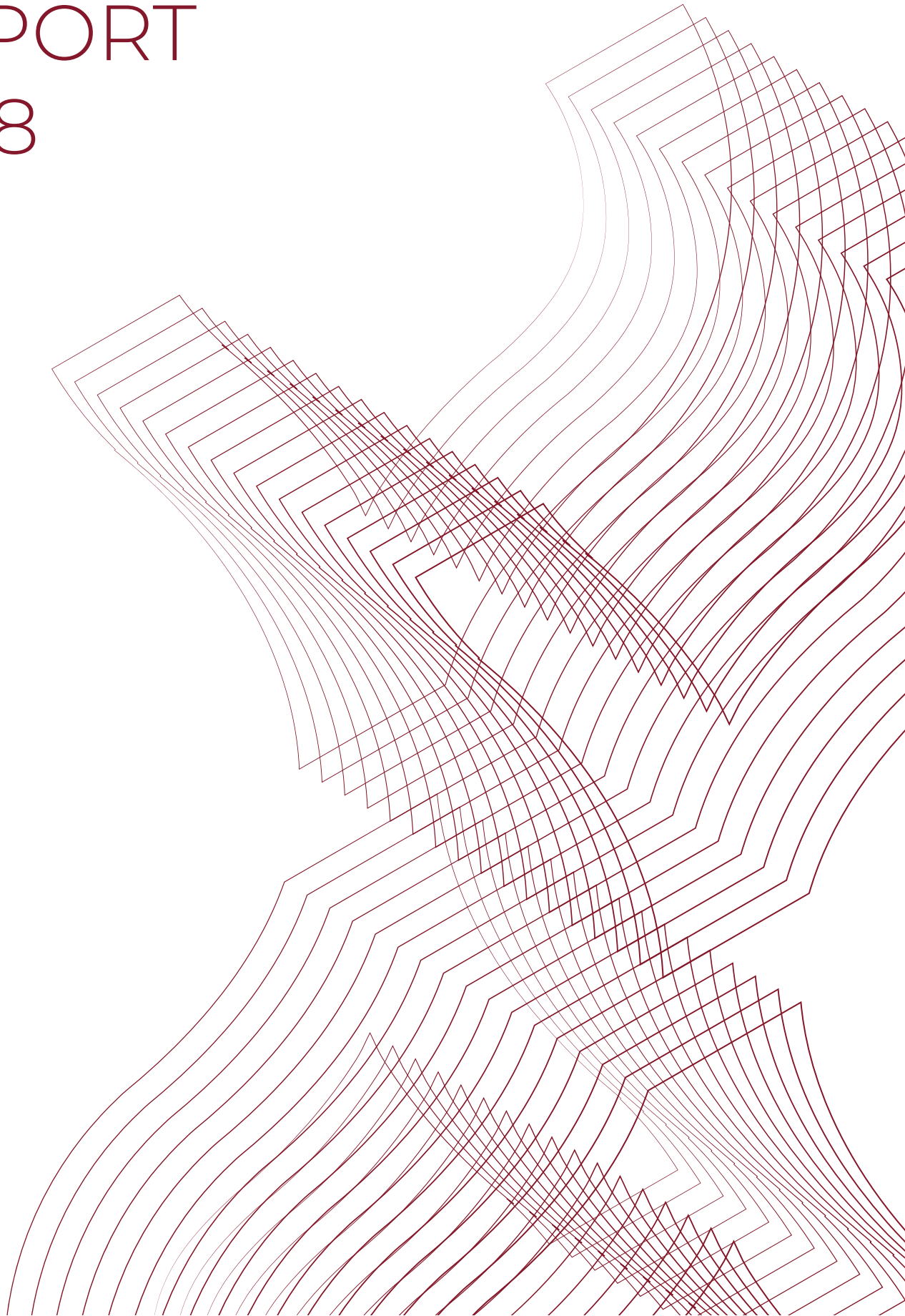
EUROPEAN VACCINE INITIATIVE

ANNUAL REPORT 2018



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FOREWORD

by Clemens Kocken

Without any doubt, this year´s major highlight for EVI has been the celebration of the organisation´s 20th anniversary. EVI´s origin goes back to 1998 when it was established as the European Malaria Vaccine Initiative (EMVI). Later, in 2009, in the context of a strategic revision combined with the move to Heidelberg, EVI acquired its new name and broader mission.

Thanks to this progressive change and with crucial support from many people throughout these years, EVI has left its teenager years behind. It is a mature organisation, trusted and respected by funders, policy and decision makers and other stakeholders alike in its mission to accelerate the development of vaccines for infectious diseases that threaten global health.

It is therefore my special pleasure to share with you the EVI Annual Report 2018, a year that beyond EVI´s anniversary offered plenty of other achievements that deserve highlighting here.

To start with, EVI was awarded a new grant from EDCTP surrounding the clinical development of a therapeutic vaccine for prevention of post Kala-azar dermal leishmaniasis, a project that receives additional co-funding from the Wellcome Trust. Moreover, EVI is partner in a second grant awarded by EDCPT in 2018 coordinated by our long-standing partner University of Oxford that aims to conduct a series of coordinated clinical trials related to the development of high-efficacy multi-stage malaria vaccines.

Regarding other vaccine candidates in EVI´s portfolio, three vaccine candidates finished phase I clinical trials in 2018. An age-de-escalation phase Ib clinical trial of the BK-SE36 vaccine candidate in exposed children was completed in Burkina Faso, and the results indicate that the vaccine is well tolerated and immunogenic. Also, two vaccines against placental malaria supported by EVI - PRIMVAC and PAMCPH/PlacMalvac - concluded their phase Ia/b clinical trials. Both vaccine candidates could be shown to be safe and well-tolerated, discussions are currently ongoing regarding the further development of these vaccines.

Concerning LEISHDNAVAX, the second vaccine against leishmaniasis that already formed part of the EVI portfolio, the preclinical studies related to the assessment of the prophylactic and therapeutic effect against cutaneous leishmaniasis of this vaccine further advanced during 2018. Results that will be obtained during 2019 should inform the decision of whether or not to prepare the conduct of a phase I clinical trial in Europe.

Finally, the immunogenicity and efficacy of a lead vaccine candidate for the Zika virus were assessed in a non-human primate challenge model. A phase I clinical trial of this vaccine candidate is foreseen to start in mid-2019.

Although on a global level the burden of disease caused by infectious diseases is declining, they remain a major threat. In Africa, for example, infectious diseases are still a major cause of disease and death, and worldwide the threats from emerging infectious diseases and from increasing antimicrobial resistance are growing.

The urgent need for vaccines to address such challenges therefore remains. I am convinced that by strengthening and accelerating future vaccine innovation also during its third decade of existence, EVI will make its proper and important contributions to tackling these issues.

