvac

Outreach and Communication

Sodiomon Sirima (CNRFP, Burkina Faso) and Toshi Horii (RIMD, Japan) presented "Clinical development of the BK-SE36 malaria vaccine candidate" at the GHIT annual partners meeting, 7 June, Tokyo, Japan.

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

Toshi Horii (RIMD, Japan) presented "Development and Sustainability of Malaria Vaccine Clinical Research Center in Uganda and Clinical Development of BK-SE36 Malaria Vaccine Candidate" and Nirianne Palacpac (RIMD, Japan) presented "Developmental pathway for the blood-stage malaria vaccine candidate BK-SE36" at the TICAD VI Pre-event: The 3rd International Symposium for the Promotion of Science and Technology, Innovation Cooperation between Africa and Japan: Life Innovation and Green Innovation, 13 July, Tokyo, Japan.

Toshi Horii (RIMD, Japan) presented "Uniqueness of the Blood-stage malaria vaccine candidate BK-SE36" at the Translational Vaccinology for Global Health keystone symposia, 25-29 October, London, United Kingdom.

Alfred Tiono (CNRFP, Burkina Faso) presented "Preliminary safety and tolerability of BK-SE36 in young African children (SEmalvac)" at the 8th EDCTP forum, EVI symposium "Importance of Blood-stage malaria vaccine candidates in the development of a next generation malaria vaccine", 7 November, Lusaka, Zambia.

Toshi Horii (RIMD, Japan) presented "What's new with BK-SE36, a Blood-stage malaria vaccine candidate" at the Joint International Tropical Medicine Meeting 2016, Amari Watergate, 8 December, Bangkok, Thailand.

Sodiomon Sirima (CNRFP, Burkina Faso) presented the SEmalvac project update during the EVI Rendez-Vous, 14 December, Paris, France.

SEmalvac2

The SEmalvac2 project has been launched in parallel of the SEmalvac project to explore the safety and improved immunogenicity of the BK-SE36 vaccine when administered with CpG ODN K3 adjuvant, a Toll-Like Receptor (TLR) 9 ligand.

Pre-clinical studies have shown safety, immunogenicity and enhanced protective efficacy of the BK-SE36 vaccine formulated with CpG ODN K3 (BK-SE36/CpG) as compared to BK-SE36 alone[31].

BK-SE36 (SE36 adsorbed onto aluminium hydroxide gel) and CpG ODN K3 were produced under GMP conditions.

A phase Ia clinical trial using BK-SE36 mixed with CpG (BK-SE36/CpG) was conducted in healthy adults in Japan where the vaccine was deemed safe and elicited antibody titres were 3-4 fold higher than BK-SE36 alone. These promising results suggest that the combination of TLR9 ligand adjuvant with BK-SE36 can induce higher humoral and cellular immune responses compared to BK-SE36 alone and that the combined SE36/AHG with K3 ODN formulation affords a level of protection that could substantially inhibit parasite growth.

The main objective of the SEmalvac2 project supported by the GHIT Fund is to assess the safety and immunogenicity of the BK-SE36/CpG vaccine in in healthy malaria exposed African adults and children living in Burkina Faso. This phase Ib clinical trial is an age de-escalation trial where the BKG/SE36/CpG vaccine safety will be confirmed in adults aged 21-45 years before proceeding to the evaluation of the vaccine in younger population, children aged 5-10 years and 12-24 months.

The project started in November 2016 and the budget is ¥278,158,892 from a GHIT Fund grant.

PARTNERS

- Centre national de recherche et de formation sur le paludisme (CNRFP), Burkina Faso
- European Vaccine Initiative (EVI), Germany
- Research Institute for Microbial Diseases (RIMD), Japan
- Nobelpharma, Japan
- Pharmalys, United Kingdom/ Senegal
- London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

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 (Japan).

CpG-ODN (K3) is manufactured under cGMP at GeneDesign (Japan).

Clinical Development

The age de-escalation phase Ib clinical trial is designed to assess safety and immunogenicity of recombinant *E. coli* BK-SE36 malaria vaccine candidate formulated with CpG adjuvant administered intramuscularly in healthy malaria exposed African adults and children living in Burkina Faso. The clinical trial site is the Unité de Recherche Clinique de Banfora, CNRFP Burkina Faso; Dr Sodiomon Sirima (CNRFP, Ouagadougou, Burkina Faso) is the principal investigator and the sponsor is Nobelpharma (Japan).

The clinical trial protocol, subject documents and IB have been prepared late 2016 and will be submitted to the institutional and national ethics committees in Burkina Faso in January 2017. The clinical trial is scheduled to start in the second quarter of 2017 with the immunisation of the first cohort, adults aged 21-45 years. The trial will expand to the second cohort, children aged 5-10 years once safety of the vaccine is confirmed after three vaccinations in adult participants and to the third cohort, children aged 12-24 months, once safety of the vaccine is confirmed after two vaccination in the second cohort. The randomised, controlled, double blind trial active phase should be completed in the fourth quarter of 2018.

Outreach and Communication

Toshi Horii (RIMD, Japan) presented a poster entitled "Uniqueness of the Blood-stage malaria vaccine candidate BK-SE36" at the Translational Vaccinology for Global Health keystone symposia, 25-29 October, London, United Kingdom.

Sodiomon Sirima (CNRFP, Burkina Faso) presented the SEmalvac2 project during the EVI Rendez-Vous, 14 December, Paris, France.

31. Tougan *et al.* Hum Vaccin Immunother. 2013 PMID: 22863735

MALARIA BLOOD-STAGE VACCINES THAT PREVENT

placental malaria

Placental malaria is a major health problem manifesting as severe disease and anaemia in the mother, impaired foetal development, low birth weight or spontaneous abortion. While women living in malaria endemic areas gradually develop immunity to clinical malaria, women become susceptible to placental malaria during their first pregnancy. Every year, more than 100 million pregnant women are at risk of placental malaria, which causes the deaths of 80,000-200,000 children[32].

Prevention of placental malaria currently relies on intermittent preventive treatment during pregnancy (IPTp) and long lasting insecticide treated nets. However, these interventions only offer partial protection. Indeed, sulfadoxine-pyrimethamine used for IPTp is losing its effectiveness due to parasite resistance and women receive their first IPTp dose at their first antenatal visit (between 16-24 weeks' gestation)[33],[34],[35]. As placental parasite tropism is established during the first trimester of pregnancy, parasites cause irreversible damage, probably by impeding placental development, before women access antenatal healthcare. Therefore, an effective vaccine that prevents *P. falciparum* placental malaria would be an attractive, cost-effective complement to preventive placental malaria.

Placental malaria is caused by parasite-infected red blood cells adhering 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. 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[36],[37]. This relatively fast acquisition of protection has raised hope that a vaccine for placental malaria can be developed.

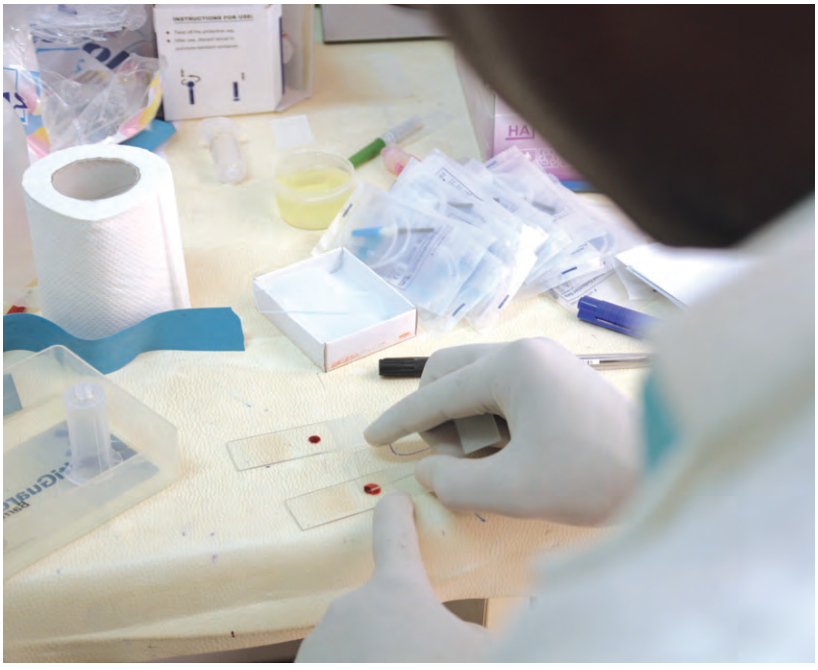
EVI has raised funds from BMBF, Institut national de la santé et de la recherche médicale (Inserm), the EU and the Danish National Advanced Technology Foundation (HTF) through University of Copenhagen (UCPH), with further co-funding from Irish Aid, Department of Foreign Affairs and Trade (Ireland) and 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.

32. Hartman *et al.*, Annals of Tropical Paediatrics 2010, doi:10.1179/146532810X12858955921032
33. Doritchamou *et al.*, J Infect Dis. 2012 Dec 15;206(12):1911-9.
34. Schmiegelow *et al.*, PLoS ONE. 2013;8(1):e53794.
35. Moussiliou *et al.*, Malar J. 2013;12:195.
36. Brabin *et al.*, Bull World Health 1983 PMC2536236
37. 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[38],[39]. 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[40]. 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[41],[42]. 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[43],[44]. These data indicate that vaccines designed to block interactions between the parasite and CSA should be based on the N-terminal region of VAR2CSA.



Blood spots for DNA extraction

MAJOR OUTCOMES ON THE CLINICAL DEVELOPMENT PLAN OF PLACENTAL MALARIA VACCINE

- Phase Ia and Ib clinical trials could be a single Phase I staggered clinical trial.
- The Phase Ia stage of the clinical trial would be in adults from malaria non-endemic population in Europe and the Phase Ib stage would target nulligravid adults from endemic population.
- Phase II clinical trials will target nulligravid women from an endemic region and will include dose escalation, age group de-escalation, and exploratory data on interactions with other vaccines.
- Phase III clinical trials would be in the target nulligravid population in endemic region.

38. Baruch *et al.*, Cell 1995 doi:10.1016/0092-8674(95)90054-3
39. Su el al., Cell 1995 doi:10.1016/0092-8674(95)90055-1
40. Fried *et al.*, Nature 1998, doi:10.1038/27570
41. Avril *et al.*, Malaria Journal 2011; doi:10.1186/1475-2875-10-36
42. Dahlback *et al.*, J Biol Chem 201, doi:10.1074/jbc.M110.1915101
43. Bordbar *et al.*, Bioelectrochemistry 2011, doi:10.1016/j.bioelechem.2011
44. Bigey *et al.*, J Inf Dis 2011, doi:10.1093/infdis/jir499

Harmonisation

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

Toward this aim, common immunoassays for the measurement of antibody titres by ELISA, antibody recognition of the surface of *P. falciparum* infected erythrocytes by flow cytometry and CSA-binding inhibition by antibodies using a Petri dish-based binding inhibition assay have been selected.

In 2016, common reference panel of negative and positive control sera for the ELISA, as well as the other immunoassays have been prepared by IRD, validated against both vaccine antigens and shared with both teams. The negative control is pooled sera from European malaria-naïve population and the positive control is a sera pool from 147 women from a malaria endemic region in Benin. The selection criteria included HIV negative test, high reactivity for *P. falciparum* in flow cytometry and high ELISA reactivity to different VAR2CSA antigens.

As a result of the workshops held previously, a summary of the harmonisation activities was jointly published by the teams in *Malaria Journal* in September 2016: "Clinical development of placental malaria vaccines and immunoassays harmonization: a workshop report".

In addition, the different placental malaria vaccine candidates from Inserm, NIH/NIAID and UCPH are evaluated side-by-side in the PlacID project that aims at validating an *Aotus* monkey placental malaria model. The study procedures were harmonised for the different vaccine candidates of these three leading groups working on placental malaria vaccine development. All samples will be analysed in comparative assays by NIH/NIAID. In addition, protocols were shared and assays will be repeated in the Inserm and UCPH laboratories using comparable assay procedures and reagents.

PAMCPH

The overall objective of PAMCPH was to manufacture a vaccine that protects both the foetus and the mother against the adverse effects of malaria during pregnancy. The specific aims of the project were to define the optimal antigen and adjuvant formulation, to show that it can be produced in a scalable manner, and to confirm that it is safe to use in animals. Supplemental funding covered the immunoassay harmonisation activities and the testing of an additional adjuvant in the clinical trial. PAMCPH had a total budget of €2,816,722.08 and it was funded by the BMBF through KfW, with co-funding from UCPH through the HTF. The project started in September 2012 and ended in May 2016.

In 2003, VAR2CSA was identified as the parasite protein which enables parasite accumulation in the placenta[45]. 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 supported the production of a recombinant VAR2CSA vaccine under GMP conditions, allowing it to be used in the clinical trial supported by the PlacMalVac project.

RECENT ACHIEVEMENTS Extension of PAMVAC shelf-life based on supportive stability data, the continuous efforts in immunoassay harmonisation and the start of the PlacMalVac phase Ia/Ib clinical trial in Germany and Benin.

PARTNERS

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

Preclinical, process development, production, IMPD

In 2015, 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 Benin. The IMPD and 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

Wian de Jongh (ExpreS2ion, Denmark) presented "Development of *Drosophila* S2 based Malaria sub-unit antigen vaccine production processes", at the New Technologies New Vaccines conference, 21 March, Wilmington, USA.

Wian de Jongh (ExpreS2ion, Denmark) presented "Development of *Drosophila* S2 based vaccine production processes" at the ISBiotech, 7 March, Boston, USA.

Morten Nielsen, (UCPH, Denmark) presented "PAMVAC placental malaria vaccine candidate; production and adjuvants selection" at the EVI Rendez-Vous, 14 December, Paris, France.

45. 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 of three years was extended to February 2017.

RECENT ACHIEVEMENTS Completion of the vaccination of the malaria-naïve subjects in Germany and the start of the vaccination of the malaria exposed subjects in Benin.

PARTNERS

- Eberhard-Karls Universität Tübingen (EKUT), Germany
- European Vaccine Initiative (EVI), Germany
- ExpreS2ion Biotechnologies, Denmark
- University of Copenhagen (UCPH), Denmark
- Institut de recherche pour le développement (IRD), France
- Université d'Abomey-Calavi (UAC), Benin

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 (PAMVAC) 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 Ministry of health/ethics committee in Benin in November 2015 and authorisation to start the trial in Benin was granted in March 2016.

The clinical trial started in Germany with the first administration of the lowest dose of the PAMVAC vaccine to the first subject in May 2016. Escalation to the next dosage was conditioned by safety assessment performed by an independent safety monitoring board. The PAMVAC vaccine was well tolerated and the third and last vaccine dose was administered to the last malaria-naïve participant in August 2016. Total specific PAMVAC IgG measured by ELISA in samples collected in German participants indicate that the vaccine is immunogenic with a higher response when the antigen is administered with GLA-SE as compared to aluminium hydroxide.

After a second safety assessment following the first administration of the PAMVAC highest dosage in malaria-naïve subjects, the trial started in Benin with the first administration of the PAMVAC vaccine to malaria exposed participants in November 2016. As observed in malaria-naïve subjects, the vaccine was well tolerated and the independent safety monitoring committee recommended, after a third safety review, to proceed with the highest dosage administration. The last vaccination is scheduled in April 2017 and the trial active phase will end in November 2017. Immunogenicity evaluation including functionality of the induced antibodies will proceed in parallel. ...

Capacity strengthening, Workshops, Training

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 clinical trial site.

EVI provided support in the implementation of the quality assurance system in the phase Ib new clinical trial site whose construction was completed in 2015 and became operational in 2016.

Outreach and Communication

Komi Gbédandé (UAC, Benin) presented "Clinical development of a VAR2CSA-based placental malaria vaccine PlacMalVac: Quantifying vaccine antigen-specific memory B & T cell activity in Beninese primigravidae" at the 65th Annual Meeting American Society of Tropical Medicine Hygiene, November 13-17, 2016, Atlanta, Georgia USA.

Guillaume Escriou (Université Paris Descartes,France and UCPH, Denmark) presented " Decryption of the antibody acquisition against the vaccine candidate Id1-Id23 at the 65th Annual Meeting American Society of Tropical Medicine Hygiene, November 13-17, 2016, Atlanta, Georgia USA.

Nicaise Tuikue Ndam (IRD, France) presented "Identification of a major dimorphic region in the functionally critical N-terminal ID1 domain of VAR2CSA3 at the 5th Molecular approaches to malaria Conference, 21-25 Feb 2016 Lorne, Australia.

Morten Nielsen, (UCPH, Denmark) presented "PAMVAC placental malaria vaccine candidate; production and adjuvants selection" at the EVI Rendez-Vous, 14 December 2016, Paris, France.

PRIMALVAC

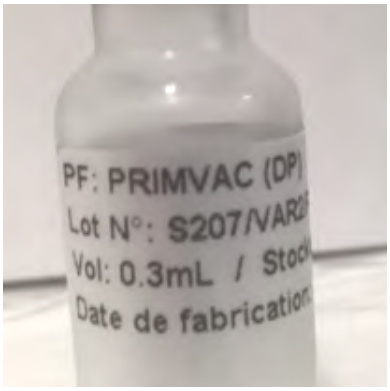
PRIMALVAC aims to develop a placental malaria vaccine to improve pregnancy outcomes. The main objective is to obtain proof of concept that VAR2CSA-based vaccines induce long-lasting or rapidly-boosted cross-reactive and inhibitory antibodies suitable for human use. Recombinant forms of VAR2CSA were generated,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

PRIMALVAC has a total budget of €7,180,606.93 provided by the BMBF through KfW, EVI, Inserm, the Institut national de la transfusion sanguine (INTS) and Irish Aid, Department of Foreign Affairs and Trade (Ireland). The project started in December 2011, activities are on-going.

RECENT ACHIEVEMENTS Release of PRIMVAC, placebo and the adjuvants to clinical trial and the start of the phase Ia arm of the clinical trial in France in May and of the phase Ib arm in Burkina Faso in November.

PARTNERS

- 4Clinics, France
- BIOTEM, France
- Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso
- Centre d'investigation clinique en Vaccinologie Cochin-Pasteur (CIC1417), France
- CiToxLAB, France
- Creapharm, France
- EUropean CLInical Trials Platform & Development, France
- European Vaccine Initiative (EVI), Germany
- F-CRIN stands for: French Clinical Research Infrastructure Network, France
- GTP Technology, France
- Infectious Diseases Research Institute (IDRI), United States of America
- Institut national de la santé et de la recherche médicale (Inserm), France
- Nova Laboratories, United Kingdom
- Novasep (formerly Henogen), Belgium
- Novavax, United States of America (formerly ISCONOVA, Sweden)
- Output Pharma, Germany
- Pfenex Inc., United States of America
- Voisin Consulting Life Sciences, France



Preclinical, process development, production, IMPD

Novasep manufactured the GMP batch of PRIMVAC and the PRIMVAC drug product was released. Short-term and accelerated stability studies were performed and long-term stability studies are ongoing at Novasep, allowing a shelf-life extension to September 2017. Toxicology studies were conducted by CiToxLAB 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. The GLA-SE was released in Europe by Output Pharma for clinical trial use. Alhydrogel® filled by EVI at Nova Laboratories Ltd. is used for the clinical trial.