GLOBAL PARTNERS MAP

EUROPE

Austria
Belgium
Denmark
France
Germany
Ireland
Italy
Luxembourg
Norway
Spain
Sweden
Switzerland
The Netherlands
United Kingdom

NORTH AMERICA

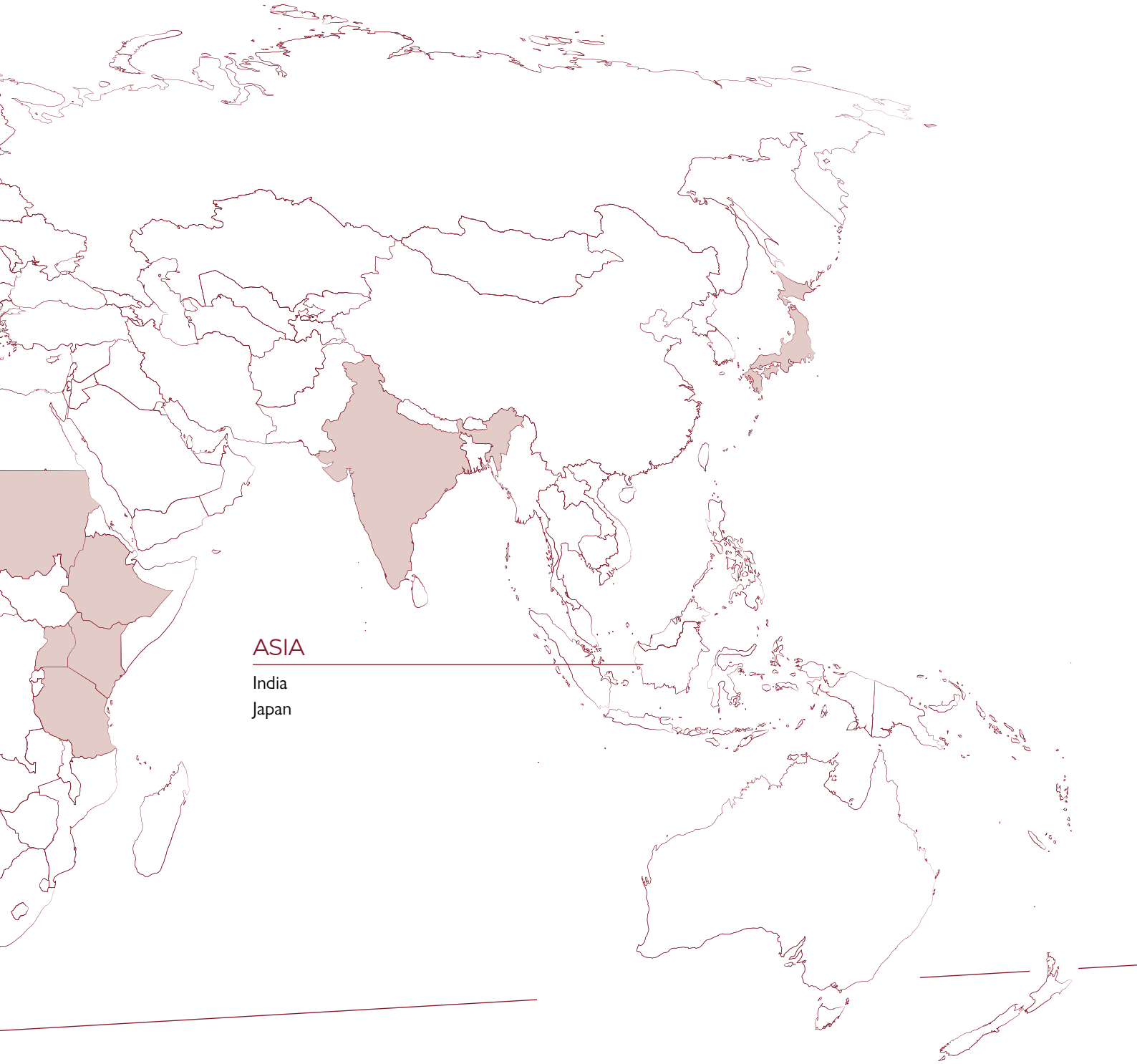
United States

SOUTH AMERICA

Columbia

AFRICA

Benin
Burkina Faso
Ethiopia
Gabon
Ghana
Guinea
Kenya
Mali
Nigeria
Senegal
Sierra Leone
Sudan
Tanzania
The Gambia
Uganda



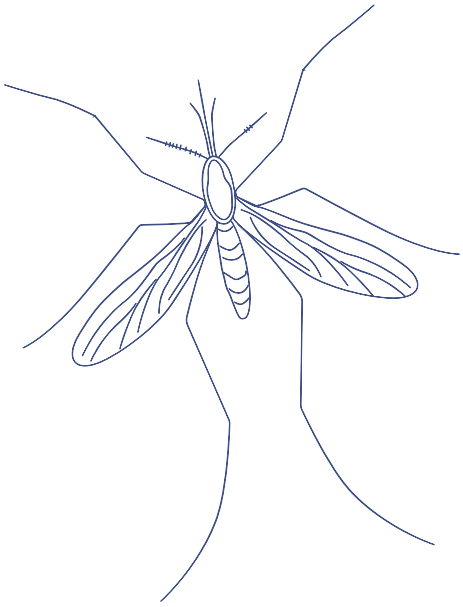
ASIA

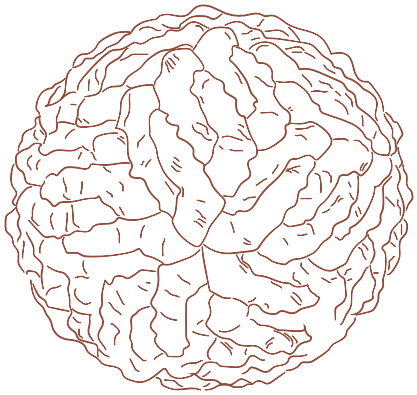
India
Japan

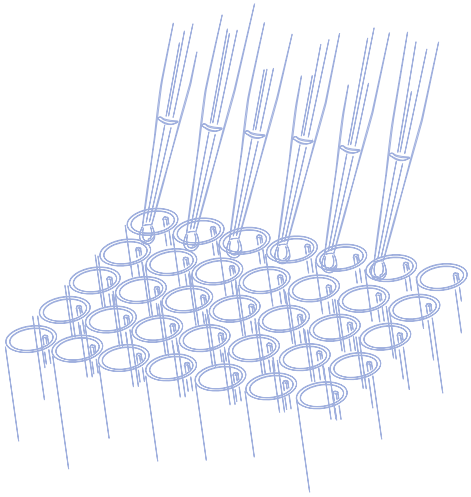
EVI'S 20TH ANNIVERSARY SYMPOSIUM

This year marked EVI's 20th anniversary, an event we duly celebrated with a symposium in Heidelberg in November 2018. Since its beginning in Bergen, Norway, EVI has come a long way. Initially only concentrating on malaria, since then we have broadened our scope and built a portfolio that addresses critical challenges and opportunities related to vaccine research and development for a variety of diseases of poverty and emerging infectious diseases. In addition to malaria, EVI is currently working on vaccines for influenza, Zika and leishmaniasis, and we are implementing several cross-cutting projects highly relevant for vaccine research and development at large.

The anniversary symposium allowed for a look back on EVI´s history, but the programme was also designed to show and explore where EVI may go in the future. The programme encompassed several key aspects in vaccine development: from novel vaccine concepts and emerging technology, to innovative clinical trial designs and controlled human infection models as tools to accelerate efficacy testing, emerging and pandemic infectious diseases and lastly the "One Health" concept.