Clinical Development

The PRIMALVAC project is currently carrying 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 or GLA-SE. The inventor of the vaccine is Dr Benoît Gamain and the sponsor of the clinical trial is Inserm. The coordinating investigator is Prof Odile Launay (CIC1417, Paris, France), the principal investigators of the clinical trial are Dr Pierre Loulergue (CIC1417, Paris, France) and Dr Sodiomon Sirima (CNRFP, Balonghin, Burkina Faso). Authorisation for the clinical trial in France was obtained by the end of 2015; the site initiation visit was performed in January 2016. The first vaccination of the first subject in France was on 9 May, follow-up is on-going. The phase Ib clinical trial at CNRFP in Burkina Faso received full authorisation in September 2016. In September, the DSMB reviewed the safety data of the two cohorts in the phase Ia arm of the clinical trial and recommended the continuation of the protocol. The phase Ib clinical trial arm started in November 2016; inclusions, vaccinations and follow-up are on-going.

Capacity strengthening, Workshops, Training

EVI supported and mentored the clinical trial sponsor, Inserm, during the set-up and conduct of the pharmacotoxicological studies, during the preparation of the dossiers relevant for the clinical trial (e.g. IB, IMPD, clinical trial protocol), and during the manufacture, the release of the drug product and adjuvants to the clinical trial and/or clinical trial activities.

Outreach and Communication

Arnaud Chêne (Inserm, France) presented "Towards the development of a Placental Malaria Vaccine." at the 12th Annual BioMalPar/Evimalar Conference on the Biology and Pathology of the malaria parasite, 18-20 May, Heidelberg, Germany.

Nicola Viebig (EVI, Germany) presented "Development of a placental malaria vaccine" at the Malaria Vaccines for the World 2016, 2-4 May, Leiden, The Netherlands.

Nicola Viebig (EVI, Germany) presented "Development of a placental malaria vaccine – the PRIMALVAC project" at the International Congress for Tropical Medicine and Malaria, 18-22 September, Brisbane, Australia.

Sodiomon Sirima (CNRFP, Burkina Faso) presented "Clinical development of the VAR2CSA placental malaria vaccine candidate" at the symposium "Importance of Blood-stage malaria vaccine candidates in the development of a next generation malaria vaccine" organised by EVI during the 8th EDCTP Forum in Lusaka, Zambia, in November.

Sodiomon Sirima (CNRFP, Burkina Faso) presented "PRIMALVAC" at the EVI Rendez-Vous, 14 December, Paris, France.

PlacID

The overall objective of PlacID is to validate a novel non-human primate 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 non-human primate 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 non-human primate 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 with a total project budget of €866,720.99.

RECENT ACHIEVEMENTS Passive transfer commenced in 2015 and the team is expecting to unblind the study and obtain the first set of data in mid-2017. In the vaccination studies, all animals were vaccinated and follow-up will continue in 2017. First unblinded results are expected by the end of 2017.

PARTNERS

- European Vaccine Initiative (EVI), Germany
- Institut national de la santé et de la recherche médicale (Inserm), France
- National Institute of Allergy and Infectious Diseases (NIAID) - Laboratory of Malaria Immunology and Vaccinology (LMIV), United States of America
- University of Copenhagen (UCPH), Denmark

MAJOR OUTCOME

• Passive immunity studies: 5 animals have reached the study endpoint (caesarean section).

• All vaccinations are completed, 16 monkeys have completed pregnancy with seven premature deliveries and nine caesarean sections allowing to assess primary endpoint of this study: induction and boosting of functional antibodies.

Preclinical, process development, production, IMPD

Passive immunity studies using IgG from malaria-immune multigravid women and malaria-naïve individuals were initiated in the *Aotus* non-human primate model in November 2015. An interim analysis is planned by the biostatistician as soon as three monkeys in each of the two groups have reached the endpoint "placental parasitaemia" after caesarean section.

In the vaccination study, all the vaccinations with PAMVAC, PRIMVAC and the NIH/NIAID vaccine candidate were completed and the follow-up is ongoing. The primary endpoint of this study is induction and boosting of functional antibodies. Secondary endpoint is placental parasitaemia. First immunological analyses were performed at NIH/NIAID, but the study will remain blinded until the biostatistician has performed an interim analysis and proposed a study end. Interim results for both studies are expected by the end of 2017.

Capacity strengthening, Workshops, Training

During the PlacID project, good animal handling practices were established as evidenced by the high pregnancy rate of the *Aotus* animals at NIAID-LMIV. This is a particular achievement appreciated by the scientific community. Despite that the animals are handled on a regular basis for ultrasound examinations and sampling, the pregnancy rate has been even higher than that expected in a breeding colony.

Outreach and Communication

Nicola Viebig (EVI, Germany) presented "PlacID" at the EVI Rendez-Vous, 14 December, Paris, France.

MALARIA VACCINES THAT PREVENT INFECTION AND MORBIDITY/MORTALITY:

Combination vaccines

The Malaria Vaccine Technology Roadmap that was updated in 2013[46] defined the strategic goals for 2030 as licensed vaccines targeting *Plasmodium falciparum* and *Plasmodium* vivax with the following objectives:

- To develop malaria vaccines with protective efficacy of at least 75 percent against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas.
- To develop malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection.

The development of a highly effective subunit malaria vaccine suitable for widespread deployment is likely to require a multi-component vaccine including antigens from more than one stage of the parasite's life cycle as indicated in the "WHO Preferred Product Characteristics (PPC) for Malaria Vaccines"[47]. This strategy could overcome the limited efficacy of single antigen components. Critical aspects to consider are the choice of the most suitable combination of vaccine components, delivery systems and adjuvants suitable for all components, and the design of Combination vaccine clinical trials. Vaccine candidates that have already demonstrated efficacy are currently the most suitable candidates for multi-component and multi-stage vaccines[48].

MultiMalVax

The aim of the MultiMalVax project is to develop the concept of a highly-effective multi-stage malaria vaccine to proof-of-concept phase IIa efficacy testing in Europe, prior to clinical trials in malaria-endemic regions.

The overarching aim of this four and a half 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 project will undertake a series of phase Ia/IIa 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 challenges to measure efficacy prior to field testing. MuliMalVax is building on the remarkable advances in the design of vaccines against all four stages of the *P. falciparum* life-cycle that now allows the testing of multi-stage vaccine candidates for the first time, with strong chances of success.

The EU FP7 funded MultiMalVax project started in October 2012 with a budget of €8,000,000. 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.

RECENT ACHIEVEMENTS The main achievements of the MultiMalVax project thus far include the completion of the R21, AS01B pre-erythrocytic clinical trial, the (ChAd63/MVA) PfRH5 blood-stage clinical trial, the full enrolment of the clinical trial using the viral vectored transmission-blocking vaccine candidate Pfs25-IMX313, the completion of the phase I/IIa combination trial based on AS01 adjuvanted RTS, S and viral vectored ME-TRAP as well as the start of the combination trial assessing the safety, immunogenicity and efficacy of R21 adjuvanted with Matrix-M1 in comparison to R21/Matrix-M1 in combination with ME-TRAP vectored vaccines in a phase I/IIa challenge trial. In addition to the clinical activities, the mechanism of *in vitro* killing activity of vaccinees T cells has been investigated.

PARTNERS

- European Vaccine Initiative (EVI), Germany
- GlaxoSmithKline (GSK) (formerly Novartis Vaccines and Diagnostics s.r.l., Italy, acquired by GSK), Belgium
- ReiThera s.r.l. (formerly Okairòs s.r.l.,), Italy
- Université Pierre et Marie Curie (UPMC), France
- University of Oxford (UOXF), United Kingdom

46. http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1
47. http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14.09_eng.pdf
48. Viebig N.K. *et al.* Vaccine 2015, doi:10.1016/j.vaccine.2015.09.074.

TABLE 1 CLINICAL TRIAL DESIGN TO ASSESS SAFETY, IMMUNOGENICITY AND EFFICACY OF R21 ADJUVANTED WITH MATRIX-M1 IN COMPARISON TO R21/MATRIX-M1 IN COMBINATION WITH ME-TRAP VECTORED VACCINES

Weeks	Group 1 (n=12)	Group 2 (n=12)	Group 3 (n=12)	Group 4 (n=6)	Group 5 (n=6)
0	10 µg R21/50µg Matrix M1	50 µg R21/50µg Matrix M1	10 µg R21/50µg Matrix M1		
1			chAd63 ME-TRAP		
4	10 µg R21/50µg Matrix M1	50 µg R21/50µg Matrix M1	10 µg R21/50µg Matrix M1		
8	10 µg R21/50µg Matrix M1	10 µg R21/50µg Matrix M1	10 µg R21/50µg Matrix M1		
9			MVA ME-TRAP		
12	CHMI	CHMI	CHMI	CHMI	
32-40	Repeat CHMI of sterile protected volunteers	Repeat CHMI of sterile protected volunteers	Repeat CHMI of sterile protected volunteers		CHMI

MultiMalVax

Preclinical, process development, production, IMPD

ChAd63 and MVA vectors expressing PfRH5 were produced under GMP conditions by ReiThera/Advent and were released for the clinical trial. ChAd63 and MVA vectors expressing Pfs25-IMX313 were produced under GMP conditions at Clinical BioManufacturing Facility UOXF and were released for the clinical trial. A R21 GMP batch was produced at Clinical BioManufacturing Facility 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 carrier protein. Fusion to the IMX313 DNA sequence led to oligomerisation of the recombinant protein because the IMX313 carrier protein 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 or Matrix-M1 adjuvant.

Clinical Development

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 started 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 2015 and by the MHRA on 25 June 2015. The first vaccination started in the Southampton trial site on 12 October 2015 with the ChAd63-Pfs25-IMX313 vector and the vaccine showed a good safety profile. The ChAd63-Pfs25-IMX313 / MVA Pfs25-IMX313 groups started in 2016 and all vaccinations have now taken place with the last volunteer's clinical visit scheduled in June 2017.

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 RH5 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, UK) presented "Multi-component malaria vaccines: Challenges and new solutions" at the Malaria Vaccines for the World 2016, 2-4 May 2016 Leiden, The Netherlands.

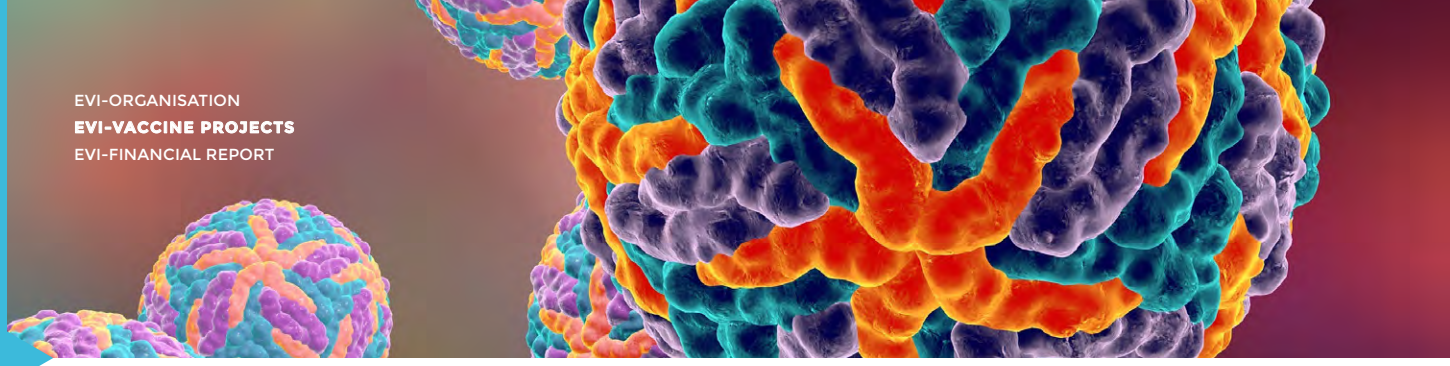
Simon Draper (UOXF, UK) presented the "Development of a PfRH5-based vaccine against the *Plasmodium falciparum* merozoite" at the Malaria Vaccines for the World 2016, 2-4 May 2016 Leiden, The Netherlands.

Sumi Biswas (UOXF, UK) presented "Pre-clinical and clinical development of novel virus-like-particles for induction of high titre functional antibody responses against the transmission-blocking candidate antigen, Pfs25" at the Malaria Vaccines for the World 2016, 2-4 May 2016 Leiden, The Netherlands.

Ruth Payne (UOXF, UK) presented "Safety and Immunogenicity of the Novel *Plasmodium falciparum* Blood-Stage Vaccine ChAd63-MVA RH5 in a Phase Ia Clinical Trial" at the ASTMH 65th Annual Meeting, 13-17 November 2016, Atlanta, USA.

Adrian Hill (UOXF, UK) presented "MultiMalVax 2016" at the EVI Rendez-Vous, 14 December in Paris, France.

The MultiMalVax project was presented at various other occasions.



Dengue vaccine

Dengue is a fast emerging vector-borne disease, with slightly below 4 billion people worldwide at risk of infection. Currently, the disease is endemic in more than 100 countries with an estimate of 390 million dengue virus infections annually, of which 96 million show clinical manifestations with about 500,000 hospitalizations.

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.[49] The current licenced vaccine Dengvaxia® which has been approved in Mexico, The Philippines, Brazil, El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand and Singapore does not provide equal protection against all four known dengue serotypes. After review of the safety data, it was decided to exclude those aged 6-8 years due to an excess of hospitalisation related to dengue illness, and start the indicated age range at 9 years[50]. Other candidates currently in preclinical or clinical development also focus on B-cell response and are predicted to encounter similar problems leading to 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 due to an antibody enhanced disease phenotype. Besides Dengvaxia®, two other vaccine candidates entered phase III clinical trials in 2016: the live-attenuated tetravalent dengue vaccine candidate TAK-003 from Takeda and the tetravalent live-attenuated lyophilised vaccine from Butantan Institute.

MVDVax

MVDVax is a GHIT-funded project with a budget of ¥61,290,240, which commenced in October 2015 and will finish in March 2017.

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

MVDVax target populations are primarily children and adults 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 single vector live dengue vaccine, allowing the more balanced and controlled expression of the tetravalent 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).

PARTNERS

- European Vaccine Initiative (EVI), Germany
- Institut Pasteur Paris (IPP), France
- Institute of Tropical Medicine Nagasaki University (NEKKEN), Japan

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.

RECENT ACHIEVEMENTS During 2016 all preparatory work and the actual immunisation of non-human primates were completed. Very good safety and immunogenicity with 100% seroconversion for all four Dengue serotypes were observed.

MVDVax

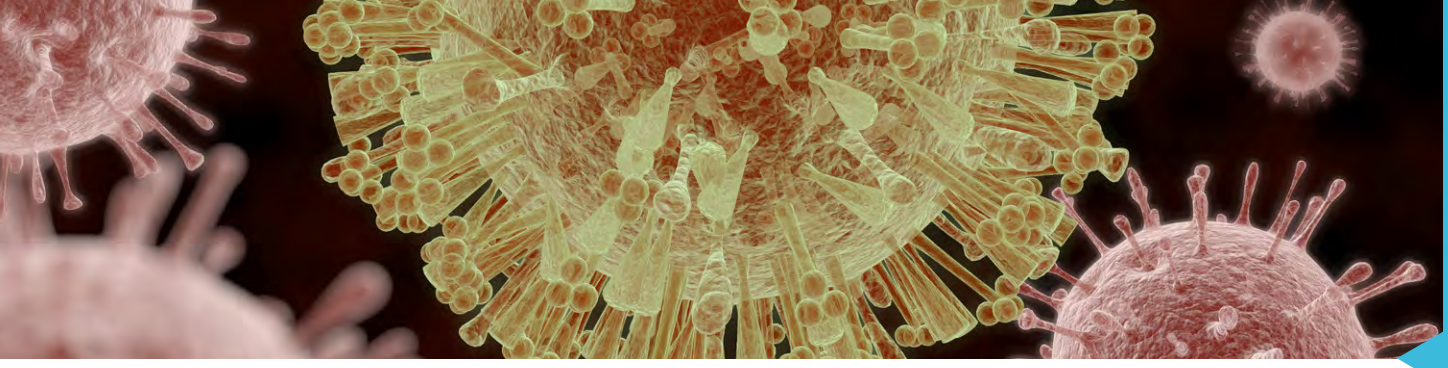
Preclinical, process development, production, IMPD

The stability of the MVDVax vector and stable EDIII expression across different vector batches was demonstrated. Immunisation of non-human primates was completed.

Delivery Platform, Adjuvants and Viral Vectors

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

49. http://www.who.int/mediacentre/factsheets/fs117/en/
50. Dengue vaccine: WHO position paper – July 2016.. Wkly Epidemiol Rec. 2016 Jul 29;91(30):349-64. http://www.who.int/wer/2016/wer9130.pdf?ua=1 (accessed 29-05-2017)

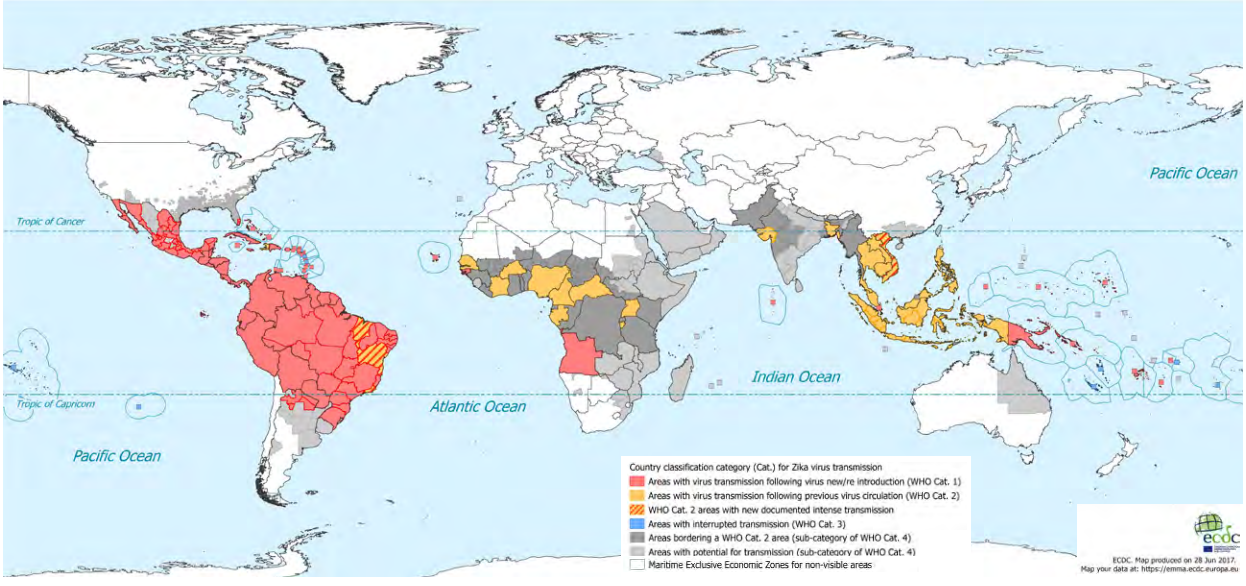


Zika vaccine

Zika virus infection is a vector borne disease which recently has called the attention of the international community due to a large outbreak that started in 2015 that affected more than 70 countries and territories[51].