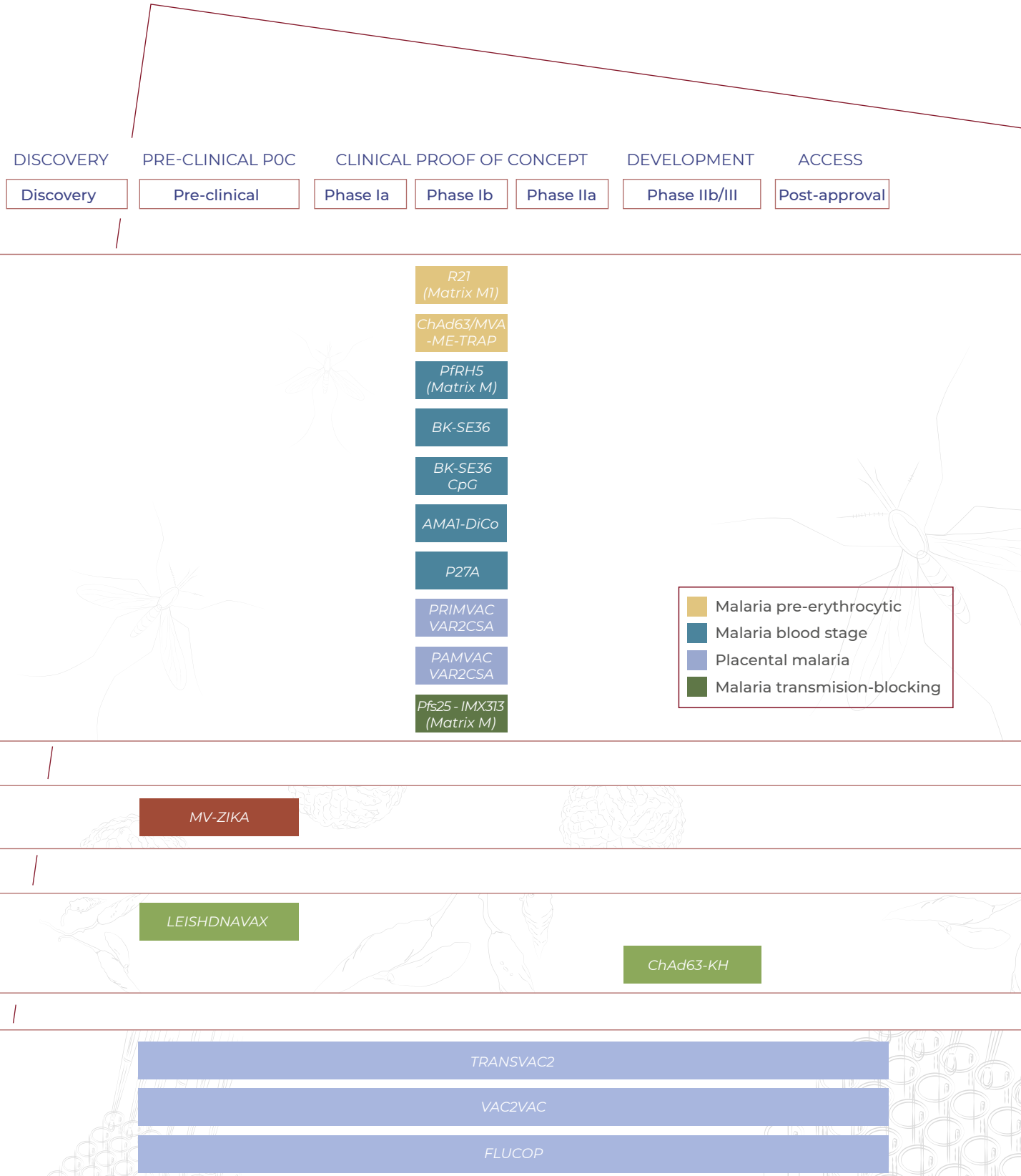




EVI PORTFOLIO

Malaria
Leishmaniasis
Viral
Cross cutting

2018 EVI VACCINE PROJECTS



KEY ACHIEVEMENTS IN 2018

MALARIA

ZIKA

LEISHMANIASIS

CROSS CUTTING

Malaria Vaccines

Blood-stage malaria vaccines: BK-SE36 and PfRH5

BK-SE36

The age-de-escalation phase Ib clinical trial of BK-SE36 vaccine candidate in exposed children aged 1–5 years analysis is completed. The results indicate that the BK-SE36 vaccine is well tolerated and immunogenic. The BK-SE36/CpG phase Ib age de-escalation trial commenced in May 2018 with the immunisation of adults, and, following a safety review, progressed toward the immunisation of children aged 5 to 10 years old in December 2018.

PfRH5

After the initial successful assessment of virally vectored PfRH5, the next generation PfRH5 based vaccines have entered clinical trials. Within the EDCTP-funded MMVC project (2018 – 2023), the preparation of a phase I/II clinical trial was initiated in 2018, with the start of the clinical trial in Tanzania in 2019.

Placental malaria vaccines: PAMVAC, PRIMVAC

The development of placental malaria vaccines has been advanced to major milestones by the research groups led by Thor Theander and Morten Nielsen in Denmark, Benoit Gamain in France, and Patrick Duffy in the USA.

PAMVAC and PRIMVAC

The PAMCPH/PlacMalvac project aimed at conducting 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 results obtained in non-exposed German volunteers indicate that PAMVAC is safe and well tolerated at all tested formulations and dosages. PAMVAC induces functional antibodies that persist for more than six months. PAMVAC in GLA-SE is superior to Alhydrogel and GLA-LSQ formulations. The results were published in January 2019.

A pre-clinical manuscript on the PRIMAVAC vaccine candidate down-selection was published in NPJ Vaccines in 2018. The preliminary results of the phase Ia/b clinical trial assessing the safety and immunogenicity of the placental malaria vaccine candidate PRIMVAC adjuvanted with Alhydrogel or GLA-SE in France and Burkina Faso, were presented at various international conferences in 2018, e.g. the MIM conference, the EDCTP Forum and the ASTMH. The follow-up period was one year. Preliminary data suggest that adjuvanted PRIMVAC was safe and well tolerated in all cohorts and induced functional antibodies. As for PAMVAC, PRIMVAC adjuvanted with GLA-SE induced better immune responses. Publication of the clinical trial results is envisaged for 2019.

In PlacID, EVI is also supporting the development of a non-human primate (NHP) model for placental malaria at NIH/NIAID in the USA. PAMVAC, PRIMVAC as well as a placental malaria vaccine candidate from NIH/NIAID were assessed in a comparative vaccination study. Pre-liminary results in this animal study confirm the results of the phase I clinical trials and will inform future phase II clinical studies.

Pre-erythrocytic malaria antigens: R21

The pre-erythrocytic malaria vaccine candidate R21 is based on the circumsporozoite protein fused to the Hepatitis B surface antigen to produce virus like particles. First clinical trials in adults in the UK and Burkina Faso with R21 adjuvanted with Matrix M have shown promise in terms of safety, immunogenicity and efficacy. The preparation of 1) an age-de-escalating clinical trial in Kenya and 2) a phase I/II efficacy trial in 5-17month old children in Burkina Faso assessing Matrix M adjuvanted R21 was initiated in 2018, with starts of the clinical trials in 2019; as part of the MMVC project.

Transmission-blocking vaccine: Pfs25

Within MMVC, the direct membrane feeding assay was further evaluated as a tool to determine efficacy of transmission blocking vaccines at IRSS in Burkina Faso. The next generation transmission blocking vaccines are expected to induce higher antibody titres leading to functional transmission blocking activities. Adjuvanted Pfs25 will enter clinical trials in this programme in 2020/2021 only.

Leishmaniasis Vaccines

LEISHDNAVAX

LEISHDNAVAX is a candidate DNA vaccine against leishmaniasis that has been successfully tested for antigenicity in humans in ex vivo studies, and for efficacy in a mouse model for visceral leishmaniasis. The partners of the current LEISHDNAVAX GHIT-funded project are now completing the preclinical development to assess the vaccine prophylactic and therapeutic effect against cutaneous leishmaniasis and will prepare a phase I trial in Europe to test safety and immunogenicity of the vaccine in humans.

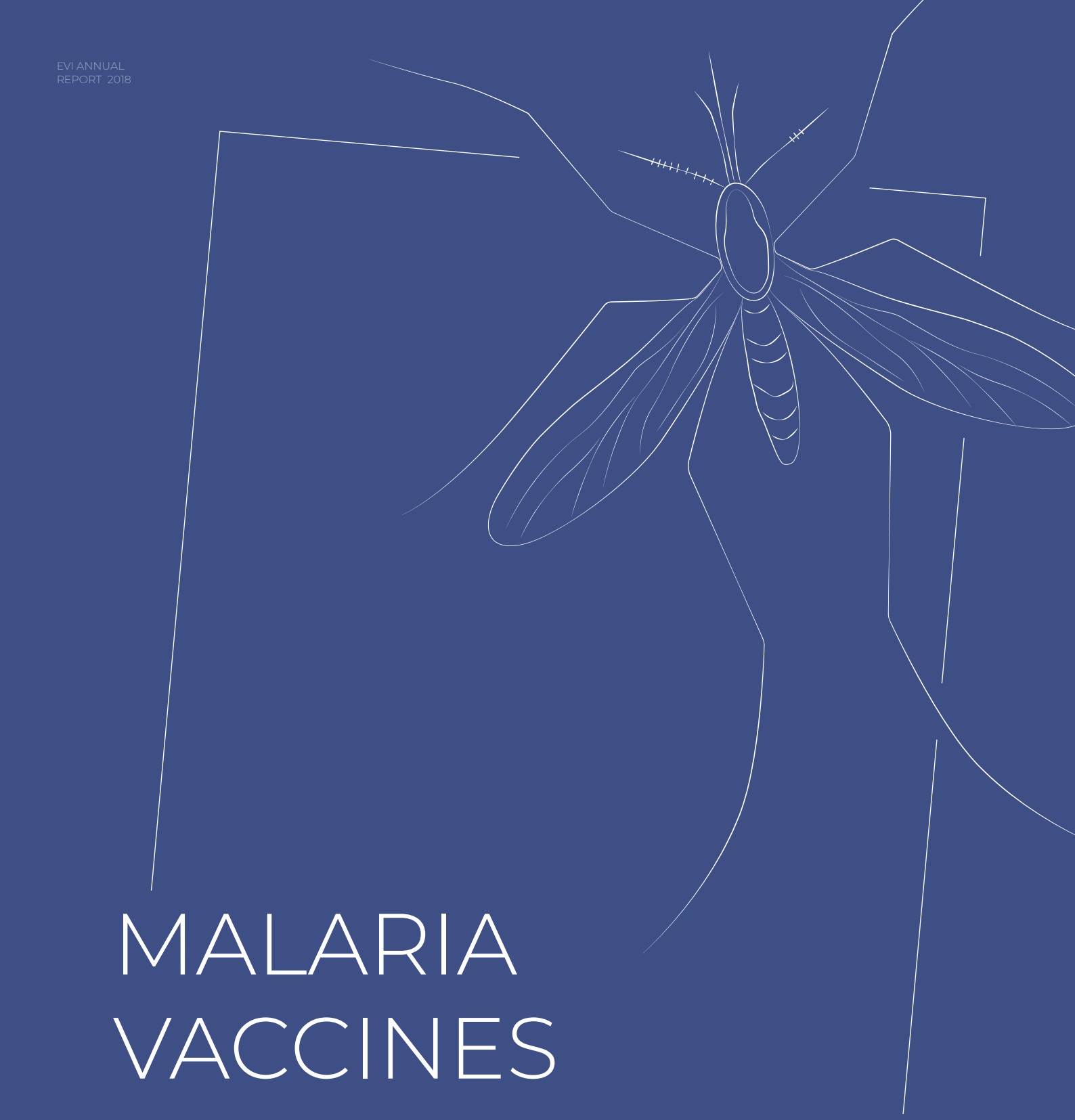
PREV_PKDL

In April 2018 EVI has started a new partnership under the EDCTP2-funded project PREV_PKDL to advance the clinical development of a promising vaccine candidate, ChAd63-KH, to prevent post kala azar dermal leishmaniasis (PKDL). This vaccine has already been shown to be safe, well tolerated and able to induce a good immune response in healthy subjects and is currently in a further safety study in Sudanese PKDL patients. The project aims at conducting a phase II trial in Sudan to evaluate the safety and efficacy of the vaccine in patients diagnosed with and treated for visceral leishmaniasis. The project partners also plan to conduct research studies in different endemic countries (Sudan, Ethiopia, Kenya and Uganda) to better understand the pathogenesis of the disease and the underlying immune mechanisms. The results of these studies, and the development of research capacity for monitoring immune responses, will help to underpin future research and product evaluation.

Viral Vaccines

ZIKAVAX

In October 2016, EVI and partners embarked on the development of a safe and effective preventive vaccine against Zika virus infection. The vaccine concept is based on the use of the measles vector (MV) as a delivery platform technology for the Zika antigen(s). Preclinical studies were conducted in order to down select the vaccine candidates that were subsequently evaluated for immunogenicity and efficacy in the mouse model. Immunogenicity and efficacy of the lead vaccine candidate are currently assessed in a non-human primate challenge model for Zika virus infection that was established at CEA. A phase I clinical trial will start in Mid-2019.



MALARIA VACCINES

The malaria parasites of the genus *Plasmodium* are transmitted by the bite of an infected female *Anopheles* mosquito. Symptoms usually begin ten to fifteen days after transmission and typically include fever, chills, tiredness, vomiting, and headaches, ranging from absent or very mild symptoms to severe disease and even death. In general, malaria is a curable disease if diagnosed and treated promptly and correctly. Left untreated, patients may develop severe complications and die. Life-threatening complications may include e.g. pulmonary oedema leading to breathing difficulties, kidney failure, abnormal liver function leading to jaundice and liver failure, aplastic anaemia and severe infection of the brain (cerebral malaria), with seizures, confusion, and increasing tiredness leading to coma and death. Immunity to *P. falciparum* malaria only develops slowly and leads to partial and short-lived immunity in response to repeated infections.

Epidemiology and disease burden

Despite intensive control efforts over the past decade, malaria remains one of the most significant global public health problems. In 2017, an estimated 219 million cases of malaria occurred worldwide (95% confidence interval [CI]: 203–262 million), compared with 239 million cases in 2010 (95% CI: 219–285 million) and 217 million cases in 2016 (95% CI: 200–259 million)[1]. Although there were an estimated 20 million fewer malaria cases in 2017 than in 2010, data for the period 2015–2017 highlight that no significant progress in reducing global malaria cases was made in this timeframe. In 2017, there were an estimated 435,000 deaths from malaria globally, compared with 451,000 estimated deaths in 2016, and 607,000 in 2010. The WHO African Region accounted for 93% of all malaria deaths in 2017. 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 with severe potential impact on the developing foetus.

Control measures & prevention

Malaria is a preventable disease and effective interventions are available. Current malaria control strategies rely on the use of insecticide treated bed nets and indoor residual spraying to limit human contact with vectors, combined with early detection and treatment of malaria patients. Over the past couple of decades, a significant reduction in transmission rates and malaria incidence was observed due to the implementation of these malaria control measures. However, these control measures need to be applied continuously, are resource-intensive and do not reach all in need. According to WHO's World Malaria Report 2018, 15.7 million children in 12 countries in Africa's Sahel subregion were protected through seasonal malaria chemoprevention (SMC) programmes in 2017. However, about 13.6 million children who could have benefited from this intervention were not covered, mainly due to a lack of funding, 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 currently used malaria therapy[2]. While other antimalarial drugs are in development, *P. falciparum* parasites have become resistant to every drug used routinely so far, indicating 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 efforts to the eliminate and ultimately eradicate malaria.

Vaccine landscape

Despite many malaria vaccines having entered clinical development over the last decades, the highly polymorphic nature of many *P. falciparum* proteins results in significant challenges to vaccine design. Novel strategies in vaccine design will therefore be required to meet the strategic goal set in the Malaria Vaccine Technology Roadmap[3] to licence vaccines targeting *P. falciparum* and *P. vivax* i) with a protective efficacy of at least 75% against clinical malaria suitable for administration to appropriate at-risk groups in malaria-endemic areas, and ii) reducing transmission of the parasite and thereby substantially the incidence of human malaria infection.

The vaccine candidates currently under development target different parasite stages within the malaria lifecycle. Vaccine candidates are directed against the pre-erythrocytic stages including sporozoites and liver-stages, and the blood-stages that are replicating within the erythrocytes, in addition to vaccine candidates that target antigens on sexual stages, the so-called transmission-blocking vaccines.