The recent rapid spread of the Zika virus in previously unaffected regions has provided strong epidemiological evidence that infection with this virus might be associated with neurological complications in adults and with an increase in severe congenital brain and central nervous systems malformations of newborns, the congenital Zika syndrome. Consequently, in February 2016, the WHO has declared the recent outbreak of the Zika virus a Public Health Emergency of International Concern, a declaration that was lifted by WHO in November 2016. Nevertheless, WHO indicated that Zika virus and associated consequences remain a significant public health challenge requiring intense action.
There is not specific treatment or vaccine available against Zika virus. Preventive measures are centred on avoiding mosquito bites, reducing other forms of transmission (e.g. sexual transmission) and controlling the vector (mosquitos)[52]. These measures can, however, be challenging and have variable efficacy.
Although disease symptoms are generally mild, the possible complications to pregnancy, new-borns and neurologic complications in adults, highlight the need of effective measures to prevent this disease. In this context, in March 2016, experts gathered at WHO agreed that the development of a preventive vaccine is a major priority to respond to Zika epidemics in the future[53]. A first target product profile (TPP) for Zika vaccines was recently finalised and published jointly with UNICEF[54],[55].

FIGURE 1 CURRENT ZIKA TRANSMISSION WORLDWIDE



Source: https://ecdc.europa.eu/en/zika-virus-infection/threats-and-outbreaks/zika-transmission (accessed 06.07.2017)

51. http://apps.who.int/iris/bitstream/10665/252762/1/zikasitrep5Jan17-eng.pdf?ua=1
52. Petersen LR, *et al.* Zika Virus. N Engl J Med. 2016 doi: 10.1056/NEJMra1602113.
53. WHO and experts prioritize vaccines, diagnostics and innovative vector control tools for Zika R&D. (2016, March 9). Retrieved from: http://www.who.int/mediacentre/news/notes/2016/research-development-zik...
54. Vannice KS, *et al.* doi: 10.1016/j.vaccine.2016.10.034.
55. WHO. Zika virus vaccine product development. (2016, November). Retrieved from: http://www.who.int/immunization/research/development/zika/en/index2.html

ZIKAVAX

ZIKAVAX is a collaborative project funded under the EU's H2020 Research and Innovation Programme and coordinated by EVI. This four-year project was initiated in October 2016 and has an overall budget of approximately € 5 million. The project is the joint effort of leading European experts from academia and industry with unique and specific technological expertise in viral vectors and vaccine development.

The ZIKAVAX project aims at developing a safe, effective, and affordable preventive vaccine against Zika virus infection. To achieve this goal, ZIKAVAX will use a delivery platform technology based on a measles vector with demonstrated proof of principle in humans and a preclinical track record of rapid adaptability and effectiveness for a variety of pathogens. In ZIKAVAX, following antigen selection and expression, immunisation studies will be conducted with the Zika vaccine candidate in mice and in a non-human primates challenge model that will be developed by the consortium. The ultimate goal of ZIKAVAX is the demonstration of safety and immunogenicity of a recombinant measles-Zika vaccine candidate (MV-ZIKA) in adult volunteers in a phase Ia clinical trial.

PARTNERS

- Commissariat à l'énergie atomique et aux énergies alternatives (CEA), France
- European Vaccine Initiative (EVI), Germany
- Institut Pasteur, France
- Themis Bio, Austria

Preclinical, process development, production, IMPD

Institut Pasteur has initiated to work on the selection of soluble Zika virus antigens. The sequences of these antigens were amplified from the Zika virus strain isolated from the ongoing outbreak in Brazil. The sequences are codon optimised and adapted to measles vector cloning. Several constructs have been generated and the expression level of the selected antigens is currently being evaluated in HEK293 cells. The best antigen sequences will then be cloned into the measles vaccine vector in different transcription units, according to the desired level of expression. After sequencing of the measles vector plasmids expressing the different Zika antigens, the replicating recombinant vectors will be generated by reverse genetics using a cell-based system developed by Institut Pasteur and will be further characterised for antigen expression, growth characteristics and genetic stability.

To demonstrate preclinical immunogenicity and protective efficacy of the recombinant MV-Zika vaccine candidate(s) in non-human primates, CEA is working on the establishment of the non-human primate challenge model for Zika virus infection. Different doses of Zika virus inoculated subcutaneously were tested to infect non-human primates. All animals were infected as shown by PCR on viral DNA in the plasma and, upon re-challenge, full protection was achieved. Further analysis is on-going to define the clinical, immunological and virological endpoints that will be used to assess the effectiveness of the ZIKAVAX vaccine candidate(s).

Profiting from the knowledge acquired on manufacturing its MV-based Chikungunya vaccine candidate (MV-CHIK) currently in phase II clinical trial, Themis has already started some preliminary work to adapt and optimise the upstream and downstream processes previously established.

Delivery Platform, Adjuvants and Viral Vectors

For the fast track development of the envisaged Zika virus vaccine, the live attenuated measles vaccine, one of the safest and most efficacious vaccines available, will be used as a delivery vector for Zika virus protective antigens.

This delivery platform technology consists of a genetically modified live attenuated measles virus (Schwarz strain) that allows expression of heterologous antigens. Antigens of different arboviruses such as Chikungunya, Dengue or West Nile virus have already been successfully inserted into the measles vaccine vector and their strong immunogenicity or protective capacity has been established in preclinical and clinical studies, also in the presence of pre-existing immunity to the vector[56],[57],[58],[59].

The manufacturing process for these MV-based vaccines has been optimised to give higher yields and purity than the standard measles vaccine manufacturing process. It uses standard equipment and lends itself to further scale up as well as technology transfer to low and middle income countries, thus ensuring the timely availability of a preventive vaccine whenever a new epidemic occurs.

Harmonisation

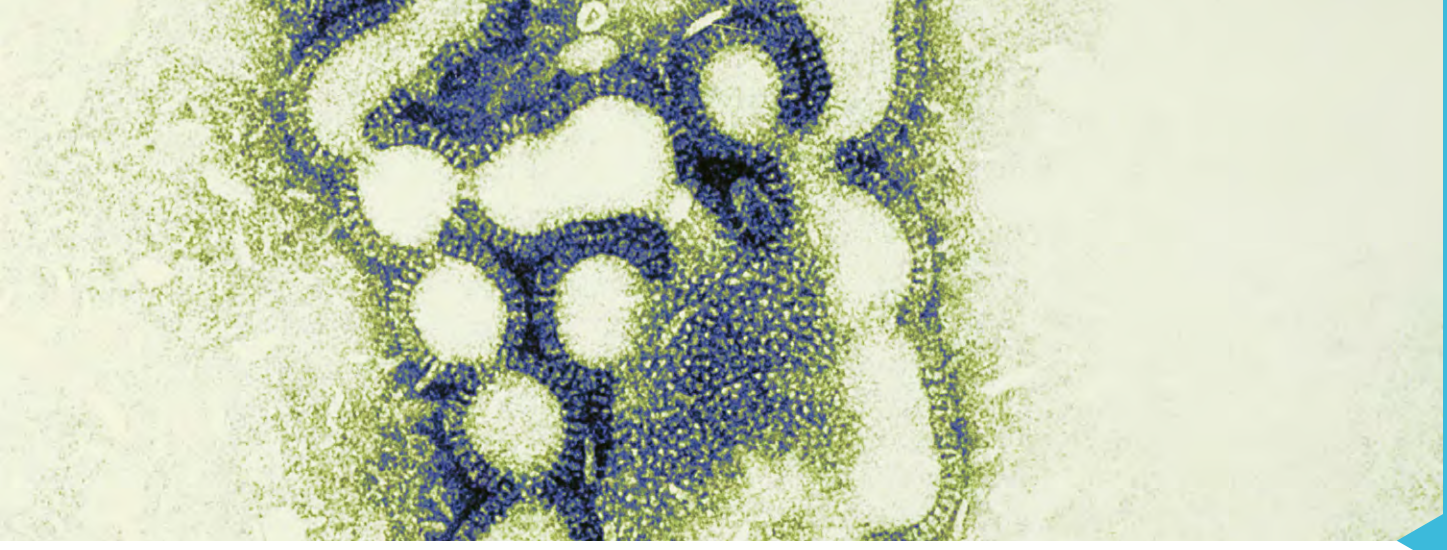
The ZIKAVAX consortium will actively interact with other European networks working on Zika virus infection (e.g. ZIKAlliance, ZikaPLAN and ZIKaction) to help filling the knowledge gaps on Zika infection, epidemiology, and pathogenesis and to investigate options for treatment and prevention. CEA is also a partner of the ZIKAlliance EU-funded project and will facilitate networking activities with this consortium.

Outreach and Communication

Nicola Viebig (EVI, Germany) presented a poster on the ZIKAVAX plan and objectives at the GloPID-R Zika Virus Research Workshop" in Sao Paulo, Brazil on 30 November – 2 December 2016. The workshop's aim was to identify and establish collaboration and synergies between the research and capacity development projects in support of the Zika virus response in Latin America and the Caribbean funded by GloPID-R members worldwide.

Frédéric Tangy (Institut Pasteur Paris, France) presented the ZIKAVAX projects at the the EVI Rendez-Vous, 14 December in Paris, France.

56. Ramsauer, Lancet Inf. Dis 15:519, 2015
57. Brandler, J Infect Dis 206:212, 2012
58. Brandler, Vaccine 28:6730, 2010
59. Escriou, Virology 452-453:32, 2014



Universal influenza vaccine

Each year during seasonal epidemics, influenza infects up to 10% of adults and 20-30% of children, resulting in three to five million cases of severe illness and 250,000-500,000 deaths worldwide.[60]

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 would allow considerably longer intervals between re-vaccination than at present, avoid vaccine failures due to drifted seasonal variants, and provide a high level of protection against pandemic viruses. Furthermore, it would facilitate vaccination campaigns in low and middle-income countries and thereby also confer protection against influenza in hitherto untargeted groups with limited health care programmes.

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

PARTNERS

- Biomedical Primate Research Centre (BPRC), The Netherlands
- ETNA BIOTECH s.r.l., Italy
- European Vaccine Initiative (EVI), Germany
- Instituto de Biologia Experimental e Tecnológica (iBET), Portugal
- National Institute for Biological Standards and Control (NIBSC), a centre of the Medicines and Healthcare Products Regulatory Agency, United Kingdom
- Redbiotec AG, Switzerland
- Wageningen Bioveterinary Research (WBVR), The Netherlands

60. WHO. Influenza (seasonal) fact sheet. Available from: <http://www.who.int/mediacentre/factsheets/fs211/en/> [updated 2016; cited 2016 Mar 22].

vaccine candidates. Proof of principle will then be demonstrated for the EDUFLUVAC strategy in challenge studies using ferret and non-human primate models. Furthermore, an optimised process suitable for the GMP-compliant manufacture of VLPs will be developed. The project will take note of new influenza vaccine regulatory guidance and will be geared towards the development of a complete IMPD ready for transfer into GMP production for early-phase clinical testing. Finally, the knowledge generated in the project will be disseminated through networking activities including targeted workshops.

RECENT ACHIEVEMENTS

The main achievements in 2016 were:

- the optimisation of the manufacturing process to produce VLPs at a larger scale and with higher purity for ferret and non-human primate studies and suitable for further GMP production
- completion of mouse immunogenicity studies
- organisation of a successful workshop on experimental animal models for universal influenza vaccines that took place at BPRC.

Preclinical, process development, production, IMPD

Redbiotec has generated all baculovirus vectors for the expression of the selected influenza HA and NA antigenic variants. The design of the expression cassettes (promoters, polyadenylation signals and order of the HA sequences) was further improved for some vectors in order to increase the stability and the expression levels of the recombinant baculovirus vectors. Those vectors have been provided to iBET, which has generated all VLPs intended for the mouse studies. A rational upstream and downstream process optimisation was then undertaken in order to increase the yield and the purity of influenza VLPs to conduct ferret and non-human primate challenge studies. As part of the EDUFLUVAC analytical development plan, several potential batch release assays have been implemented at iBET. Additional analytical techniques for in-process monitoring of influenza VLPs during the production and purification processes, and for rational process optimisation were also developed.

All mouse immunisation studies were completed and sera were analysed by quantitative ELISA at ETNA BIOTECH and also by MN assays performed at NIBSC. The MN assay is the main decision making assay, measuring the ability of sera to neutralise both homologous and heterologous influenza viruses, for further antigen down-selection. Competitive ELISA will further provide insights into the mechanisms and demonstrate the broadening of the antibody response. Mouse results suggest that epitope dilution phenomena also apply to influenza virus HA and that the Abs response can be broadened beyond the vaccine components.

Following mouse immunogenicity results, the proof of concept challenge studies in ferrets and non-human primates started in July 2016 at WBVR and BPRC respectively. Such immunogenicity and efficacy studies were preceded by the preparation and validation of the corresponding heterologous challenge models.

Delivery Platform, Adjuvants and Viral Vectors

The EDUFLUVAC project uses 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 was completed at Redbiotec AG, Switzerland, and at iBET, Portugal, respectively.

Capacity strengthening, Workshops, Training

During 2016 one master student and one PhD students continued their work at iBET on the EDUFLUVAC project supporting the upstream and downstream processes of VLPs:

- Sofia Carvalho (PhD student): her work was mainly related to setting-up specific in-process techniques to monitor and improve purification of influenza VLPs. Her PhD thesis will be discussed in 2017.
- Daniela Sequeira (Master student): her work at iBET focused on analysing the versatility of insect cells for the production of influenza VLPs.

The iBET staff attended the Cell culture-based viral vaccines - ESACT Course, 1st Edition on 21-23 September 2016, Llafranc, Spain.

Harmonisation

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

Outreach and Communication

Cristina Peixoto (iBET, Portugal) presented "Improving and monitoring an influenza VLP downstream process using a click chemistry strategy" at ISBioTech 6th Spring Meeting, 7-9 March, Washington, USA.

Antonio Roldão (iBET, Portugal) presented "Combining stable insect cell lines with baculovirus-mediated expression for production of multi-HA influenza VLPs" at Vaccine Technology VI, 12-17 June, Albufeira, Portugal.

Antonio Roldão (iBET, Portugal) presented "Insect cells platforms for fast production of Pseudo-Typed VLPs for drug and vaccine development" at Vaccine Technology VI, 12-17 June, Albufeira, Portugal.

Sofia Carvalho (iBET, Portugal) presented "A click chemistry strategy to specifically monitor and improve purification of influenza virus-like particles" at Vaccine Technology VI, 12-17 June, Albufeira, Portugal.

Sofia Carvalho (iBET, Portugal) presented "Universal and in-process analytical tool for influenza quantification using a label-free technology" at Vaccine Technology VI, 12-17 June, Albufeira, Portugal.

Antonio Roldão (iBET, Portugal) presented "Combining stable and baculovirus-mediated expression towards production of a universal influenza VLP-based vaccine" at Virus-Like Particle & Nano-Particle Vaccines, 22-24 June, Leiden, Netherlands.

Sofia Carvalho (iBET, Portugal) presented "Universal label-free in-process analytical tool for Influenza virus-like particles quantification" at Virus-Like Particle & Nano-Particle Vaccines, 22-24 June, Leiden, Netherlands.

Ricardo Silva (iBET, Portugal) presented "Process Design Strategy to Monitor and Improve Purification of Influenza Virus-like Particles using Click Chemistry" at the PREP 2016 meeting, 17-20 July, Philadelphia, USA.

Othmar Engelhardt (DH-MHRA, United Kingdom) presented "Immunological evaluation of next-generation influenza vaccines" at the Eighth WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses, 23-24 August, Chicago, USA.

Antonio Roldão (iBET, Portugal) presented "Universal influenza VLP-based vaccine: What can we learn from producing over thirty different VLPs?" at the 10th Vaccine Congress, Amsterdam, 17-20 September, Amsterdam, The Netherlands.

Sofia Carvalho (iBET, Portugal) presented "Universal and in-process influenza virus-like particles quantification tool using Octet technology" at the PALL FortéBio User Meeting, 29 September, Lyon, France.

Odile Leroy (EVI, Germany) presented the EDUFLUVAC project at the meeting in Luxembourg with the other EC-funded consortia on universal flu vaccine and representatives of DG-Health on 07 October.

Sofia Carvalho (iBET, Portugal) presented "Process design strategy to monitor and improve purification of influenza virus-like particles using click chemistry" at the SPICA 16th meeting, 9-12 October, Vienna, Austria.

Antonio Roldão (iBET, Portugal) presented "Lessons learnt on producing and purifying over thirty different VLPs for a universal influenza vaccine" at the World Vaccine Congress Europe, 10-12 October, Barcelona, Spain.

Sofia Carvalho (iBET, Portugal) presented "Monitoring and improving influenza Virus-like particles downstream processing using a click chemistry approach" at the ISPPP 2016 meeting, 6-9 November, Salzburg, Austria.

Gerrit Koopman (BPRC, The Netherland) presented "Diversity Covering approach for universal influenza vaccines: the EDUFLUVAC EC-FP7 Project" at the EVI Rendez-Vous, 14 December, Paris, France.

EDUFLUVAC Workshop on immunoassay standardisation for universal flu vaccines

The manuscript describing the outcome of the first EDUFLUVAC workshop held at NIBSC in 2015 was accepted in 2016 for publication in the Influenza and Other Respiratory Viruses journal.

EDUFLUVAC workshop on experimental animal models for universal flu vaccines

The second EDUFLUVAC workshop on experimental animal models for universal influenza vaccines took place on 23-24 June 2016 at BPRC, Rijswijk, The Netherlands.

This workshop was organised by the EDUFLUVAC consortium with the financial support of Sanofi Pasteur and Viroclinics.

Influenza experts from academia, industry, European and American regulatory authorities and other key stakeholders met to initiate discussions on how the influenza vaccine community should address the choice of animal models for preclinical evaluation of universal influenza vaccines. The programme included a diversity of influenza models from well established, widely accepted models to cutting edge, newly developed animal models as well as ex-vivo approaches and human models. The workshop concluded that animal models need to be chosen carefully, depending on the questions asked, and that no one animal model could be considered the best for all purposes.