1. World Health Organization, "World Malaria Report 2018" (2018).
2. F. Arieyet al., A molecular marker of artemisinin-resistantPlasmodium falciparummalaria.Nature505, 50-55 (2014).
3. Malaria Vaccine Technology Roadmap (2013): http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1

Vaccines that prevent malaria infection: pre-erythrocytic malaria vaccines

Malaria vaccines targeting the **pre-erythrocytic stages** are designed to prevent sporozoite 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.

The pre-erythrocytic malaria vaccine RTS,S (Mosquirix™) developed jointly by the Malaria Vaccine Initiative (MVI PATH) and GSK is the most advanced malaria vaccine. To assess the vaccine's protective effect in real-life settings, the RTS,S vaccine will be rolled out in pilot implementation projects in Ghana, Kenya and Malawi in 2019. A similar approach based on the R21 malaria vaccine candidate adjuvanted with Matrix M is currently developed by the University of Oxford and collaborators. Another approach, which has provided some evidence for significant efficacy is immunisation with irradiated sporozoites. Attempts to increase the efficacy against heterologous strains and the duration of protection are underway.

In 2018, the pre-erythrocytic vaccine development in which EVI was involved was developed in the context of the MMVC project. For more details please refer to the corresponding project description under section "Multi-component malaria vaccines" in this annual report (p. 17).

Vaccines that prevent mortality and morbidity: blood-stage malaria vaccines

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. They 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[4]. Vaccines are expected to induce neutralising antibodies that i) prevent interactions between ligands of the invasive blood-stage merozoite and protein receptors present on the host red blood cell surface[5]; ii) prevent the interaction of the parasite antigens displayed on the red blood cell surface with host cell receptors[6]; iii) recognise antigens that get exposed upon parasite egress[7] and/or iv) activate monocytes that inhibit parasite growth[8]. Studies in humans and animals have shown that controlling parasite density can reduce the generation of gametocytes in the bloodstream, thus also limiting transmission.

However, the development of an effective blood-stage malaria vaccine has proved challenging due to the polymorphic nature of most antigens. Recently, the *Plasmodium falciparum* blood-stage vaccine RH5.1/AS01B has shown promise in a 'Safety, immunogenicity and efficacy in a Phase I/IIa clinical trial' with efficacy assessment after controlled human malaria infection (ClinicalTrials.gov Identifier: NCT02927145). Vaccine candidates based on PfRH5 will be further developed within MMVC. Other blood-stage vaccines under development by EVI include the development of the recombinant SE36 antigen (SEmalvac/SEmalvac2) and a synthetic peptide (P27A).

SEmalvac

Blood-stage malaria vaccine

Description

The SEmalvac project aims at advancing the clinical development of the *P. falciparum* serine repeat antigen-5 (SERA5), a blood-stage antigen that plays an essential role in the parasite life cycle and is physiological substrate for a serine protease involved in parasite egress. The SERA 5 has been recently described as playing a role in the molecular camouflage of the *P. falciparum* merozoite[9].

The N terminal domain of the SERA5 (SE36) was selected as blood stage malaria vaccine on the basis of the following results:

- 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.

The recombinant form of SE36 was produced in E. coli and formulated with aluminium hydroxide gel to yield the BK-SE36 vaccine. The safety and immunogenicity of the BK-SE36 vaccine was demonstrated in a phase Ia clinical trial in malaria-naïve Japanese adults and in a phase Ib clinical trial conducted in healthy subjects aged 6–32 years from a malaria-endemic area in Northern Uganda[10].

4. Goodman A.L. et al. Ann Trop Med Parasitol 2010, doi:10.1179/136485910X12647085215534.
5. Wright G.J. and Rayner J.C. PloS Pathogens 2014, doi:10.1371/journal.ppat.1003943.
6. Chan J.A. et al. Cell Mol Life Sci. 2014, doi:10.1007/s00018-014-1614-3.
7. Kulangara C. et al. PLOS ONE 2012, doi:10.1371/journal.pone.0046112.
8. Olugbile S. et al. Infection and Immunity 2009, doi:10.1128/IAI.00652-09.
9. Tougan T et al.2018 Scientific Reports | (2018) doi:10.1038/s41598-018-23194-9
10. Palacpac NM et al..PLoS ONE. 2013 doi:10.1371/journal.pone.0064073

The main objective of the SEmalvac project supported by the GHIT Fund ($999,999) and by Nobelpharma Co., Ltd ($500,000) was to assess the safety and immunogenicity of the BK-SE36 vaccine candidate in healthy malaria exposed African children aged 1-5 years living in Burkina Faso. This phase Ib trial will allow to test the vaccine in a younger age group (1-5 years), generate additional data on safety, immunogenicity and allow comparison of clinical trial results from two countries with different malaria endemicity - Uganda (previous clinical trial) and Burkina Faso. The trial was a double blinded, randomized, controlled, age de-escalating, phase Ib trial using either intramuscular or subcutaneous vaccination of BK-SE36 vaccine (100 µg SE36 and 1000 µg aluminium). The participants aged 12-24 months or 25-60 months received the vaccine on three occasions and were followed for one year.

A second objective of the SEmalvac project is to conduct a one year follow-up study of Japanese volunteers that participated in the first-in-man phase Ia trial of BK-SE36 vaccine combined with CpG-ODN (K3) adjuvant that is expected to enhance immune response, to assess the vaccine long term safety and immunogenicity. The phase Ib clinical trial was completed in 2017 and data analysis was completed in 2018

Recent achievements

The recombinant *E. coli* malaria antigen SE36 adsorbed onto aluminium hydroxide gel in the BK-SE36 vaccine was manufactured at BIKEN (Japan).

An age de-escalating phase Ib clinical trial was designed to assess the safety and immunogenicity of the BK-SE36 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 Co Ltd. (Japan). The clinical trial is registered on www.pactr.org (PACTR201411000934120).

The clinical trial results indicate that the BK-SE36 vaccine is well tolerated and immunogenic. A statistical report has been prepared during 2018. The integrated clinical report will be finalised in 2019.

The results support the continuation of the clinical development of the BK-SE36/CpG in children living in malaria endemic regions, the target population of the vaccine.

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 Co, Ltd, Japan*
- *Pharmalys, United Kingdom/Senegal*
- *London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom*

Outreach and communication

Article:
Tougan T, Edula JR, Takashima E, Morita M, Shinohara M, Shinohara A, Tsuboi T, Horii T. Molecular Camouflage of Plasmodium falciparum Merozoites by Binding of Host Vitronectin to P47 Fragment of SERA5. *Sci Rep. 2 018 Mar 22;8(1):5052. doi: 10.1038/s41598-018-23194-9.*

Conference presentations:
Edith C. Bougouma presented "Safety and Immunogenicity of the malaria vaccine candidate BK-SE36 in young children living in Burkina Faso" on 17 April 2018 at 7th MIM Pan African Malaria Conference in Dakar, Senegal.

Alfred B. Tiono presented a poster entitled "A study to evaluate the safety and immunogenicity of the malaria vaccine candidate BK-SE36 in young children naturally exposed to malaria transmission in Burkina Faso" on 1-5 July 20181 at the Malaria World Congress in Melbourne, Australia

Edith C. Bougouma presented "Safety and Immunogenicity of the malaria vaccine candidate BK-SE36 in young children living in Burkina Faso" EDCTP forum, on 18 September 2018, Lisbon, Portugal

Toshi Horii presented "Pushing ahead for the blood-stage malaria vaccine SE36" at EVI 20th anniversary on 20 Nov 2018 in Heidelberg, Germany.