The presentations from the workshop are available on the EDULFUVAC website: http://www.edufluvac.eu/node/269

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

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 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 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.

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.

PARTNERS

- Abbott,NL The Netherlands
- Artemis One Health Research BV, The Netherlands
- AstraZeneca AB, Sweden
- Erasmus Universitair Medisch Centrum Rotterdam (EUMCR), The Netherlands
- European Medicines Agency (EMA), United Kingdom
- European Vaccine Initiative (EVI), Germany
- Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Italy
- Biomedical Primate Research Centre (BPRC), The Netherlands
- GlaxoSmithKline (GSK),Belgium
- Istituto Superiore di Sanità, Italy
- Janssen, The Netherlands
- MHRA-Department of Health,United Kingdom
- Novartis, Italy
- Paul-Ehrlich-Institut, Bundesinstitut Für Impfstoffe Und Biomedizinische Arzneimittel, Germany
- QUINTEN, France
- Sanofi Pasteur, France
- Sclavo Vaccines Association, Italy
- The Chancellor, Masters and Scholars of the University of Oxford, United Kingdom
- Università degli Studi di Siena, Italy
- Universiteit Gent, Belgium
- Universitetet i Bergen, Norway
- University of Surrey, United Kingdom

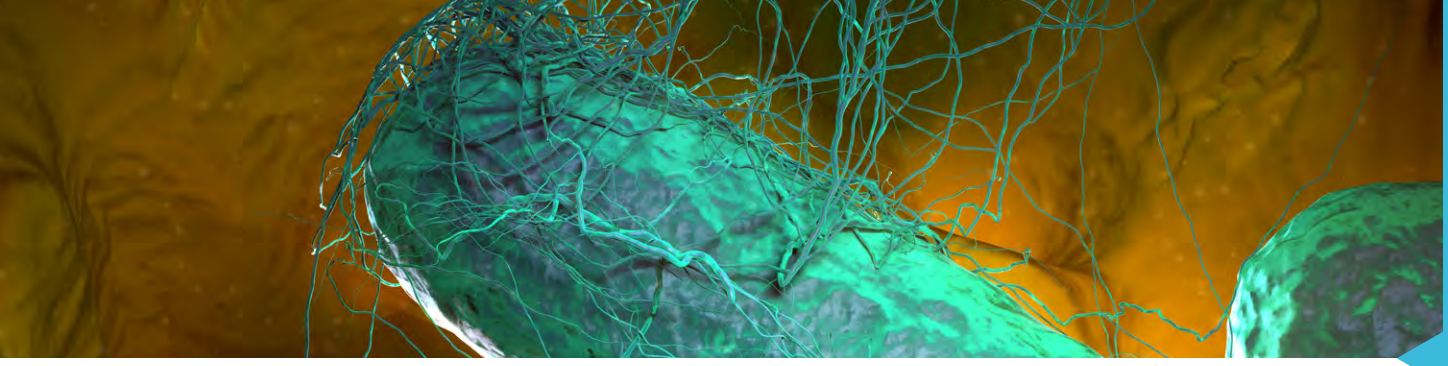
Harmonisation

The FLUCOP team collected influenza haemagglutination inhibition assay protocols from a variety of labs and assessed factors influencing variability. Based on this analysis a pilot study has commenced in order to limit the variables to be analysed in a full scale study, which will take in 2017.

Outreach and Communication

The FLUCOP website was continuously updated with relevant information for and related to FLUCOP: (http://www.flucop.eu). In 2016 the website had over 3,000 visitors.

The progress of the FLUCOP project was disseminated via newsletter to an audience of about 1,400 relevant people (www.flucop.eu/NL2).



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[61].

The highest number of cases occur in South and Southeast Asia. While infection with *S. Typhi* accounts for the majority of enteric fever cases, epidemiological evidence suggests that an increasing proportion of the enteric fever burden is attributable to S. Paratyphi infection meriting further attention and interest in vaccine development. 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.

PARTNERS

- European Vaccine Initiative (EVI), Germay
- Novartis Vaccines Institute for Global Health, Italy
- University of Oxford (UOXF), United Kingdom
- Wellcome Trust Sanger Institute, United Kingdom

PIM

The PIM project was selected for funding by the EVI SAC and approved by the EVI Board in 2013. The project was successfully concluded in 2016. 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 aimed 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.

The total project total budget provided by EVI was of €325,000 and was complemented by co-funding from BMGF.

RECENT ACHIEVEMENTS In 2016, a paper describing the safe establishment of the first ever human challenge study for *S. paratyphi A* was accepted for publication on the Clinical Infectious Diseases journal.

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.

Clinical Development

The PIM project aimed at developing 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.

The primary objective of the study was to determine the dose in Colony Forming Units (CFU) of S. Paratyphi A strain NVGH308 required to achieve an attack rate of 60-75% when ingested with sodium bicarbonate solution. Secondary objectives were to describe the clinical response to S. Paratyphi A challenge; to evaluate criteria for paratyphoid diagnosis; to describe bacterial dynamics after challenge, including onset and duration of bacteraemia, quantitative blood culture at diagnosis and patterns of stool shedding; and to describe the humoral immune response to S. Paratyphi A challenge.

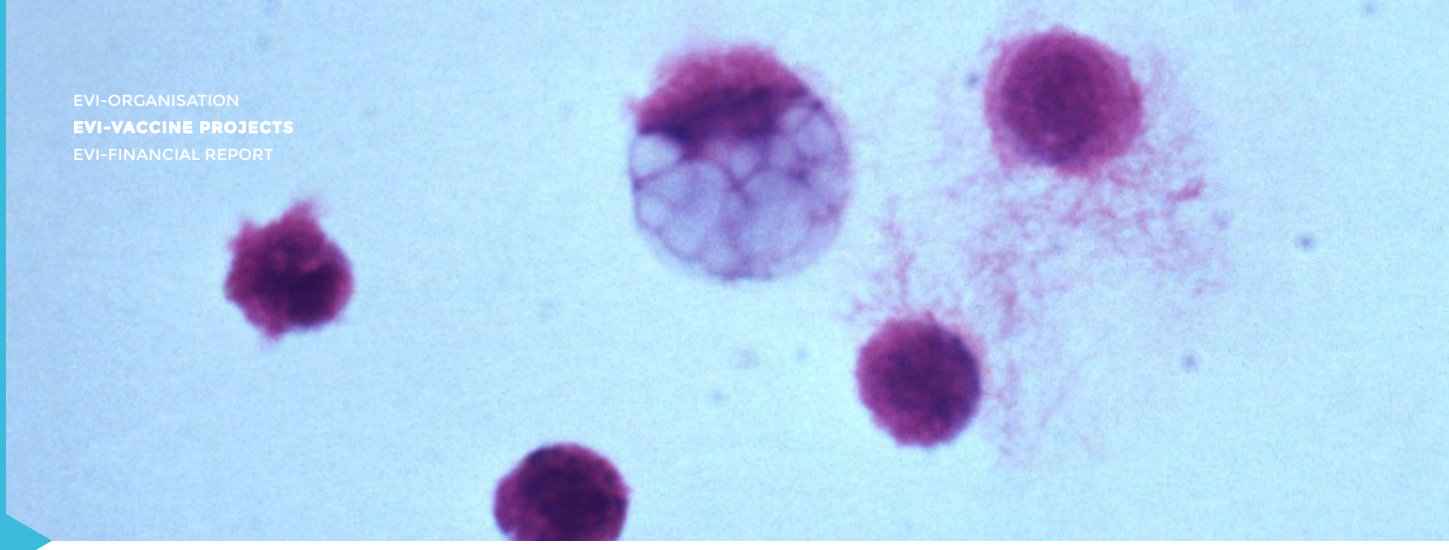
The clinical trial was completed in 2015. The primary study objective was achieved following challenge with 1-5 x 103 CFU. The outpatient management of participants challenged with *S. paratyphi* A was shown to be safe and well-tolerated. The frequency and persistence of bacteraemia in the absence of clinical symptoms was notable, and markedly different from that seen in previous typhoid challenge studies.

Thus, the safety and practicality of the first ever human challenge study for *S. paratyphi* A was successfully demonstrated. The paratyphoid challenge model can be used to expedite the evaluation of novel vaccine candidates and provides insight into the clinical and immune response to paratyphoid infection.

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.

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



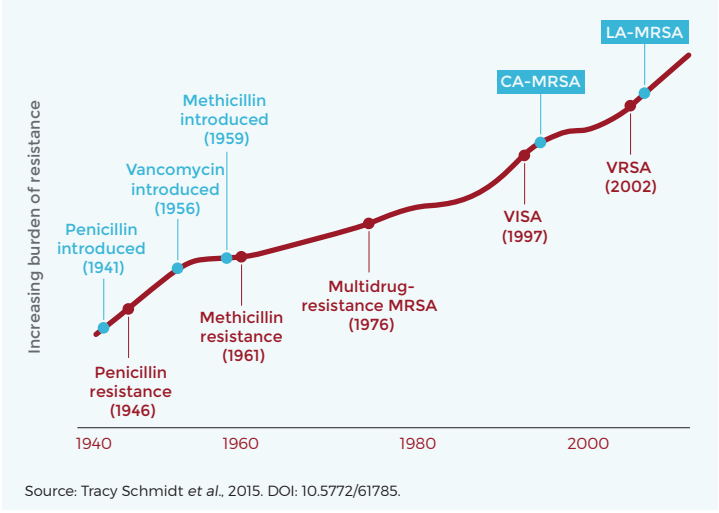
New vaccine technologies and a vaccine against *S. aureus*

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 (FDA) 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)[62].

FIGURE 2 THE EMERGENCE OF ANTIBIOTIC RESISTANCE IN *S. AUREUS*. (VISA, VANCOMYCIN-INTERMEDIATE *S. AUREUS*; VRSA, VANCOMYCIN-RESISTANT *S. AUREUS*; CA-MRSA, COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *S. AUREUS*; LA-MRSA, LIVESTOCK-ASSOCIATED METHICILLIN-RESISTANT *S. AUREUS*).



Source: Tracy Schmidt *et al.*, 2015. DOI: 10.5772/61785.

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

BELLEROPHON

BELLEROPHON is an EU FP7 project with a budget of approximately €5,500,000, which commenced in September 2013 and finished in September 2016.

The bacterium *Staphylococcus (S.) aureus*, is one of the most important bacterial pathogens, causing skin lesions, and deep infections in both the community and in hospitals. Treatment is difficult and expensive and may require prolonged intravenous antibiotic therapy. Since there is no vaccine licensed by the US FDA or European Medicines Agency (EMA), interception also relies heavily on antimicrobials to which antibiotic resistance is developing.

BELLEROPHON is a pan-European project that is addressing these shortcomings in the fight against *S. aureus* infections by designing and evaluating vaccine candidates against both methicillin sensitive and methicillin resistant (MRSA) strains of *S. aureus*. BELLEROPHON partners comprise four European institutions involved in vaccine development, each contributing with specialised expertise and technology. IMAXIO is a French biotech company focused on immunology. The Jenner Institute at the University of Oxford, UK, is an academic institution with key expertise in *S. aureus* antigens and viral vector delivery systems, and is coordinating the overall project. EVI is involved in project management and advising on production and the clinical aspects of the project. The fourth member is Preclin Biosystems, a Swiss contract research organisation with strong expertise in preclinical efficacy models for various infectious diseases.

RECENT ACHIEVEMENTS 2016 was a very active and successful year for the consortium. Several of its findings were published in peer reviewed journals and presented at several conferences to the scientific and general public. Most significantly, a new promising vaccine candidate was identified and tested preclinical in animal models.

Preclinical, process development, production, IMPD

The BELLEROPHON team has worked on selecting the optimal vaccine candidate combination. While the project timelines did not allow proceed to clinical development within with the most promising antigen combination, one major achievement in 2016 was the discovery of a new promising antigen that show significant protective effects in several animal models.

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.

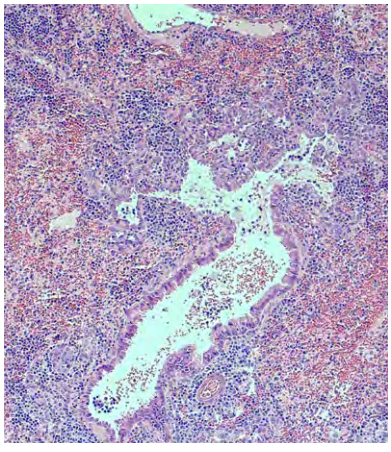
Outreach and Communication

Amy Flaxman (UOXF, UK) presented a poster "A novel experimental murine *Staphylococcus aureus* colonisation model" at the ISSSI 2016 Conference on 31 August 2016, Seoul, South Korea.

Claudia Lindemann (UOXF, UK) presented the topic "Natural mutations in a *S. aureus* virulence regulator attenuate cytotoxicity but permit bacteremia and abscess formation" at the ISSSI 2016 Conference on 02 September 2016, Seoul, South Korea.

PARTNERS

- European Vaccine Initiative (EVI), Germany
- Imaxio SA, France
- Preclin Biosystems AG, Switzerland
- University of Oxford (UOXF), United Kingdom



Pneumonia histopathology

Development and validation of quality testing approaches

for human and veterinary vaccines using non-animal methods

In contrast to small-molecule, pharmaceuticals and well-characterised biological products such as monoclonal antibodies or vaccines are difficult to characterise due to their complexity as well as the extent of the consequent immune response.

At present, final product and – for some vaccine groups such as several clostridial vaccines – in process testing (as part of quality control) often involve animal tests that cause severe pain and distress. The current paradigm of quality control is based on the consistency of each batch produced, requiring extensive testing, particularly of the final batch, generally by relying on animal models for safety and potency (aiming at making the link to efficacy). In some cases for veterinary vaccines these can also be direct target species challenge tests. Many of these animal tests have been used for decades and are historically part of Ph.Eur. monographs but lack the true rigours of validation as would be required in the current regulatory environment.

The VAC2VAC project aims therefore at implementing the consistency approach for several types of established human and veterinary vaccines as a new paradigm to assure safety and efficacy demonstration in vaccine testing, by improving the scientific basis of vaccine quality control while assuring consistency in vaccine production by replacing the use of animals.

VAC2VAC

VAC2VAC (Vaccine batch to vaccine batch comparison by consistency testing) is a wide ranging collaborative research project funded by IMI2 (www.imi.europa.eu) which aims to develop and validate quality testing approaches for both established human and veterinary vaccines using non-animal methods.

The initiative that started on 1 March 2016 aims to provide the data to support the "Consistency Approach" for quality control of established vaccines, where current quality control approaches are often relying on *in vivo* methods.

PARTNERS

- Biomedical Primate Research Centre (BPRC), The Netherlands
- Boehringer Ingelheim (BI), Germany
- European Commission, Joint Research Centre (JRC) Italy
- European Vaccine Initiative (EVI), Germany
- GSK Biologicals (GSKBio), Belgium
- Institute for Translational Vaccinology (Intravacc), The Netherlands
- International Alliance for Biological Standardization for Europe (IABS-EU), France
- Istituto Superiore di Sanità (ISS), Italy
- Merck Sharp & Dohme (MSD), The Netherlands
- Merial (Merial), France
- National Institute for Biological Standards and Control (DH-NIBSC), United Kingdom
- National Institute for Public Health and the Environment (RIVM), The Netherlands
- Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (Austrian Agency for Health and Food Safety: AGES), Austria
- Paul-Ehrlich Institute (PEI), Germany
- Sanofi Pasteur (SP), France
- Scientific Institute of Public Health (WIV-ISP), Belgium
- University Medical Center Groningen (UMCG), The Netherlands
- University of Applied Sciences Utrecht (HU), The Netherlands
- University of Utrecht (UU), The Netherlands
- Zoetis Belgium SA (Zoetis), Belgium

Preclinical, process development, production, IMPD

The first objective of the project is to have developed, optimised and evaluated non-animal methods that cover key-parameters for demonstrating vaccine batch consistency and therefore safety and efficacy. The focus will be on physicochemical (Work Package (WP) 1 and immunochemical (WP2) methods, cell-based assays (WP3) and multiparametric assays & bioinformatics (WP4). Proof of concept for use of these methods will be obtained for several types of human and/or veterinary vaccines on the market: toxoid, inactivated bacterial, and inactivated viral vaccines as well as different adjuvants.

The second objective of the project is to have (pre-) validated the methods that have been developed, modified and/or optimised in the VAC2VAC project, and selected by the steering committee to enter the (pre-) validation process, and to work with regulators to define procedural guidance for regulatory approval and routine use. This objective will be achieved in close collaboration of the consortium partners (OMCLs (Official Medicines Control Laboratories), academia, translational research organisations and vaccinology alliances, veterinary and human vaccine industry) and external collaboration with EU and international regulatory bodies.

Output parameters include:

- drafted criteria for method development and (pre-) validation studies (WP5);
- (pre-)validated methods (WP5);
- provision of guidance on implementation strategies (WP6).

The overall ambition of the VAC2VAC project is:

- to develop and validate non-animal tests for batch release testing,
- to generate vaccine specific toolkits of consistency tests with clearly defined acceptance criteria for batch quality assessment,
- to increase scientific understanding of vaccine quality and the factors affecting quality that are critical to ensure consistency with batches of proven safety and efficacy, and
- to contribute to regulatory acceptance and routine use of the non-animal tests for batch final release testing.

Capacity strengthening, workshops, training

WP5 will organise a workshop with all stakeholders to develop guidance for the design of multi-centre validation studies covering the general aspects of validation and product-specific validation needs.

In WP6, the strategy for regulatory acceptance and successful implementation of the consistency approach for batch release testing will be developed by OMCL partners and industry partners, in close consultation with the scientific and ethics advisory committee. This will include dissemination of information and provision of additional support through organisation of dedicated meetings. It will be key to involve regulators at all stages of discussion of data, validation strategies and approaches to regulatory implantation in dossiers.

Harmonisation

WP5 will focus on establishing criteria to evaluate the readiness of a method or panel of methods to enter the validation process and proceed to the next steps. For this, WP5 will organise small-scale collaborative studies to assess the transferability and inter-laboratory reproducibility of methods developed and optimised in WP1-4 and selected by the steering committee to enter the validation process. Industry partners will provide conforming and non-conforming vaccine samples for these pre-validation studies. (Pre-)validation studies will be preceded by training to familiarise participants with the new tests. Methods having successfully passed pre-validation studies and being supposed for inclusion in monographs or other regulatory documents will be submitted to the European Directorate for the Quality of Medicines & HealthCare (EDQM) Biological Standardisation Programme to be considered for full validation.

Outreach and Communication

The launch of the project has been announced with a press release.

The VAC2VAC website has been launched.

A VAC2VAC general slide set has been prepared and the project has been presented at the following meetings:

- Biomarkers of Vaccine Adjuvant Potency & Safety in Porto 7-8 April 2016
- Danish 3R symposium 13 September 2016
- Lorentz workshop Leiden 19-23 September 2016: Agricultural Immunology
- EUPertstrain meeting 12-13 October 2016, Utrecht, The Netherlands
- Immunity for health Gent 20-21 October 2016
- World Life science conference in Beijing 01-03 November, 2016
- 3Rs Asian congress in Fukuoka (Japan) 05-18 November, 2016

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[63]. 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 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[64]. 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.

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

RECENT ACHIEVEMENTS The project was successfully completed in 2015. Four manuscripts have been published in 2016 presenting some of the results obtained during the clinical trials that were conducted within the project. New publications are expected in 2017.

63. Eziefula AC et Brown M, Curr Opin Infect Dis, 2008, doi:10.1097/QCO.0b013e32830f97fd
64. http://www.who.int/en/

PARTNERS

- Academisch Medisch Centrum bij de Universiteit van Amsterdam, The Netherlands
- Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, The Netherlands
- Agence nationale de recherches sur le sida et les hépatites virales, France
- Centre Hospitalier Universitaire Vaudois (CHUV), CH
- Centre de Recherches Médicales de Lambarene (CERMEL), Gabon
- Eberhard Karls Universitaet Tübingen (EKUT), Germany
- École Polytechnique Fédérale de Lausanne, Switzerland
- European Vaccine Initiative (EVI), Germany
- EuroVacc Foundation, The Netherlands
- Fondation internationale de l'Hôpital de Dr. Albert Schweitzer de Lambarene, Gabon
- Ifakara Health Institute (IHI), Tanzania
- Institut national de la santé et de la recherche médicale (Inserm), France
- Istituto Nazionale Malattie Infettive L.Spallanzani – IRCCS, Italy
- Kenya Medical Research Institute (KEMRI), Kenya
- London School of Hygiene and Tropical Medicine, United Kingdom
- Ludwig Maximilians Universität München, Germany
- Malaria Consortium LBG, United Kingdom
- Medical Research Council on behalf of its MRC/UVRI Uganda Research Unit on AIDS, United Kingdom
- National Institute for Medical Research - Mbeya Medical Research Program, Tanzania
- Swiss Tropical and Public Health Institute (Swiss-TPH), Switzerland
- University of Ibadan, Nigeria
- University of Oxford (UOXF), United Kingdom
- Vaccine and Gene Therapy Institute Florida, United State of America

Clinical Development

The IDEA work package measuring the impact of intestinal helminth infections on the immune response to malaria, TB and HIV vaccines, was 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. Unblinding of the data was postponed to 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 aimed 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 results will be published later on.

Capacity strengthening, workshops, training

The IDEA project has strongly supported capacity strengthening, workshops and training activities in sub-Saharan Africa. In total, IDEA has 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.

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 harmonisation and implementation of novel immunological and diagnostic assays, and data management for clinical trials in African settings, led by African principal investigators, represents an important achievement within the IDEA project. IDEA also leveraged 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.

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.

Vaccine research and development policy

To further advance its mission, EVI enhanced its engagement with policy and decision makers to maintain and strengthen their commitment to global health R&D. Main focus of the engagement was on European R&D policies but EVI was also actively involved in supporting the establishment of a new global coalition that aims to overcome barriers in the development of vaccines against epidemic diseases by promoting a new funding model.

IPROVE

IPROVE is an EU FP7 policy project that developed a vision for the future of vaccine R&D in Europe.

Using a bottom-up approach involving all major key stakeholder groups in vaccine-development in Europe, a comprehensive roadmap was developed that will provide guidance for strategic decisions in future EU vaccine R&D projects and for the prioritisation of technologies and innovations for immunisation.

RECENT ACHIEVEMENTS

In 2016, the roadmap was officially launched during a dedicated summit at the European Parliament.

PARTNERS

- Vaccines Europe / European Federation of Pharmaceutical Industries and Associations, Belgium
- European Vaccine Initiative (EVI), Germany
- European Advanced Translational Research Infrastructure in Medicine (EATRIS), The Netherlands
- Sclavo Vaccines Association, Italy

IPROVE

Outreach and Communication

Official launch of the IPROVE Roadmap at a special event at the European Parliament on 16 March, hosted by the Members of the European Parliament Francoise Grossetête, Cristian-Silviu Busoi and Markus Ferber.

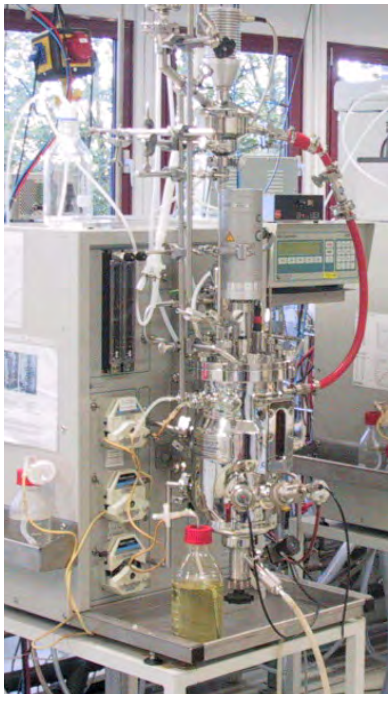


TABLE 2 IPROVE ROADMAP RECCOMENDATIONS

Main priorities	Specific recommendations
Challenge 1 – R&D	
Support an integrated, multidisciplinary approach to antigen selection	> Research on host-pathogen interactions in vivo > Research for the refining of animal models > Development and exploration of new assays to rapidly screen antibody and T cell functions > Explore emergent in-vitro bioassay technologies and improve in-vitro assay for antibody functional screening > Research for selection and analysis of epitopes > Develop new bioinformatics tools applied to genomics, antigen diversity and antigen expression > Support research on structural vaccinology
Strengthen the science of vaccine adjuvants	> Create toolbox of adjuvants with well-defined profile to shape the immune response > Employ systems/omics analysis to improve the discovery of biomarkers predictive of adjuvants' effect > Develop toxicology research on adjuvant-induced inflammation > Combine different adjuvants in prime-boost studies > Cross-species studies of vaccine adjuvants to pinpoint predictability of animal models
Sustain research on vectors and alternative routes of immunisation	> Better approach to a combined use of vectors, adjuvants, routes of immunisation > Evidence-based development of heterologous prime-boost strategies to induce long-lasting immunity of alternative routes of immunisation and their testing in pre-clinical and clinical studies > Development of more potent synthetic nucleic acid-based vectors for rapid outbreaks response > Research for the development of novel strategies for mucosal vaccination using purified subunit antigens
Innovative design and harmonisation of clinical trials data and development of analyses frameworks	> Enable access to "big data" at the micro and macro level > Build capacities to enable data aggregation across functions, inclusive of data descriptors > Rapidly develop multi-parametric technologies in cell biology > Identify innovative design of clinical trials and methodologies to profile volunteers earlier on in the process
Continue to invest in biomarkers of safety in vaccines, and correlates of protection and of efficacy	> Develop expertise and support infrastructures to perform controlled challenges in humans > Set up collaborative cost-sharing programmes in the EU and at international levels (Transatlantic, Asia) to facilitate access to advanced technologies, large populations, rare outcomes, and avoid duplication in investments
Challenge 2: therapeutic vaccines	
Establish collaborative cross-expertise network at eu level	> Exchange best-practice, including successful and unsuccessful approaches, share know-how and technology > Design and perform multi-centre clinical studies
Foster early dialogue with regulatory bodies	> Facilitate early interactions and regular dialogue with regulators, e.g. through EC led workshops > Regulators to assess the feasibility of developing EU-level guidance for therapeutic vaccines, including in specific disease areas
Develop targeted funding opportunities	> Bridge the gap between research and market and create efficient financial markets > Government policies to improve equity financing > Lower financial risk perception through appropriate mechanisms, including interactions with payers
Challenge 3: innovative processes for vaccine manufacturing and quality control	
Translate innovations into technologies	> Promote closer collaboration among scientists, engineers and regulators > Offer continuity of funding beyond concept demonstration > Set up a task force of regulators and policy-makers to support plans based on scenario planning
Develop flexible manufacturing systems	> Investigate how to decentralise manufacturing capacity through a more localised supply base > Support the adoption of single use systems and technologies to minimise variations between sites
Bridge technology and science: collaboration between engineers and biologists	> Investing in thermostability enabling technologies > Test alternative delivery devices: increasing vaccine stability and new fill-in > Investment in formulation expertise in the research process > Develop and validate improved potency assays to increase relevance while simplifying testing > Develop assay platforms allowing for rapid characterization for different manufacturing systems > Develop robust assays for in-process control for both up-stream and down-stream processing
Improve manufacturing operations and identify new purification techniques	> Improved chromatographic techniques adapted to adenoviruses or particle-based vaccines

Main priorities	Specific recommendations
Challenge 4: research infrastructures	
Reinforce vaccine Research Infrastructures	> Develop the network of existing EU facilities and cross border connection to rapidly set-up trials and recruit subjects > Upgrade or create new infrastructures in the areas where gaps exist or capacity is insufficient > Promote harmonisation/standardisation among facilities in five key areas: genomics and bioinformatics facilities; repository and collections ; high throughput protein production and crystallography facilities; animal facilities; immunisation technologies > Develop and promote access to innovative technology platforms: live vectors, adjuvant, formulation > Consolidate and provide access to repository and collections: biobanks and well-characterised pathogen strains
Provide support to clinical research infrastructure	> Map centres with methodological competences and map volunteers/specific populations > Identify or develop cohorts (registries) > Enable human challenge models > Further develop and structure clinical trial centers coupled with immunomonitoring, imaging, laboratory testing and functional monitoring of physiological parameters
Improve GMP manufacturing capabilities	> Secure clear guidance on GMP level for manufacturing and quality control > Establish funding schemes to fund the GMP manufacturing of vaccines for testing up to phase 2 > Facilitate the access to infrastructure required for GMP manufacturing > Establish a central European platform to measure the purity of GMP vaccine batch
Challenge 5: vaccine SMEs	
Establish a network of vaccine sMes involved in human vaccine R&D at EU-level	> Create forums and a European network to push innovation, share knowledge and experience, as well as to conduct a comprehensive needs assessment > Create a vaccine innovation community portal to improve the exchange information, opportunities, services and infrastructures at EU level
Ease SMEs access to scientific and technical resources and skills at the most critical phases	> Facilitate SMEs' access to new technologies to reduce R&I costs and timing > Effective matchmaking and interaction between SMEs and large companies
Support better SMes early access to regulatory expertise	> Facilitate the establishment of early stage contacts with regulatory bodies > Enhance the visibility of services that regulatory bodies can provide at national and EU level
Foster competitive collaborative projects between sMes and larger companies	> Develop an advising mechanism to provide SMEs with easier access to existing facilities and platforms > Organise commercial contact-making workshops > Set-up new instruments allowing SMEs to share R&D projects on the 'Bio-Europe' partnering model > Establish an EC "window" awards to successful large pharma-SMEs R&I collaborations
Sharpen financial instruments and attracting risk capital towards SMes	> Invest in improving the public perception of vaccines as a strategic public health tool > Better adapt current instruments to vaccines SMEs needs
ChALLenGe 6: tRAInInG	
Identify and profile target groups for training	> Adapt the training offering in terms of content and format to specific groups > Map out and describe competency profiles for different vaccinology related functions
Review and adapt training formats, accessibility and recognition	> Collaborate with higher education organisations and companies to incentivise training in vaccinology and increase accreditation > Set-up specialised initial and life-long training including courses covering the entire process from vaccine R&D to licensure
Invest in training the trainers	> Establish vaccine training platforms to allow the sharing and shipment of equipment required for training > Fund the establishment of facilities devoted to training for GMP manufacturing and train the trainers

Main priorities	Specific recommendations
Challenge 7: communication on immunisation and the hesitancy challenge	
Implement stratified monitoring of acceptance attitudes and sentiments towards vaccination	> Establish a tool capable of monitoring acceptance attitudes, risk awareness, sentiments towards vaccines and vaccination programmes at EU level > Develop metrics of vaccination acceptance > Design and pilot interventions
Establish multi-disciplinary networks of expertise and an eu level center of excellence	> Support regional and national immunisation advisory groups with regards to vaccine hesitancy > EU institutions to facilitate the formation of a European community of practice on vaccination uptake > Bring together experts from social and behavioural science, neuroscience, social marketing, communication and health education
Make healthcare professionals and public health stakeholders effective advocates of vaccination	> Implement innovative shifts in the curricula offerings for healthcare workers to equip them with the right skills and confidence to appropriately assess vaccination needs and effectively communicate on vaccination > Fund vocational and on-the-job communication training programmes for public health staff and immunisation programme managers > Educate future generation about infectious disease, immunology and public health, e.g. through school-based educational programmes, with a view to institutionalising the role of vaccination as a cornerstone of public health
Engage with civil society organisations	> Provide appropriate funding and build partnerships to collaborate with such organisations to help building awareness, disseminating and creating knowledge on vaccination needs

LIVE

"Leading International Vaccinology Education" (LIVE), is a new Erasmus Mundus - Joint Master Degrees funded by the Education, Audiovisual and Culture Executive Agency (EACEA) of the European Commission, which started in 2016. EVI is an associated partner. Dr. Odile Leroy is a member of the Academic and Management Board.[65]

The general objective of the new LIVE programme is to train the next generation of vaccinologists who will have to manage an increasing number of infectious and non-infectious vaccine targets for many important issues: unsolved and still emerging infectious diseases, immune-senescence in an era where there is exponential aging of the population, non-infectious but immune-related diseases (e.g. allergy, cancer and chronic inflammatory diseases such as atherosclerosis, obesity, diabetes, addictions...).

Such needs parallel the global need to decrease health care expenditures while increasing quality and health care outcomes. Meeting these needs starts with providing the funding, teachers, excellent training and career pathways for smart and dedicated students who will devote their professional careers to Vaccinology. LIVE is a two-year programme for talented and motivated students interested in multidisciplinary studies in Vaccinology.

It is a joint project between five European universities (Barcelona, Antwerp, Saint-Etienne and Lyon), each one awarding a Master degree of excellent quality. Academic internationality is enriched by a worldwide network of 12 academic universities from Brazil, Canada, China, Cuba, Europe, and USA and 13 industrial partners and vaccine manufacturers. LIVE students will develop a trans-national appreciation for vaccine issues by in-residence participation in educational activities in at least three different countries during the programme.

Graduates are also well prepared for doctorate research in Ph.D. programmes funded by associated partners. We anticipate that the LIVE programme, designed as an interdisciplinary teaching approach and an internationally composed student community, will provide students with these five fundamental keys to engage in successful careers in vaccinology, and to build an international network of professionals who will help to solve the current and future challenges of the field.

65. http://live.univ-lyon1.fr/webapp/website/website.html?id=3743907&pageId=275152 (accessed 29-05-2017)

Advocacy and International Fora

Throughout 2016 EVI continued its advocacy activities at national and European/ international level with the aim to maintain and strengthen the commitment of funders and policy and decision makers to vaccine development for diseases of poverty and global health R&D in general. In addition to many bilateral meetings and visits organised, EVI participated in a variety of events.

ADVOCACY

Towards universal immunization coverage as a cornerstone for health and development in Africa, 24-25 February, *Addis Ababa, Ethiopia*

The conference included sessions covering sustainable financing for immunisation, the role of communities in coverage and demand, building stronger systems to improve child health, and leveraging regional partnerships to ensure high and equitable vaccination coverage. The event brought together advocates, technical experts, policymakers, donors and journalists. EVI was represented by Nathalie Imbault.

The Meningitis Vaccine Project (MVP) Closure Conference: Ending and new beginnings, 22-23 February 2016, *Addis Ababa, Ethiopia*

MVP is a partnership between PATH and WHO. The mission of MVP is to eliminate meningitis as a public health problem in sub-Saharan Africa through the development, testing, introduction, and widespread use of conjugate meningococcal vaccines. EVI was represented by Nathalie Imbault.

European Conference of Life Science Funders and Foundations, 26-27 April, *Heidelberg, Germany*

The event explored opportunities to positively influence and accelerate the realisation of life sciences research and the transformation of discoveries into applications that benefit all. EVI was represented by Stefan Jungbluth.

EU advocacy on Global Health R&D: Strategy Workshop, 7 September, *Brussels, Belgium*

Meeting organised by DSW involving different global health R&D stakeholders that aimed to give an overview of ongoing and upcoming EU processes with relevance for global health R&D in Europe and to discuss corresponding advocacy opportunities. EVI was represented by Stefan Jungbluth.

SAP SELECT meeting, 15-17 November, *Berlin, Germany*

The SAP Select meeting brought together business leaders from SAP customers, SAP Board Members, executives and experts. The event provided a platform for top innovators and thinkers to engage in discussions, exchange ideas, and network with peers. EVI was represented by Odile Leroy and Sten Larsen.

Access to new medicines, 12 December, *Brussels, Belgium*

Forum organised by the EC to discuss issues surrounding approaches and experiences in negotiating and implementing access provisions in partnership agreements and how to contribute and promote the rational use of drugs in low and middle income countries. EVI was represented by Stefan Jungbluth.

INTERNATIONAL FORA ATTENDED

First Medical Infrastructures/ Users Forum (MIUF) meeting, 25-26 January, *Paris, France*

This meeting focused on the pivotal role played by the Research Infrastructures (RIs), as they represent a powerful instrument to promote, facilitate and enhance regional, national and transnational collaborations by giving a shared access to facilities. RIs could be seen as the centre of the knowledge triangle of research, education and innovation. Close collaboration with medical research communities is needed to ensure appropriate development of tools and services, and open access for researchers to RIs across Europe. EVI was represented by Odile Leroy.

Annual TBVAC2020 Meeting, 01-05 February, *Les Diablerets, Switzerland*

TBVAC2020 annual project meeting that brought together TB vaccine researchers who presented an update of the project and that allowed to discuss the latest developments in the field and to exchange new ideas. EVI was represented by Nathalie Imbault.

2016 Global Vaccine & Immunization Research Forum (GVIRF), 15-17 March, *Johannesburg, South Africa*

At the 2016 GVIRF major research agendas were discussed in support of the objectives of the Global Vaccine Action Plan (GVAP), covering discovery, development and delivery sciences. The forum gathered leading experts from academic and private sector institutions, public health, regulation and civil society organisations. EVI was represented by Odile Leroy who is member of the Scientific Committee.

11th Edition of BIOVISION & future vaccines workshop, 12-14 April, *Lyon, France*

This workshop, co-organised with CoReVac and Aviesan, aimed at boosting research and innovation in vaccinology. Experts from academic, industrial and worldwide organisations debated about: how to derisk vaccine innovation, how to develop vaccine open innovation, how to facilitate vaccine clinical development and how to monitor vaccine security. Biovision 2016 pattern was dedicated to strengthen action & interaction for innovation. EVI was represented by Odile Leroy.

Symposium on European Funding Instruments for the development of Research Infrastructures, 19 April, *Madrid, Spain*

The meeting provided comprehensive view of the financial possibilities that the European research infrastructures can consider in order to fully exploit their research capacities and services. Information was facilitated on the different funding instruments available and their connection to the research infrastructure ecosystem at European level. EVI was represented by Stefan Jungbluth.