SEmalvac2

Blood-stage malaria vaccine

Description

The SEmalvac2 is the continuation of the clinical development of the SE36 vaccine and builds on the SEmalvac project. The project intends at exploring the improvement of the vaccine immunogenicity with the addition of a DNA sequences containing CpG motifs. K3 CpG in non-human primate studies was identified as an effective TLR9 ligand that can induce both humoral and cellular immunity when compared to BK-SE36 alone[11]. The use of K3 CpG may be one approach to broaden immune responses and may overcome immune tolerance or help immunocompromised individuals through the activation of multiple innate receptors that could target redundant pathways of innate responsiveness[12]. The BK-SE36 vaccine mixed with K3 CpG (BK-SE36/CpG) vaccine was assessed in a phase Ia clinical trial in healthy adults in Japan and was found safe and elicited antibody titres 3-4-fold higher than BK-SE36 alone. Sera of vaccinated volunteers inhibited *in vitro* parasite growth.

The SEmalvac2 project, supported by GHIT ($2,781,588) and by Nobelpharma Co, Ltd, aims at assessing the safety and immunogenicity of the BK-SE36/CpG vaccine 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 first evaluated in adults aged 21-45 years before proceeding to younger populations of children aged 5-10 years and 12-24 months.

11. Tougan T et al. 2013. Hum Vaccin Immunother. 9(2):283-290.
12. Scheiermann J, Klinman DM. Vaccine. 2014 Nov 12;32(48):6377-89. doi: 10.1016/j.vaccine.2014.06.065

Recent achievements

The malaria antigen SE36 is adsorbed onto aluminium hydroxide gel in the BK-SE36 vaccine manufactured at BIKEN (Japan) and mixed prior to administration with K3 CpG manufactured at Gene Design (Japan).

The age de-escalating phase Ib clinical trial is designed to assess the safety and immunogenicity of the BK-SE36/CpG vaccine in healthy malaria exposed African adults and children living in Burkina Faso. The principal investigator is Dr Sodiomon Sirima (IRSS, Ouagadougou, Burkina Faso) and the sponsor is Nobelpharma Co Ltd. (Japan).
The clinical trial is registered on www.pactr.org (PACTR201701001921166)

The trial commenced in May 2018 with the immunisation of adults, and, following a safety review, progressed toward the immunisation of children aged 5 to 10 years old in December 2018

Partners

- *Institut de Recherche en Sciences de la Santé (IRSS), Burkina Faso*
- *European Vaccine Initiative (EVI), Germany*
- *Research Institute for Microbial Diseases (RIMD), Japan*
- *Nobelpharma Co, Ltd, Japan*
- *Pharmalys, United Kingdom/Senegal*
- *London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom*

Partner Profile

Prof Toshihiro Horii

Toshihiro Horii is currently Professor, Department of Molecular Protozoology and Director, Research Center for Infectious Disease Control of the Research Institute for Microbial Diseases, Osaka University, Japan.

He was awarded his PhD in Physiology from Osaka University (1981) and has more than 170 peer reviewed publications to date. Prof. Horii launched SE36 malaria vaccine development study in 1993 and has since been enthusiastically conducting the project.

He plays an integral role in several professional Japanese societies including the Society of Parasitology, Society of Vaccinology and Society of Tropical Medicine. Prof. Horii is also a recipient of the Koizumi Prize from the Japanese Society of Parasitology (2004) and Masamichi Aikawa Prize from the Japanese Society of Tropical Medicine (2014). Toshihiro Horii and the SEmalvac2 partners along with EVI are pursuing the clinical development of the SE36 vaccine.

Multi-component malaria vaccines

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"[13]. 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[14].

The MMVC project is targeting this multi-component, multi-stage approach based on antigens that have shown promise in clinical trials assessing the single components, e.g. 1) the RTS,S biosimilar R21 that is expected to elicit an improved malaria-specific immune response, 2) 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, 3) the PfRH5 in various formulations and delivery systems, as well as 4) a transmission blocking component that is expected to inhibit the transmission of the parasite from humans to mosquitoes.

13. http://apps.who.int/iris/bitstream/10665/149822/1/WHO_IVB_14.09_eng.pdf
14. Viebig N.K. et al. Vaccine 2015, doi:10.1016/j.vaccine.2015.09.074.

MMVC

Multi-component malaria vaccines

Description

A high-efficacy malaria vaccine is urgently required to reduce the unacceptable burden of malaria mortality and morbidity in Africa and to assist efforts towards malaria elimination. An ideal malaria vaccine would target all stages of the parasite's lifecycle, but no such vaccine has reached clinical trials in Africa.

The "Multi-Stage Malaria Vaccine Consortium: field efficacy testing of a multi-stage malaria vaccine (MMVC)", funded by EDCTP for a duration of 66 months with a total budget of €15m.

The MMVC consortium proposes to develop a multi-stage vaccine which will progress to a large phase IIb efficacy trial in West and East African 5-9 month olds. All four potential components of the vaccine have strong validation. The anti-sporozoite vaccine component, R21, is a next-generation RTS,S vaccine with a simpler but equally potent adjuvant, Matrix M. This recently showed 82% sterile efficacy in a UK phase II sporozoite challenge trial using just 10µg of R21 per dose. The liver-stage vaccine employs adenoviral and MVA vectors that showed good safety and high efficacy in EDCTP-supported African trials. The blood-stage component is the leading conserved PfRH5 antigen that induces high-titre cross-strain neutralising antibodies in phase I trials. The sexual-stage antigen is the conserved Pfs25, multimerised as a nanoparticle thereby enhancing antibody immunogenicity.

MMVC will undertake a tightly co-ordinated series of lead-in trials in 2018-2020 building towards a phase IIb efficacy trial in 5-9 months olds from late 2020 to2023. MMVC will first evaluate in East Africa the efficacy of the vaccine and selected components in controlled human malaria infection trials, availing of this new capacity in Kenya and Tanzania. MMVC will undertake age de-escalation trials of both the R21 component and the combination vaccine documenting safety and immunogenicity, and identifying a preferred deployable immunisation regime, at likely 6, 7 and 9 months of age with a delayed booster. This will lead to a phase IIb trial in infants at sites of differing malaria endemicity in Kenya, Sierra Leone and Burkina Faso. We will measure primarily impact on malaria clinical episodes aiming to meet or exceed the WHO Roadmap target of 75% efficacy.

This consortium, comprising very experienced and new African trial sites with leading northern institutions and companies, offers an unprecedented opportunity for rapid development of a deployable high-efficacy multi-stage malaria vaccine.

· Institut de Recherche en Sciences de la Santé (IRSS), Burkina Faso

EVI is leading work package 5 on capacity strengthening and networking. MMVC's aim is to develop capacity in controlled human malaria infection (CHMI), malaria vaccinology, immunology and clinical trials in East and West African centres. MMVC will build new capacity to test the ability of the combination vaccine and/or its transmission-blocking component to block human-to-mosquito transmission in African adults, foreseeing the potential use of the combination vaccine in elimination campaigns. Three PhD and two Master's course places will be allocated to students at partner field units.

Recent achievements

The kick-off meeting was held in Dakar, Senegal on 14 April 2018. The first nine months of the project were mainly allocated to the preparation of the clinical trial activities in various sites. First MMVC clinical trials will start in 2019. The capacity to conduct direct membrane feeding assays were strengthened in Burkina Faso and will be used to further assess the transmission-blocking component of the vaccine. Planning of short courses and PhD/Master's fellowships has started. PhD fellows will be recruited in 2019.

Partners

- *Oxford University (UOXF), UK including Wellcome-KEMRI Kilifi Programme (KEMRI)*
- *London School of Hygiene and Tropical Medicine (LSHTM), UK including MRC Gambia Unit (MRCG)*
- *Institut de Recherche pour le Développement (IRD), France*
- *European Vaccine Initiative (EVI), Germany*
- *College of Medicine and Allied Health Sciences (COMAHS), Sierra Leone with the National Malaria Control Programme*
- *Ifakara Health Institute (IHI), Tanzania*
- *Institute of Research in Health Sciences (IRSS), Bobo-Dioulasso, Burkina Faso*
- *IRSS, Clinical Research Unit of Nanoro (IRSS-CRUN), Burkina Faso*
- *Groupe de Recherche Action en Santé sarl (GRAS), Ouagadougou, Burkina Faso*
- *Epicentre (part of MSF), France*
- *Novavax AB, Sweden*
- *Serum Institute of India Pvt Ltd (SII), India*
- *Janssen Vaccines and Diagnostics, Netherlands*

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. Every year, more than 100 million pregnant women are at risk of placental malaria. It is estimated that at least 25% of pregnant women are infected with malaria which attribute to more than 20% of all maternal deaths in malaria endemic areas. Globally, malaria infection during pregnancy accounts for over 10,000 maternal and 200,000 neonatal deaths annually[15].