Malaria Vaccines for the World (MVW), 02-04 May, *Leiden, The Netherlands*

The MVW 2016 conference focused on different aspects of vaccine development, assessment and deployment, as well as funding and regulatory aspects of vaccine implementation and testing. The conference also highlighted research on the use of animal models and (controlled) clinical trials to study the immunological basis of protection and to identify novel candidate vaccine antigens. Odile Leroy, Sophie Houard and Nicola Viebig represented EVI at the meeting.

Controlled human infection models (CHIM) for malaria and other Infectious diseases, 04-06 May, *Leiden, The Netherlands*

The CHIM workshop aimed to bring together scientists working on controlled human infection models, looking back, reviewing actual activities (as well as risks and benefits), and looking forward. EVI was represented by Odile Leroy and Nicola Viebig.

GIHT on the ground

During the 8th EDCTP Forum EVI organised a symposium on "Importance of Blood-stage malaria vaccine candidates in the development of a next generation malaria vaccine".

The main objectives were to:

1. Present recent progress in strategies used to down-select Blood-stage malaria vaccine candidates in the context of next generation malaria vaccine development.

2. Discuss he challenges faced during the clinical development and the results of current clinical trials of Blood-stage malaria vaccines.

In this symposium, experienced vaccine developers from Africa and Europe presented findings from blood-stage vaccine candidate clinical trials as well as *P. falciparum* novel blood-stage antigen discovery, validation and prioritisation.

BioMalPar XII: Biology and Pathology of the Malaria Parasite, 18-20 May, *Heidelberg, Germany*

This conference addressed fundamental questions of the biology of the malaria parasite, its vector, the immune response of the host and the disease that it causes, and showcased the latest technological approaches. Objectives of the conference were to offer opportunities for sharing ideas and for the development of new collaborations and to provide training opportunity for the next generation of malaria researchers. EVI was represented by Nicola Viebig.

New approaches to vaccines for human and veterinary tropical diseases, 22-26 May, *Cape Town, South Africa*

Keystone symposia to stimulate crosstalk between the human and veterinary vaccine communities by highlighting cross-cutting technical advances and new science and knowledge from laboratory and field research. The meeting also provided opportunities for scientists from the Northern and Southern hemispheres to interact and get engaged. EVI was represented by Stefan Jungbluth.

Workshop on the development and implementation of anti-tick vaccines in Europe, 3 June, *Berlin, Germany*

The aim of the workshop was to bring together key stakeholders to identify and explore strategic steps that need to be taken for successful implementation of anti-tick vaccines in health systems in Europe. EVI was represented by Odile Leroy.

GHIT Annual Partners Meeting 2016, 7 June, *Tokyo, Japan*

During the meeting several researchers involved in projects funded by GHIT presented their progress to date and discussed their potential impact discussed. An interactive discussion followed on the value of cross-sector collaboration for global health R&D. EVI was represented by Stefan Jungbluth.

3rd WHO Product Development for Vaccines Advisory Committee (PDVAC) meeting, 08-10 June, *Geneva, Switzerland*

The main objectives of this third PDVAC meeting were to revisit the pathogen areas where there has been significant progress to report since recommendations from the 2015 meeting, to refine the work plan and strategic directions for specific pathogen areas and to consider how to better align PDVAC's vaccine development activities and strategies with other areas of research, for example the anti-microbial research (AMR) agenda. EVI was represented by Odile Leroy.

8th WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses, 23-24 August, *Chicago, USA*

The Global Vaccine Action Plan calls for at least one licensed universal influenza vaccine by 2020. WHO Initiative for Vaccine Research monitors progress toward the achievement of the plan through regular consultations of experts in the field. Through periodic meetings of experts, WHO monitors research and development of universal influenza vaccines, highlights areas of unmet global need, and advocates for vaccine development that addresses this unmet global need. EVI was represented by Odile Leroy.

4th WHO/TDR & EDCTP Alumni Clinical Research & Development Fellows Meeting, 8-10 June, *Geneva, Switzerland*

The workshop was organised by EDCTP and TDR and was attended by the current and former fellows as well as home institution and host supervisors of the EDTCP-TDR Clinical Research and Development (CRD) Fellowship programme and of its precursor the TDR Career Development Fellowship (CDF) programme. Objectives were to review the program content and progress, to identify needs and opportunities for best use of capacity and to facilitate the networking. EVI was represented by Nicola Viebig, Eric Nébié and Fabrice Somé.

Vaccine Technology VI, 12-17 June, *Albufeira, Portugal*

The Vaccine Technology conference series addressed technical and scientific issues in the development and manufacturing of vaccines. It also discussed broader issues related to vaccine development and access that will be of interest to institutional and academic participants. Emphasis

was particularly placed on emerging diseases and developing world. A satellite workshop on academic-industrial collaborations was organised during the conference. EVI was represented by Odile Leroy.

8th EDCTP Forum "Defeating poverty-related and neglected diseases in Africa: harnessing research for evidence informed policies", 6-9 November, *Lusaka, Zambia*

The EDCTP Forum is one of the major conferences on neglected, infectious, poverty-related diseases in Africa attracting a diverse audience. The meeting provided an international platform for the presentation and discussion of frontier research to address the disease burden, as well as capacity development and networking activities. EVI organised the symposium "Importance of Blood-stage malaria vaccine candidates in the development of a next generation malaria vaccine". EVI was represented by Nicola Viebig.

ADITEC annual meeting, 07-09 November, *Brussels, Belgium*

The three day Advances Immunization Technologies (ADITEC) annual meeting was attended by over one hundred participants from the 42 ADITEC partner institutions and focused on the year's project accomplishments. An event at the European Parliament, dedicated to the ADITEC project and its continual success, was organised for the morning of the 8th. EVI was represented by Odile Leroy.

ASTMH 65th Annual Meeting, 13-17 November 2016, *Atlanta, Georgia, 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 will host global health professionals representing academia, government, non-profits, philanthropy, NGOs, industry, military and private practice. Approximately 4,000 attendees participated in research findings, clinical updates, and topical discussions on the most pressing issues in global health. EVI was represented by Fabrice Somé.

Joint Coordination Group meeting of the Coalition for Epidemic Preparedness Innovations (CEPI), 18 November, *Geneva, Switzerland*

Aim of this meeting was to engage stakeholders in CEPI´s mission and formalize a platform for further involvement in the future. Moreover, CEPI´s collaboration and alignment was discussed as well as the way to move the coalition forward. Odile Leroy represented EVI at this meeting.

Aviesan - Innovation meeting in vaccinology, 22 November, *Paris, France*

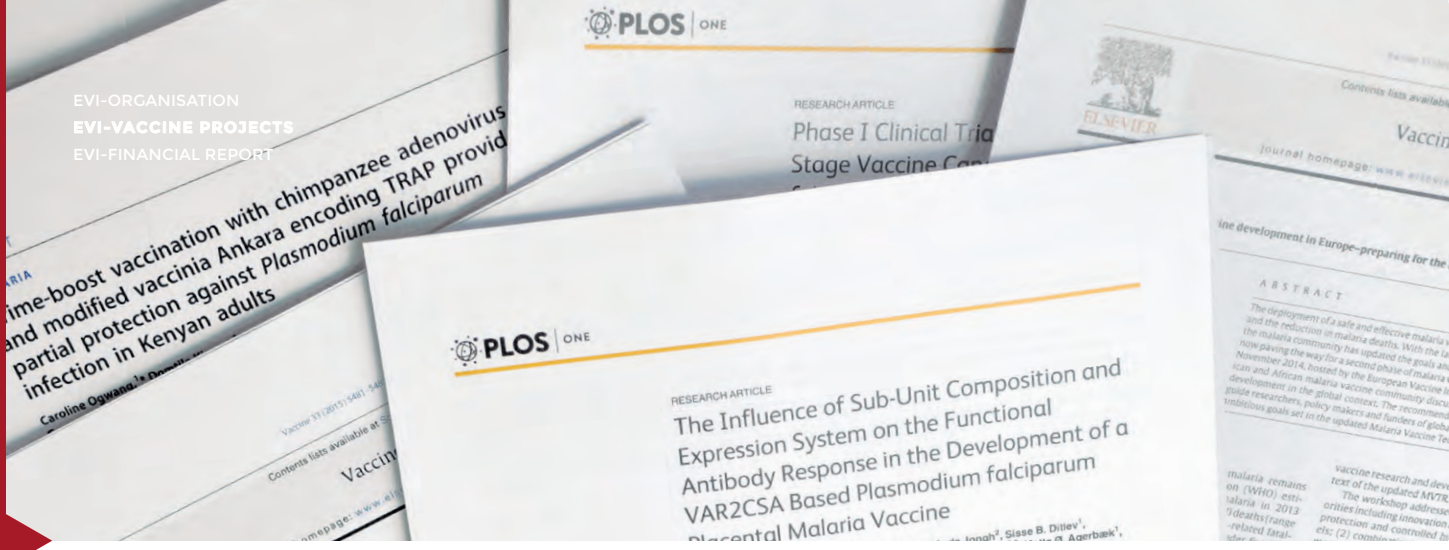
The Innovation in Vaccinology business development priority is supported by the Aviesan network and its purpose is to focus on issues surrounding translation of new developments in vaccinology into commercial use and on the obstacles currently preventing this. EVI was represented by Odile Leroy.

GloPID-R Zika Virus Research Workshop, 30 November – 02 December, *Sao Paulo, Brazil*

GloPID-R members hosted the "GloPID-R Zika Virus Research Workshop" to facilitate collaboration between members on Zika funded research projects. The workshop's aim was to identify and establish collaboration and synergies between the research and capacity development projects in support of the Zika virus response in Latin America and the Caribbean funded by GloPID-R members worldwide. EVI was represented by Nicola Viebig.

Swiss TPH Winter Symposium, 08-09 December, *Basel, Switzerland*

The Swiss Tropical and Public Health Institute (Swiss TPH) Winter Symposium 2016 gathered together medical and health sector specialists to review and discuss history, successes and future of Malaria control and elimination. Odile Leroy gave a presentation on "Challenging the Current Vaccine Pipeline".



Publications

MALARIA VACCINES

MVVC

Mensah VA, Gueye A, Ndiaye M, Edwards NJ, Wright D, Anagnostou NA, Syll M, Ndaw A, Abiola A, Bliss C, Gomis JF, Petersen I, Ogwang C, Dieye T, Viebig NK, Lawrie AM, Roberts R, Nicosia A, Faye B, Gaye O, Leroy O, Imoukhuede EB, Ewer KJ, Bejon P, Hill AV, Cisse B; MVVC group. Safety, Immunogenicity and Efficacy of Prime-Boost Vaccination with ChAd63 and MVA Encoding ME-TRAP against *Plasmodium falciparum* Infection in Adults in Senegal. *PLoS One*. 2016 Dec 15;11(12):e0167951.

Afolabi MO, Tiono AB, Adetifa UJ, Yaro JB, Drammeh A, Nébié I, Bliss C, Hodgson SH, Anagnostou NA, Sanou GS, Jagne YJ, Ouedraogo O, Tamara C, Ouedraogo N, Ouedraogo M, Njie-Jobe J, Diarra A, Duncan CJ, Cortese R, Nicosia A, Roberts R, Viebig NK, Leroy O, Lawrie AM, Flanagan KL, Kampman B, Bejon P, Imoukhuede EB, Ewer KJ, Hill AV, Bojang K, Sirima SB. Safety and Immunogenicity of ChAd63 and MVA ME-TRAP in West African Children and Infants. *Mol Ther*. 2016 Aug;24(8):1470-7.

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Faber BW, Hellwig S, Houard S, Havelange N, Drossard J, Mertens H, Croon A, Kastilan R, Byrne R, van der Werff N, van der Eijk M, Thomas AW, Kocken CH, Remarque EJ. Production, Quality Control, Stability and Pharmacotoxicity of a Malaria Vaccine Comprising Three Highly Similar PfAMA1 Protein Molecules to Overcome Antigenic Variation. *PLoS One*. 2016 Oct 3;11.

InnoMalVac

Hjerrild KA, Jin J, Wright KE, Brown RE, Marshall JM, Labbé GM... Draper, SJ. Production of full-length soluble *Plasmodium falciparum* RH5 protein vaccine using a *Drosophila* melanogaster Schneider 2 stable cell line system. *Scientific Reports* 2016, 6, 30357.

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Tougan T, Ito K, Palacpac NM, Egwang TG, Horii T. Immunogenicity and protection from malaria infection in BK-SE36 vaccinated volunteers in Uganda is not influenced by HLA-DRB1 alleles. Parasitol Int. 2016 Oct;6 5.

PRIMALVAC/PlacMalVac

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PlacMalVac

Gbedande K, Cottrell G, Vianou B, Ibitokou S, Fernando A, Troye-Blomberg M, Theander T, Salanti A, Moutaïrou K, Massougbodji A, Tuikue Ndam N, Salanti A, Deloron P, Luty AJF, Fievet N. Infections with *Plasmodium falciparum* during pregnancy affect VAR2CSA DBL-5 domain-specific T cell cytokine responses. Malaria J, 2016, 15:485.

OTHER VACCINES

EDUFLUVAC

Carvalho SB, Freire JM, Moleirinho MG, Monteiro F, Gaspar D, Castanho MARB, Carrondo MJT, Alves PM, Bernardes GJL and Peixoto C. Bioorthogonal Strategy for Bioprocessing of Specific-Site-Functionalized Enveloped Influenza-Virus-Like Particles. *Bioconjugate Chem.*, 2016, 27 (10): 2386-2399.

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Freidl GS, van den Ham HJ, Boni MF, de Bruin E & Koopmans, MPG. Changes in heterosubtypic antibody responses during the first year of the 2009 A(H1N1) influenza pandemic. *Scientific Reports* 2016, 6:20385, https://doi.org/10.1038/srep20385

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Dobinson HC, Gibani MM, Jones C, Thomaides-Brears HB, Voysey M, Darton TC,... Pollard AJ. Evaluation of the clinical and microbiological

response to *Salmonella paratyphi A* infection in the first paratyphoid human challenge model. *Clinical Infectious Diseases*. In Press.

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Allen ER, van Diemen P, Yamaguchi Y, Lindemann C, Soilleux E, Rollier C,... Wyllie DH. MRI Based Localisation and Quantification of Abscesses following Experimental *S. aureus* Intravenous Challenge: Application to Vaccine Evaluation. *PLoS One* 2016, *11*(5), e0154705. https://doi.org/10.1371/journal.pone.0154705

Das S, Lindemann C, Young BC, MullerJ, Österreich B, TernetteN,... Fraunholz MJ. Natural mutations in a *Staphylococcus aureus* virulence regulator attenuate cytotoxicity but permit bacteremia and abscess formation. *Proceedings of the National Academy of Sciences of the United States of America* 2016, *113*(22), E3101-3110. https://doi.org/10.1073/pnas.1520255113

Flaxman A, Allen E, Lindemann C, Yamaguchi Y, O'Shea MK, Fallowfield JL,... Wyllie DH. Risk factors for dermatitis in submariners during a submerged patrol: an observational cohort study. *BMJ Open* 2016, *6*(6), e010975. https://doi.org/10.1136/bmjopen-2015-010975

Whitehouse J, Flaxman A, Rollier C, O'Shea MK, Fallowfield J, Lindsay .,... Yamaguchi Y. Population variation in anti-*S. aureus* IgG isotypes influences surface protein A mediated immune subversion. *Vaccine* 2016 *34*(15), 1792-1799. https://doi.org/10.1016/j.vaccine.2016.02.034

CROSS-CUTTING ACTIVITIES

IDEA

Chachage M, Pollakis G, Kuffour EO, Haase K, Bauer A, Nadai Y, Podola L, Clowes P, Schiemann M, Henkel L, Hoffmann D, Joseph S, Bhuju S, Maboko L, Sarfo FS, Eberhardt K, Hoelscher M, Feldt T, Saathoff E, Geldmacher C. CD25+FoxP3+ memory CD4 T cells are frequent targets of HIV infection *in vivo*. *J Virol*. 2016 pii: JVI.00612-16

Joosten SA, van Meijgaarden KE, del Nonno F, Baiocchini A, Petrone L, Vanini V, Smits HH, Palmieri F, Goletti D, Ottenhoff. THM Patients with tuberculosis have a dysfunctional circulating B-cell compartment, which normalizes following successful treatment. *PLoS Pathog*. 2016 12(6): e1005687

Toulza F, Tsang L, Ottenhoff THM, Brown M, Dockrell HM. Mycobacterium tuberculosis-specific CD4+ T cell response is increased, and Treg cells decreased, in anthelmintic-treated patients with latent TB. *European Journal of Immunology*. 2016

Obuku AE, Asiki G, Abaasa A, Ssonko I, Harari A, van Dam GJ, Corstjens PL, Joloba M, Ding S, Mpendo J, Nielsen L, Kamali A, Elliott AM, Pantaleo G, Kaleebu P, Pala P. Effect of *Schistosoma mansoni* Infection on Innate and HIV-1-Specific T cell Immune Responses in HIV-1-Infected Ugandan Fisher Folk. *AIDS Res Hum Retroviruses*. 2016 Jul;32(7):668-75.

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IPROVE consortium. A strategic European Roadmap for the vaccines of tomorrow: A joint stakeholder reflection. March 2016; http://iprove-roadmap.eu/

Denoel, P., Bietrix, F. Vaccine Vision. *Science & Technology* 2016 (19): 146

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. In 2016 EVI managed to expand its scope to other diseases of poverty.

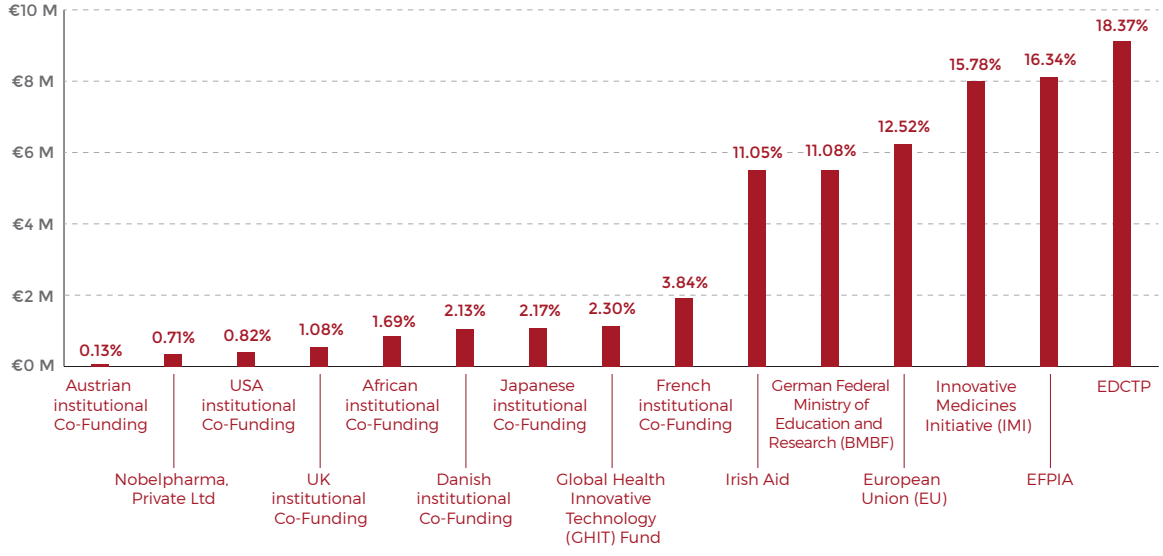
PORTFOLIO FUNDING

EVI's project portfolio as of 31. December 2016 comprises of 12 different active projects in the broad field of R&D, harmonisation, capacity building, and vaccine development. EVI succeeded in raising €15.6 million in new funds through continued efforts, the establishment of new partnerships and much appreciated continued support by its long-term partners. Further activities with additional funding are anticipated in 2017.