Prevention of placental malaria currently relies on long lasting insecticide treated nets and intermittent preventive treatment during pregnancy (IPTp). However, these interventions only offer partial protection. Women receive their first IPTp dose at their first antenatal visit (between 16-24 weeks' gestation)[16,17,18], but placental parasite tropism is established during the first trimester of pregnancy and parasites cause irreversible damage, probably by impeding placental development, before women access antenatal healthcare. Among 33 African countries that reported on IPTp coverage levels in 2017, an estimated 22% of eligible pregnant women received the recommended three or more doses of IPTp, compared with 17% in 2015 and 0% in 2010[19]. Also, sulfadoxine-pyrimethamine used for IPTp is losing its effectiveness due to parasite resistance. An effective vaccine that prevents *P. falciparum* placental malaria would therefore be an attractive, cost-effective complement to prevent 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. 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[20,21]. This relatively fast acquisition of protection has raised hope that a vaccine for placental malaria can be developed. The variant surface antigen that mediates adhesion of the infected erythrocyte to CSA (VAR2CSA) is the leading candidate for the placental malaria vaccine[22,23]. Women acquire antibodies against VAR2CSA over successive pregnancies as they become resistant to placental malaria[24]. 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.

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.

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PlacMalVac

Vaccine to prevent placental malaria

Description

The conduct of a phase I clinical trial with the PAMVAC vaccine was one objective of the EU funded PlacMalVac project with budget of approximately €5,900,000 (March 2013-February 2017). The phase I clinical trial data collected from the German participants not exposed to malaria were analysed in 2018.

Recent achievements

The phase Ia/Ib clinical trial was staggered randomised, controlled and dose-finding trial. It was designed to assess the safety and immunogenicity of different dosages (20, 50 and 100µg) of the PAMVAC VAR2CSA vaccine in healthy adult subjects not exposed to malaria in Germany and in exposed subjects living in malaria-endemic areas in Benin. The PAMVAC vaccine was mixed prior to administration with aluminium hydroxide (Alhydrogel) or GLA-SE or GLA- Liposome-QS21 formulation (LSQ).

The sponsor was EKUT (Tübingen, Germany) and the principal investigator in Germany was Dr Benjamin Mordmüller (EKUT). Principal investigator in Benin was Dr Saadou Issifou (Institut de recherche clinique du Bénin, Cotonou).

The trial active phase began in Germany in July 2015, proceeded in Benin in March 2016 and ended in August 2017. Each dosage escalation was conditioned by safety assessment performed by an independent safety monitoring board. The results obtained in non-exposed German volunteers indicated that PAMVAC is safe and well tolerated at all tested formulations and dosages. PAMVAC induces functional antibodies that persist for more than six months. PAMVAC in GLA-SE is superior to Alhydrogel and GLA-LSQ formulations. The trial is registered in clinicaltrials.gov (NCT02647489).

Partners

- *University of 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*

Outreach and communication

Article:

Mordmüller B, Sulyok M, Egger-Adam D, Resende M, de Jongh WA, Jensen MH, Smedegaard HH, Ditlev SB, Soegaard M, Poulsen L, Dyring C, Calle CL, Knoblich A, Ibáñez J, Esen M, Deloron P, Ndam N, Issifou S, Houard S, Howard RF, Reed SG, Leroy O, Luty AJF, Theander TG, Kremsner PG, Salanti A, Nielsen MA. First-in-human, randomized, double-blind clinical trial of differentially adjuvanted PAMVAC, a vaccine candidate to prevent pregnancy-associated malaria. Clin Infect Dis. 2019 Jan 10. doi: 10.1093/cid/ciy1140

PRIMALVAC

Vaccine to prevent placental malaria

Description

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. 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 met 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 and will be completed in 2019.

Recent achievements

Recombinant proteins encompassing the VAR2CSA high affinity CSA-binding site were previously generated. Analysis of the functionality and cross-reactivity of the induced antibodies allowed down-selection of the 3D7-DBL1X-2X expressed in *E. coli* as the best antigen to be transitioned to clinical development. Novasep GMP manufactured and released the PRIMVAC drug product. Short-term and accelerated stability studies were performed and long-term stability studies at Novasep indicated the PRIMVAC stability over 36 months. Toxicology studies were conducted by CiToxLAB.

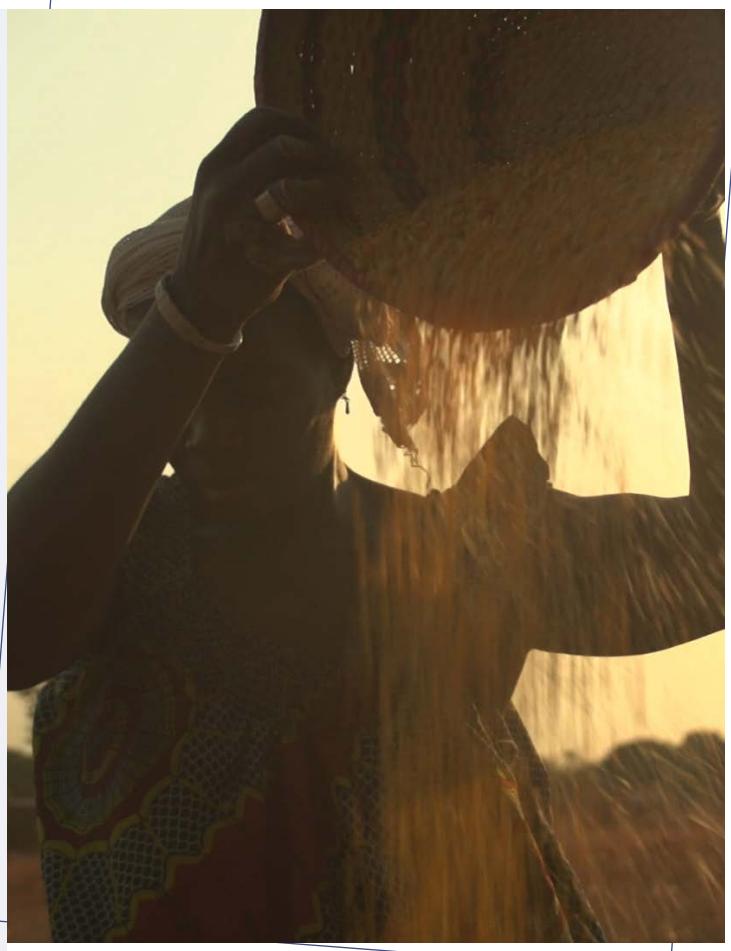
The PRIMALVAC project conducted a phase Ia/Ib clinical trial in healthy adult subjects naïve to malaria and in exposed subjects in malaria-endemic regions of sub-Saharan Africa. The inventor of the vaccine is Dr Benoît Gamain and the sponsor of the clinical trial is Inserm. The coordinating investigator 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).