FIGURE 3 SIGNED AND PROJECTED GRANTS BY EVI 2009-2016 (INCLUDING CO-FUNDING) IN K€

Since its move from Denmark and the establishment at the new premises at Heidelberg University, Germany, in 2009, EVI has raised in total more than €93 million together with its partners (of which €67 million are directly coordinated by EVI), which has been used to fund primarily its projects, scientific partners and lastly its secretariat. Furthermore, since its foundation in 2009, EVI has successfully diversified its funding sources in order to reduce its financial risks. Moreover, EVI continues with R&D innovation to target new business opportunities globally. In 2016, the funds raised (15.8M€) were slightly less than in 2015 (16.8 M€)

FIGURE 4 DISTRIBUTION OF FUNDS RECEIVED BY OR PLEDGED TO EVI AS COORDINATOR SINCE 2009 (AS OF 31/12/2016) IN K€



FINANCIAL EFFICIENCY

Between 2009 and 2016 every single euro of EVI funds invested through matched co-funding and in kind contributions has leveraged approximately €5.50 of R&D value. For EVI the key factor is synergy in all actions and processes to optimise the output.

Concerning the deployment of funds and activities in 2016, EVI has continued to focus on streamlining and improving its processes to maximise the funds in its portfolio of projects and to minimise administrative expenses. Part of this process was the replacement of the previous ERP software AESIRAS, which has served EVI during the previous five-years period, through a new resource management system, SAP Business by Design, to provide even more sophisticated options and solutions in terms of resource and financial management and reporting, that qualify as a new evolutionary step in EVI's administrative and financial processes. Through its efforts, as well as the support of its SAP Business by Design implementation partner All4Cloud and the consultancy of former AESIRAS inventor John Holdt, EVI has succeeded to finalise the implementation and going live process of the new system within just one month. EVI is currently building on the pre-existing SAP knowledges of its financial staff, as well as improving the knowledge of the project staff through additional training sessions in order to make full use of the new possibilities to further streamline and automate administrative and financial processes and by that open up even more resources to the EVI's core business.

Despite the investments made into the upgrade of the ERP system, EVI through reviewing and optimising the administrative processes has succeeded in the challenge to keep the share of administrative costs low as part of the strategy to minimise management costs at a lowest minimum possible. EVI makes utmost efforts to minimise cost factors which do not generate an added value for our ultimate beneficiaries – the people in need of the products we develop. Therefore, EVI is always striving for a maximum utilisation of funds for the benefit of vaccine development. This focus has led EVI for the fifth consecutive year to limit its management costs to below 7% of total costs per calendar year and by that investing a minimum of 93% of invested funds into its project. With regards to increased controlling and reporting requirements, EVI envisages for 2017 a slightly increased administrative budget between 10% and 15%, however continues to work on the achievement of the lowest possible administrative costs.

FIGURE 5 REALISED AND FORECASTED EVI INCOME AND EXPENSES

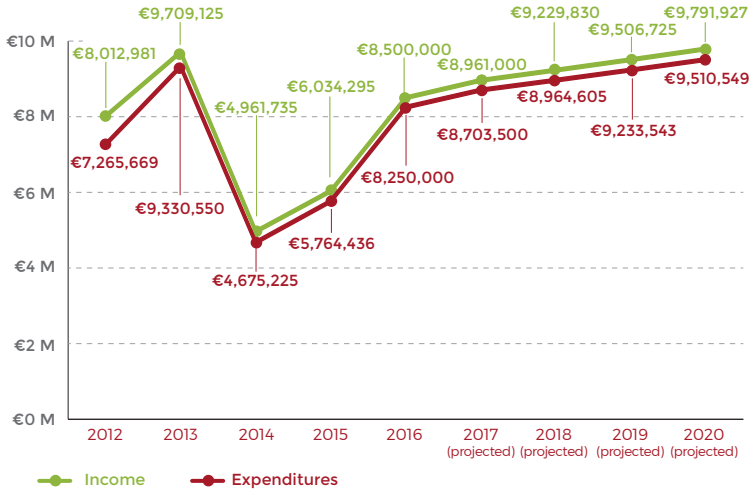
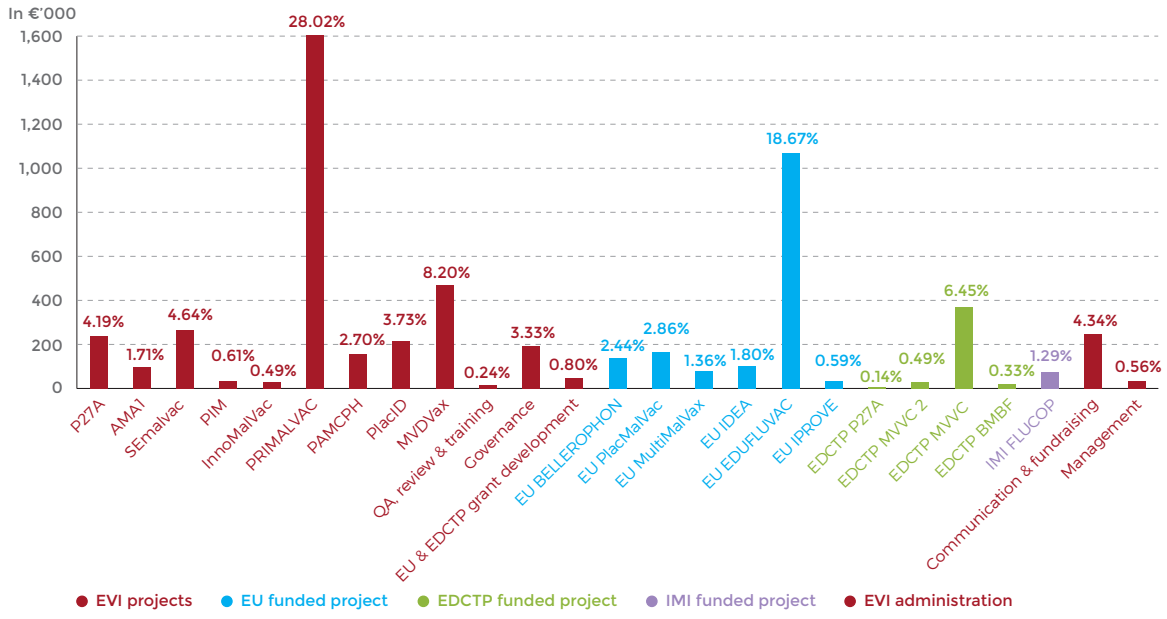


TABLE 3 DEVELOPMENT OF MANAGEMENT COSTS (IN % OF TOTAL COSTS)

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%
2016	7%	6.27%	93.73%

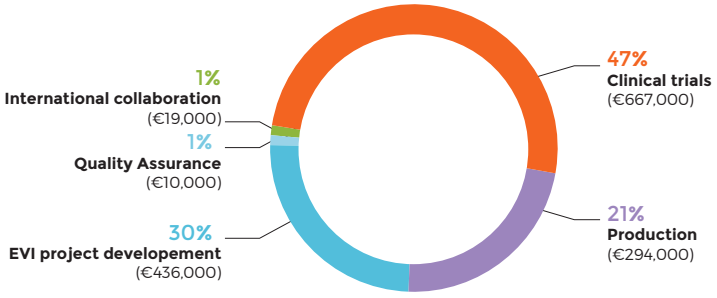
PORTFOLIO MANAGEMENT

FIGURE 6 EVI TOTAL ACTIVITIES IN 2016 (IN K€)



EVI's activities over the current reporting period - during which expenditures were covering the broad portfolio of EVI, EDCTP, IMI, GHIT and EU projects - have produced major achievements, given the level of funding. The financial conclusion of the current reporting period is that the performance of EVI has yet again been continuously efficient, and that funds have been properly utilised to accelerate the global development of vaccines against diseases of poverty.

FIGURE 7 AREAS OF INVESTMENT WITHIN EVI PROJECTS 2016



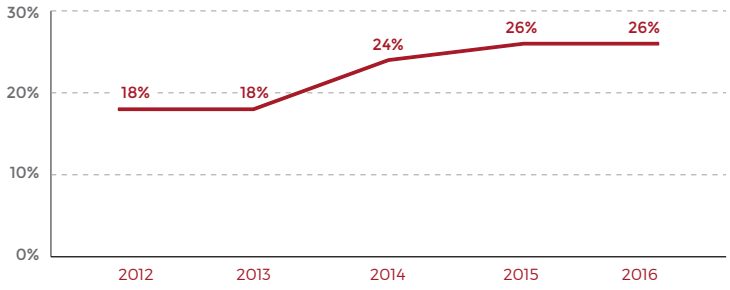
Regarding the different activities funded under EVI projects, the figures referring to the area of investment show that most funds have been spent on GMP production and clinical trials, totalling more than 67% of total expenditure and 31% for scientific project development. This highlights the core business of EVI: supporting translational vaccine R&D with focus on preclinical to early clinical development and making proper use of public funding by allocating funds to the appropriate projects and processes to make them cost effective.

KEY RATIOS

Regarding the EVI's capital structure, prudent financial budget, income and cost management have 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.[66]

EVI's current EC status in terms of key ratios is "good", which is the highest achievable grade in terms of sustainability, solvency, liquidity and profitability according to EC standards. EVI is backed by major organisations in Europe and is a financially strong organisation that appropriately incorporates possible risks and liabilities 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 8 EVI EQUITY RATIO 2012-2016



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 2016, 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 2016.

TABLE 4 EVI LIQUIDITY RATIOS 2016

Cash ratio ((Cash + Cash equivalents) / Current liabilities)	1.34
Quick ratio ((Cash + Cash equivalents + Accounts receivables) / Current liabilities)	1.35
Current ratio (Current assets / Current liabilities)	1.35

66. Equity Ratio=Total Equity Capital / Total Capital

TRANSPARENCY

For the sake of transparency and donor requirements, EVI informs herewith about the number of staff according to payroll bracket, to which they refer to, in accordance with the stipulations of the German data protection act.

Payroll Level (in K€/year)	Number of staff
< 60	5
70-100	4
>100	3

All information with regards to grants received by EVI in 2016, can be found in the following IFRS statement, as shown in note 6, including amongst others the attribution of grants to programmes and specific projects, payments, cost and revenues, as well as deferred income and expenses in 2016.

The accounting methodologies, IT system set-up and controls, as well as internal control measures in connection with financial and accounting principles of EVI ensure, that activities are adequately accounted for and attributed to the relevant projects or EVI tasks, and eliminate the possibilities of duplications of transaction accountings.

EVI confirms that all tax affairs are in compliance with requirements of the jurisdiction of where EVI or its staff members have been tax registered in 2016, namely Germany, Denmark, Belgium and France.

For reason of transparency in comparison to German GAAP and for easy comparability to German businesses and other national interest, EVI presents its cash flow statement below as according to German GAAP.

TABLE 5 EVI GERMAN GAAP CASH FLOW 2016

	2016	2015
Net Surplus	**305,043.50**	269,859.42
Depreciation	**18,127.03**	14,485.06
Provisions	**67,338.81**	(4,611.91)
Other receivables	**(4,696.47)**	9,827.20
Prepaid expenses	**3,312.36**	(8,253.56)
Liabilities to banks	**(5,992.43)**	0.00
Creditor Liabilities	**(228,485.26**	657,907.06
Accrued Expenses	**1,088,569.52**	(133,059.97)
Differed Income	**(27,787.76)**	(319,467.03)
CF from operating activities	**1,215,429.30**	486,686.27
Fixed Asset Investments	**(17,271.33)**	(14,134.91)
CF from Investment activities	**(17,271.33)**	(14,134.91)
CF from financing activities	**0.00**	0.00
Change of Liquid funds	**1,198,157.97**	472,551.36

MANAGEMENT AND AUDITING

EVI has taken further measures 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 costs, 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 losses. In accordance with its accounting and reporting obligations, EVI's 2016 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.

We formally sign and approve the EVI annual financial report for the year ending 31 December 2016 in accordance with the EVI-EEIG Board decision.

We confirm that grants given to EVI were used in accordance with the terms and conditions provided for by each individual agreement.

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

Date: xx/xx/2017	Date: xx/xx/2017	Date: xx/xx/2017
Sten Larsen Finnsson, EVI Finance & HR Director	**Odile Leroy,** EVI Executive Director	**Clemens Kocken,** Chair of EVI-EEIG

Financial presentation 2016

TABLE 6 STATEMENT OF FINANCIAL POSITION AS OF 31 DECEMBER 2016

In EUR	Notes	2016	2015
CURRENT ASSETS			
Cash and cash equivalents:			
Cash and banks - key accounts		4,257,086.13	3,558,928.16
Time deposits		3,250,000.00	2,750,000.00
Total cash and cash equivalents		**7,507,086.13**	**6,308,928.16**
Current accounts and receivables:			
Other receivables		24,496.32	19,799.85
Prepaid expenses		14,392.37	17,704.73
Total current accounts and receivables		**38,888.69**	**37,504.58**
Total current assets		**7,545,974.82**	**6,346,432.74**
Non-current assets			
Tangible fixed assets, net	**2**	24,979.00	25,834.70
Total non-current assets		**24,979.00**	**25,834.70**
Total assets		**7,570,953.82**	**6,372,267.44**
CURRENT LIABILITIES			
Creditors		0.00	5,992.43
Liability to banks	**3**	1,089,523.04	1,318,008.30
Accrued expenses	**4**	1,978,932.78	890,363.26
Other liabilities	**5**	92,181.45	24,842.64
Deferred income	**6**	2,423,016.60	2,450,804.36
Total current liabilities		**5,583,653.87**	**4,690,010.99**
Equity of organisation			
Operating result		305,043.50	269,859.42
Unrestricted operating funds		1,682,256.45	1,412,397.03
Total equity of the organisation		**1,987,299.95**	**1,682,256.45**
Total equity and liabilities		**7,570,953.82**	**6,372,267.44**

TABLE 7 STATEMENT OF COMPREHENSIVE INCOME FOR THE YEAR AS OF 31 DECEMBER 2016

In EUR	Notes	2016	2015
INCOME	**7**		
Turnover from sales		13,067.97	(4,239.95)
Public institutional funding:	**7**		
Governmental & public international organisations		2,688,438.49	3,694,707.83
EU & IMI grants		4,745,128.88	1,662,418.00
EDCTP		244,440.02	405,267.41
Total public institutional funding	**7**	**7,678,007.39**	**5,762,393.24**
Other income net		(103,329.63)	272,525.74
Total income		**7,587,745.73**	**6,030,679.03**
SOCIAL MISSION EXPENDITURE			
Research & vaccine development expenditure:	**8**		
EVI vaccine development projects		1,425,634.07	3,144,689.89
EU-funded research and vaccine development projects		2,649,385.81	1,588,550.79
IMI funded research and vaccine development projects		2,004,850.78	73,867.21
EDCTP-funded research and vaccine development projects		244,440.02	424,663.67
Advocacy & communications expenses		109,936.59	118,068.29
Total social mission expenditure		**6,434,247.27**	**5,349,839.85**
Supportive social mission expenditure	**8**		
Training, quality assurance and project development		52,854.55	14,853.13
Fundraising		185,400.92	177,236.91
Governance		151,969.60	190,846.90
Total supportive social mission expenditure		**390,225.07**	**382,936.94**
Non-social mission expenditure	**8**		
General executive administration		458,847.09	31,658.83
Total non-social mission expenditure		**458,847.09**	**31,658.83**
Total expenditure		**7,283,319.43**	**5,764,435.62**
Operating surplus / (loss)		304,426.30	266,243.41
OTHER INCOME (EXPENSES)			
Financial income, net	**7**	617.20	3,616.01
Total other income (expenses), net		**617.20**	**3,616.01**
Net surplus for the year prior to allocations		305,043.50	269,859.42
Allocation / (release) to restricted operating funds in equity		0.00	0.00
Allocation / (release) to unrestricted operating funds in equity		305,043.50	269,859.42
Net surplus for the year after allocations		**0.00**	**0.00**

TABLE 8 FUNDS FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2016 (WITH 2015 COMPARATIVE FIGURES)

Funds flow from operations (In EUR)	2016	2015
Net surplus for the year	305,043.50	269,859.42
Depreciation of fixed assets	18,127.03	14,485.06
Increase (decrease) in provisions	67,338.81	(4,611.91)
(Increase) Decrease in other receivables	(4,696.47)	9,827.20
(Increase) Decrease in prepaid expenses	3,312.36	(8,253.56)
Increase (decrease) in creditors	(234,477.69)	657,907.06
Increase (decrease) in accrued expenses	1,088,569.52	(133,059.97)
Increase (decrease) in deferred income	(27,787.76)	(319,467.03)
Funds flow from operations	**1,215,429.30**	**486,686.27**

Funds flow from investing activities (In EUR)	2016	2015
(Increase) Decrease of investments in tangible fixed assets	(17,271.33)	(350.15)
Funds flow from investing activities	**(17,271.33)**	**(350.15)**

Funds flow from financing activities (In EUR)	2016	2015
Cash increase (decrease)	1,198,157.97	472,551.36
Cash and cash equivalents – beginning of year	6,308,928.16	5,830,384.37
Cash and cash equivalents – end of year	**7,507,086.13**	**6,302,935.73**

Statement of changes in equity for the year ended 31 December 2016 (EUR)	Opening balance	Allocation	Internal fund transfers	Closing balance
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**
Internally generated funds as of 31 December 2016				
Paid-in capital	0.00	-	-	0.00
Surplus for the year	0.00	305,043.50	(305,043.50)	0.00
Restricted operating funds	0.00	-	0.00	0.00
Unrestricted operating funds	1,682,256.45	-	305,043.50	1,987,299.95
Capital of the organisation	**1,682,256.45**	**305,043.50**	**0.00**	**1,987,299.95**

NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR 2016

Note 1 - Significant Accounting Policies

(a) General comment

EVI fully complies with the demands of German General Accepted Accounting Principles (GAAP) and continuously empowers its staff working on projects to participate in budget control and the control of spending. For an 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 until end of June 2016 operated as the tool for accounting and financial management for EVI/non-profit business with a four dimensional accounting/analysis programme and matrix account analysis tool. In July 2016, EVI introduced SAP Business by Design as the new accounting tool with fully integrated features as the previous system managed in addition to many more features that are new. Thus adding to the Excellency of EVI financial and project management. The change of software was a challenge but has not made any difference to the presentations, which are as always true and fair financial presentation of EVI.

(b) Basis of accounting

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

One major basis of accounting that should be mentioned is that EVI retain the accounting treatment prescribed by International Accounting Standard (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 International Financial Reporting Standard (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:

a) Statement of financial position

b) Statement of comprehensive income (activity based method)

c) Funds flow statement

d) Statement of changes in equity

e) Notes and additional performance report.

Negative amounts are shown within brackets as required by standard.

(c) Basis of preparation

The financial statements are presented in Euro (€), since 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 in conformity with 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 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 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 post 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

Interests 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 is 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 euro at rates prevailing on the date of the transaction using xe.com, with the exception of Danish Kroner which is politically fixed at an exchange rate of 7.45. Monetary assets and liabilities denominated in foreign currencies at the 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 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 2016, made use of the following currencies: EUR, DKK, INR, USD, JPY, GBP and XOF.

(s) Financial auditors

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

The auditor issues an annual 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 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**
Net carrying amount 31/12/2016	
Cost at beginning of the period 01/01/2016	25,834.70
Additions	17,271.33
Disposals	0.00
Cost at end of the period 31/12/2016	43,106.03
Accumulated amortisation 01/01/2016	0.00
Depreciation / amortisation expense 2016	18,127.03
Net carrying amount end of the period 31/12/2016	**24,979.00**

Note 3

Creditors (EUR)	2016	2015
Creditors for grant linked payments	1,037,777.00	1,236,342.49
Other creditors	51,746.04	81,665.81
Total	**1,089,523.04**	**1,318,008.30**

Note 4

Accrued expenses (EUR)	2016	2015
Accrued paid leave	88,318.31	76,260.02
Accrued payables (grants linked)	1,783,431.77	693,692.80
Accrued direct costs	37,750.42	55,118.75
Accrued indirect costs	65,701.91	65,291.69
Accrued other expenses	3,730.37	0.00
Total	**1,978,932.78**	**890,363.26**

Note 5

Other liabilities (EUR)

Carrying period as per 31/12/2015	
Tax provisions	17,654.71
Social charges provisions	4,757.75
Other provisions	2,430.18
Total provisions 31/12/2015	**24,842.64**

Carrying period as per 31/12/2016	
Tax provisions	18,433.21
Social charges provisions	45,311.85
Other provisions	28,436.39
Total provisions 31/12/2016	**92,181.45**

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 31-12-2015	Payments received as per statement of operations	Costs/income realisation as per statement of operations	Deferred income 31-12-2016
Irish Aid - IE	EUR	5,500,000.00	5,500,000.00	**0.00**	500,000.00	500,000.00	**0.00**
BMBF - DE	EUR	5,512,025.00	5,512,025.00	**(346,848.10)**	864,129.08	517,280.98	**0.00**
GHIT - JP	JPY	347,449,127.00	3,406,175.39	**12,202.95**	1,096,604.01	131,545.98	**977,260.98**
FP7 - EU	EUR	16,229,077.00	16,229,077.00	**110,670.95**	101,801.81	570,689.35	**(358,216.59)**
H2020 – EU	EUR	4,918,137.50	4,918,137.50	**0.00**	2,377,099.79	2,083,957.46	**293,142.33**
EDCTP	EUR	9,137,281.00	9,137,281.00	**202,950.23**	17,979.91	220,930.14	**0.00**
IMI	EUR	8,000,000.00	8,000,000.00	**(25,867.21)**	2,193,160.92	2,018,482.86	**148,810.85**
Nobelpharma	USD	256,277.04	177,357.38	**177,357.38**	78,919.66	0.00	**256,277.04**
EVI reserve funds	EUR	3,321,642.18	3,321,642.18	**2,320,338.16**	0.00	1,214,596.17	**1,105,741.99**
Total			**56,201,695.45**	**2,450,804.36**	**7,229,695.18**	**7,257,482.94**	**2,423,016.60**

Deferred income

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

Donator/Grant	Type	Balance 31/12/2015	Payments Received 2016	Cost allocated 2016	Balance 31/12/2016
IE Irish Aid	Core	**0.00**	500,000.00	500,000.00	**0.00**
EVI Board Funds	Core	**2,293,331.88**	0.00	1,187,589.89	**1,105,741.99**
DE BMBF/KfW	Restricted	**(346,848.10)**	864,129.08	517,280.98	**0.00**
JP GHIT /SEmalvac	Restricted	**22,521.42**	0.00	95,665.08	**(73,143.66)**
JP GHIT /MVDvax	Restricted	**(10,318.47)**	0.00	19,838.06	**(30,156.53)**
JP GHIT /Semalvac2	Restricted	**0.00**	1,096,604.01	16,042.84	**1,080,561.17**
EU EDUFLUVAC	Restricted	**199,702.98**	0.00	154,145.87	**45,557.11**
EU BELLEROPHON	Restricted	**159,569.99**	0.00	263,130.30	**(103,560.31)**
EU PlacMalVac	Restricted	**3,730.31**	2,247.75	105,683.49	**(99,705.43)**
EU IDEA	Restricted	**(123,279.55)**	51,280.34	(71,999.21)	**0.00**
EU MultiMalVax	Restricted	**(84,046.56)**	1,666.67	118,128.07	**(200,507.96)**
EU IPROVE	Restricted	**(45,006.22)**	46,607.05	1,600.83	**0.00**
EU ZIKAVAX	Restricted	**0.00**	2,377,099.79	2,083,957.46	**293,142.33**
IMI FLUCOP	Restricted	**(25,867.21)**	73,660.92	14,722.73	**33,070.98**
IMI VAC2VAC	Restricted	**0.00**	2,119,500.00	2,003,760.13	**115,739.87**
EDCTP MVVC2	Restricted	**225,778.70**	0.00	225,778.70	**0.00**
EDCTP P27A	Restricted	**(22,828.47)**	17,979.91	(4,848.56)	**0.00**
NobelPharma / Semalvac	Core	**177,357.38**	78,919.66	0.00	**256,277.04**
EVI Administration	Core	**27,006.28**	0.00	27,006.28	**0.00**
EVI Equity Reserves	Core	**1,682,256.45**	305,043.50	0.00	**1,987,299.95**
Total core		**4,179,951.99**	**883,963.16**	**1,714,596.17**	**3,349,318.98**
Total restricted		**(46,891.18)**	**6,650,775.52**	**5,542,886.77**	**1,060,997.57**
Total EVI funds		**4,133,060.81**	**7,534,738.68**	**7,257,482.94**	**4,410,316.55**

Note 7: Income / realised (In EUR)

Funding used per project (restricted and unrestricted)

	BMBF/Irish Aid	GHIT	EU	IMI
EVI vaccine development projects	1,072,368.15	410,361.98	0.00	0.00
Supportive EVI development costs	0.00	0.00	0.00	0.00
EU R&D projects	0.00	0.00	2,649,385.81	0.00
Supportive EU development costs	0.00	0.00	0.00	0.00
IMI R&D projects	0.00	0.00	0.00	2,004,850.78
Supportive IMI development costs	0.00	0.00	0.00	0.00
EDCTP R&D projects	0.00	0.00	0.00	0.00
Supportive EDCTP development costs	0.00	0.00	0.00	0.00
Executive administration	0.00	0.00	0.00	0.00
Internal allocations	0.00	0.00	0.00	0.00
Total income	**1,072,368.15**	**410,361.98**	**2,649,385.81**	**2,004,850.78**

	EDCTP	Utilisation of reserves	Total income per activity	Overheads and interest	Total income
EVI vaccine development projects	0.00	(57,096.06)	1,425,634.07	0.00	1,425,634.07
Supportive EVI development costs	0.00	416,200.75	416,200.75	0.00	416,200.75
EU R&D projects	0.00	0.00	2,649,385.81	0.00	2,649,385.81
Supportive EU development costs	0.00	52,828.40	52,828.40	0.00	52,828.40
IMI R&D projects	0.00	0.00	2,004,850.78	0.00	2,004,850.78
Supportive IMI development costs	0.00	1,910.06	1,910.06	0.00	1,910.06
EDCTP R&D projects	244,440.02	0.00	244,440.02	0.00	244,440.02
Supportive EDCTP development costs	0.00	29,222.45	29,222.45	0.00	29,222.45
Executive administration	0.00	458,847.09	458,847.09	0.00	458,847.09
Internal allocations	0.00	0.00	0.00	305,043.50	305,043.50
Total income	**244,440.02**	**901,912.69**	**7,283,319.43**	**305,043.50**	**7,588,362.93**

Note 8

Social & non-social mission expenditure (EUR)	Notes	2016	2015
EVI vaccine development projects			
P27A	(a)	(65,295.81)	239,918.21
AMA1-DiCo	(a)	(10,806.85)	97,967.98
PlacID	(a)	238,260.52	214,476.13
PAMCPH	(a)	54,884.28	154,802.81
PriMalVac	(a)	777,835.97	1,605,827.72
InnoMalVac	(a)	0.00	27,993.91
PIM	(a)	0.00	35,040.59
MVDvax	(a)	14,013.29	470,420.86
SEmalvac	(a)	400,699.83	298,241.68
SEmalvac 2	(a)	16,042.84	0.00
Supportive vaccine development costs	(a)	416,200.75	455,148.73
Total EVI vaccine development projects		**1,841,834.82**	**3,599,838.62**
EU-funded R&D projects			
MultiMalVax		112,163.56	78,389.05
IDEA		0.00	102,511.27
PlacMalVac		91,684.22	164,135.41
BELLEROPHON		224,421.77	139,697.26
EDUFLUVAC		135,824.78	1,070,095.09
ZIKAVAX		2,083,957.46	0.00
IPROVE		1,334.02	33,722.71
Supportive project development costs		52,828.40	32,320.75
Total EU-funded R&D projects		**2,702,214.21**	**1,620,871.54**
IMI funded R&D projects			
VAC2VAC		1,991,738.16	0.00
FLUCOP		13,112.62	73,867.21
Supportive project development costs		1,910.06	0.00
Total IMI funded R&D projects		**2,006,760.84**	**73,867.21**
EDCTP funded R&D projects			
MVVC		0.00	369,895.63
P27A-EDCTP		0.00	7,516.22
MVVC 2		244,440.02	27,855.56
BMBF-EDCTP		0.00	19,396.26
Supportive project development costs		29,222.45	13,535.75
Total EDCTP funded R&D projects		**273,662.47**	**438,199.42**
Executive administration			
Executive administrative management cost		**458,847.09**	**31,658.83**
Total executive administration		**458,847.09**	**31,658.83**
Total of all projects related expenditure	**(b)**	**7,283,319.43**	**5,764,435.62**

(a) Breakdown of R&D	2016	2015
1 - Project development	435,737.24	431,737.80
2 - Process development	4,224.86	8,023.93
3 – Pre-clinical	290,399.87	853,091.74
4 - Clinical trials	666,576.40	2,099,112.74
5 - Other support services	1,018.96	7,286.74
6 - International collaboration	17,533.83	168,458.02
7 - Quality Assurance	10,142.91	32,127.65
Total	**1,425,634.07**	**3,599,838.62**

(b) Breakdown R&D coordination expenditure for preclinical and clinical activities costs per purpose in 2016 – value of above €5,000

Category 1 – Project Development

Projects	Partners	Expenditure 2016
MVDVax	NEKKA	60,912.05
SEmalvac	CNRFP	282,832.00
SEmalvac	Pharmalys	14,000.00

Category 3 – Pre-clinical

Projects	Partners	Expenditure 2016
PRIMALVAC	Inserm	202,500.00
SEmalvac	LSTHM	16,003.00

Category 4 – Clinical trial

Projects	Partners	Expenditure 2016
PAMCPH	University of Copenhagen	15,000.00
PRIMALVAC	Inserm	440,332.54
PlacID	NIH/NIAID	204,100.00

(c) Presentation of EVI expenditures per nature of expenses (EUR)	2016	2015
Payables - EVI program related	1,070,009.18	2,751,281.64
Payables - EDCTP program related	244,440.02	366,258.74
Payables – EU & IMI program related	3,901,410.33	926,054.88
Salary costs (also includes in house consultants)	1,329,316.36	1,141,839.07
Contract service expenses	209,551.37	149,699.46
Facility & equipment maintenance expenses:	112,803.37	89,651.81
Equipment, hardware & software	18,127.03	15,125.93
Travel & meetings expenses:	182,335.57	214,867.22
Other direct expenses:	16,039.10	19,536.24
Indirect business expenses:	186,020.02	71,885.86
Board, BoS and SAC expenses:	10,791.47	15,480.76
EU ISAC, SAC and SC expenses:	2,475.61	2,754.01
Total expenses	**7,283,319.43**	**5,764,435.62**

Note 9

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

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/16	Changes 2016	Quantity 31/12/16
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	EVIy002	1,378	(156)	1,222
NOVALABS	EVIy003	Adjuvant	Alhydrogel Line B	EVIy002	1,410	(20)	1,390
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line A	EVIc001	1,878	(130)	1,748
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line B	EVIc001	1,849	(44)	1,805

Independent auditor's report

FALK & Co

INDEPENDENT AUDITOR'S REPORT

To: European Vaccine Initiative EWIV, 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 EWIV as at 31 December 2016.

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 2016 of European Vaccine Initiative EWIV, Heidelberg, dated 2 May 2017.

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 EWIV as at 31 December 2016 in accordance with IFRS as endorsed by the EU relevant to preparing such Financial Presentation.

Heidelberg, 9 May 2017

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
B	**BCG**	Bacillus Calmette-Guérin
	BELLEROPHON	A project combining cellular and humoral immune responses as a vaccine strategy against the pathogen *S. aureus*
	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
	BoS	Board of Stakeholders
	BPRC	Biomedical Primate Research Centre
C	**CEA**	Commissariat à l'énergie atomique et aux énergies alternatives
	CBF	Clinical Biomanufacturing Facility
	CERMEL	Centre de Recherches Medicales de Lambarene
	CFU	Colony Forming Units
	ChAd	Chimpanzee Adenovirus
	CHUV	Centre hospitalier universitaire vaudois
	CIC	Centre d'investigation clinique
	CNRFP	Centre national de recherche et de formation sur le paludisme
	CpG	Cytosine triphosphate deoxynucleotide phosphodiester link to Guanine triphosphate deoxynucleotide DNA
	CRO	Contract Research Organisation
	CRSN	Centre de Recherche en Santé de Nouna
	CSA	Chondroitin Sulfate A
	CSP	Circumsporozoite Protein
	CVI	Central Veterinary Institute
D	**DBL**	Duffy-Binding-Like
	DGIS	Directorate General for International Cooperation at Ministry of Foreign Affairs, The Netherlands
	DiCo	Diversity Covering
	DNA	Deoxyribonucleic Acid
	DSMB	Data Safety Monitoring Board
	DSW	Deutsche Stiftung Weltbevölkerung
E	***E. coli***	*Escherichia coli*
	EATRIM	Infrastructure in Medicine
	EDCTP	European and Developing Countries' Clinical Trials Partnership
	EDQM	European Directorate for the Quality of Medicines & HealthCare
	EDUFLUVAC	Educate Influenza Vaccine
	EEIG	European Economic Interest Grouping
	EFPIA	European Federation of Pharmaceutical Industries and Associations
	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
	Fraunhofer IME	Fraunhofer Institute for Molecular Biology and Applied Ecology
	FRMC	Financial Risk Management Committee
G	**GAAP**	German General Accepted Accounting Principles
	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
	HPLC	High Performance Liquid Chromatography
	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
	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
	IRSS	Institut de Recherche en Sciences de la Santé
K	**kDa**	Kilodalton
	KE	Kenya
	KEMRI	Kenya Medical Research Institute
	KfW	Kreditanstalt für Wiederaufbau
	KHRC	Kintampo Health Research Centre
L	**LMIC**	Low- and Middle-Income Countries
	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
	MN	MicroNeutralisation virus assay
	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
	MV	Measles Vector
	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
	NGO	Non-governmental organisation
	NHP	Non-Human Primates
	NIBSC	National Institute for Biological Standards and Control
	NID	Neglected Infectious Disease
	NIH/NIAID	National Institutes of Health / National Institute of Allergy and Infectious Diseases
O	**ODN**	Oligodeoxynucleotides
	OMCL	Official Medicines Control Laboratories
	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
	PEI	Paul-Ehrlich Institute
	Pf	*Plasmodium falciparum*
	PfAMA1	*Plasmodium falciparum* Apical Membrane Antigen 1
	PfEBA-175	*Plasmodium falciparum* Erythrocyte-Binding Antigen-175
	PfEMP1	*Plasmodium falciparum* Erythrocyte Membrane Protein-1
	PfMSP	*Plasmodium falciparum* Merozoite Surface Protein
	PfRH5	*Plasmodium falciparum* Reticulocyte-binding protein Homologue 5
	PhD	Doctor of Philosophy
	PIM	Paratyphoid Infection Model
	PlacID	Modelling Placental Infection and Disease
	PlacMalVac	Clinical development of a VAR2CSA-based placental malaria vaccine candidate
	PNL	Profit and Loss
	PPC	Preferred Product Characteristics
	PRIMALVAC	Recombinant VAR2CSA protein as vaccine candidate for placental malaria
	PSC	Project Steering Committee
R	**R**	Programming language and software environment for statistical computing and graphics
	R&D	Research and Development
	R21	Circumsporozoite protein particle
	RI	Research Infrastructure
	RIMD	Research Institute for Microbial Diseases

	RIVM	National Institute for Public Health and the Environment
	RTS,S	The RTS,S vaccine was engineered using genes from the repeat and T-cell epitope of Pf malaria CSP, a hepatitis B virus envelope protein (HBsAg) and a chemical adjuvant to boost the immune response
S	***S. aureus***	*Staphylococcus aureus*
	S. paratyphi A	*Salmonella enterica* serovar *paratyphi A*
	SAC	Scientific Advisory Committee
	SE	Stable Emulsion
	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
	TLR	Toll-Like Receptor
	TRANSVAC	European Network of Vaccine Research and Development
U	**UAC**	Université d'Abomey-Calavi
	UCAD	Université Cheikh Anta Diop
	UCPH	University of Copenhagen
	UK	United Kingdom
	UNIL	University of Lausanne
	UOXF	University of Oxford
	UPMC	Université Pierre et Marie Curie
	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	**WBVR**	Wageningen Bioveterinary Research
	WP	Work Package
	WHO	World Health Organization

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