The clinical trial is designed to assess the safety and immunogenicity of different doses of the recombinant VAR2CSA DBL1-2 vaccine candidate (PRIMVAC) in Alhydrogel® or GLA-SE (IDRI). The primary objective of the study is to evaluate the safety of 3 different dosages (20µg, 50µg and 100µg) of the PRIMVAC vaccine adjuvanted either with Alhydrogel® or GLA-SE, and administered at D0, D28 and D56. Immunogenicity of the vaccine is explored as secondary objective. Within four sequential cohorts, volunteers were randomized in two arms (PRIMVAC adjuvanted with Alhydrogel® or GLA-SE) in the first phase conducted in France and then in three arms (PRIMVAC with Alhydrogel® or GLA-SE or placebo) in Burkina Faso.

The first vaccination of the first subject in France was on 9 May 2016, follow-up was completed in September 2017. The phase Ib clinical trial arm at CNRFP in Burkina Faso started in November 2016. The last subject last visit occurred in September 2018. A total of 68 subjects were recruited in four cohorts receiving three vaccinations with 20, 50 or 100 µg of PRIMVAC adjuvanted with either Alhydrogel or GLA-SE; or placebo at one-month intervals. Preliminary safety and immunogenicity results of the first placental malaria vaccine phase Ia/b clinical trial in France and Burkina Faso were presented at various meetings in 2018. The full data set will be available in 2019. The trial is registered in clinicaltrials.gov: NCT02658253.

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*
- *French Clinical Research Infrastructure Network (F-CRIN), 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*



Outreach and communication

Article:
Chêne A, Gangnard S, Dechavanne C, Dechavanne S, Srivastava A, Tétard M, Hundt S, Leroy O, Havelange N, Viebig NK, Gamain B. Down-selection of the VAR2CSA DBL1-2 expressed in *E. coli* as a lead antigen for placental malaria vaccine development. NPJ Vaccines. 2018 Jul 17;3:28. doi: 10.1038/s41541-018-0064-6.

Conference presentations:
Benoît Gamain presented "Placental Malaria Vaccine: preliminary results of the PRIMALVAC phase Ia/b clinical trial" at the 7th MIM Pan-African Malaria Conference, 15-20 April 2018 in Dakar, Senegal.

Sodiomon Sirima presented "Placental Malaria Vaccine: preliminary results of the PRIMALVAC phase Ia/b clinical trial" at the 1st Malaria World Congress, 1-5 July 2018, Melbourne, Australia.

Benoît Gamain presented "Placental Malaria Vaccine: preliminary results of the PRIMALVAC phase Ia/b clinical trial" at the Ninth EDCTP Forum, 17-21 September 2018, Lisbon, Portugal.

Benoît Gamain presented "Placental Malaria Vaccine: preliminary results of the PRIMALVAC phase Ia/b clinical trial" at the ASTMH 67th Annual Meeting, 28 October – 01 November 2018, New Orleans, USA

PlacID

Vaccine to prevent placental malaria

Description

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 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 was conducted by the biostatistician at the end of 2018 as three monkeys in each of the two groups have reached the endpoint "placental parasitaemia" after caesarean section. The analysis suggested the inclusion of additional animals into the analysis and results are expected in 2019.

In the vaccination study, the placental malaria vaccine candidates PAMVAC, PRIMVAC and the pre-clinical NIH/NIAID vaccine candidate as well as a control antigen were adjuvanted with aluminium hydroxide (Alhydrogel®). The primary endpoint of this study is induction and boosting of functional antibodies. Secondary endpoint is placental parasitaemia. All vaccinations are completed. The majority of monkeys have completed pregnancy with either premature deliveries or caesarean sections allowing to assess the primary endpoint of this study: induction and boosting of functional antibodies by placental malaria infections. Most of the immunological analyses were performed at NIH/NIAID, an unblinded results are expected in 2019.

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.

The PlacID project is a close collaboration of the major teams leading the efforts in developing a placental malaria vaccine. The PAMVAC, PRIMVAC and a preclinical NIH/NIAID vaccine candidate are evaluated side-by-side in the vaccination studies. Reagents and parasite lines were exchanged by the teams and protocols for various assays and data analysis were shared and aligned.

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*

LEISHMANIASIS VACCINES

Leishmaniasis is classified as one of the "most neglected diseases" due to the limited resources invested in diagnosis, treatment, and control, and its strong association with poverty. It represents a severe barrier to socio-economic development. Leishmaniasis is caused by a protozoa parasite from over 20 *Leishmania* species which are transmitted by the bite of infected female phlebotomine sandflies.

There are three main forms of leishmaniasis: **cutaneous leishmaniasis** (CL), **visceral leishmaniasis** (VL, also known as kala-azar), and **mucocutaneous leishmaniasis** (MCL). Whereas cutaneous and mucocutaneous leishmaniasis are chronic and non-life-threatening, visceral leishmaniasis is fatal if left untreated in over 95% of cases. The organ site and the severity of the disease depends on the *Leishmania* species, and host immune status[25].

Post kala-azar dermal leishmaniasis (PKDL), a cutaneous sequela of VL caused by *L. donovani*, develops in some patients alongside but more commonly after apparent cure from VL. It is mainly observed in Sudan and India where it follows treated VL in 50% and 5-10% of cases, respectively[26]. People with PKDL are considered to be a potential source of *Leishmania* infection.

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Epidemiology and disease burden

Leishmaniasis affects people in nearly 98 developing and developed countries where about 350 million people are living in these regions. An estimated 700,000 to 1 million new cases occur worldwide each year, of which 50,000 to 90,000 new VL cases – with 20,000 to 30,000 death annually - and 600,000 to 1 million new CL cases.

Control measures & prevention

Only few drugs are currently available for treatment of leishmaniasis. These drugs are characterised by high costs, significant adverse events and, in some cases, increasing parasite drug resistance[27]. Common treatments for VL include sodium stibogluconate (Pentostam), amphotericin B, paromomycin, and miltefosine. Without treatment, most patients with the visceral disease will die and those with diffuse cutaneous and mucocutaneous disease can suffer long infections associated with secondary life-threatening infections. Treatment should be considered even for self-healing cutaneous leishmaniasis, because of the disfiguring scars. Lesions caused by mucocutaneous leishmaniasis are normally treated with amphotericin B and paromomycin.

Vaccine landscape

To date, there are no vaccines against leishmaniasis, and control measures rely on chemotherapy to alleviate disease and on vector control to reduce transmission. However, there is consensus that in the longer term, vaccines ought to become a major tool in the control of this group of diseases. Unfortunately, the development of vaccines has been hampered by significant antigenic diversity and the fact that the parasites have a digenetic life cycle in at least two hosts (sandfly vector and human, but there is also an animal reservoir). An equally important consideration for the design and implementation of anti-parasite vaccines in general is the contribution of the genetics of the target host population and their susceptibility to infection and disease, i.e. the severity of disease manifestations.

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LEISHDNAVAX

Description

LEISHDNAVAX is a pentavalent DNA vaccine candidate against leishmaniasis coding for optimised and T cell epitope-enriched variants of the *Leishmania* antigens kmp-11, TSA, elongation factor P74, and cysteine proteases CPA and CPB[28].

These antigens were selected according to the following criteria: i) no significant similarity to human proteins; ii) conserved among the different *Leishmania* species pathogenic in humans, in different *Leishmania*-endemic regions and over extended time spans, iii) known to be immunogenic and to induce human $CD4^+$ and $CD8^+$ T cell responses in different endemic populations; iv) rich in T cell epitopes in particular in the conserved sequence stretches; and v) expressed in promastigote and amastigote forms of the parasite[3].

Each DNA sequence is delivered through the Minimalistic Immunogenically Defined Gene Expression (MIDGE) vector. They are linear double-stranded DNA molecules, only containing the antigens-coding sequences, promoter and poly-adenylation site, but no bacterial plasmid backbone sequences that have been shown to reduce transgene expression and immunogenicity[29,30]. MIDGE vectors are stabilized against exonucleases by terminal looping or L-nucleotides. Biodistribution and toxicity data for MIDGE vectors document an excellent safety profile[31, 32].

This vaccine has already been successfully tested for antigenicity in humans in *ex-vivo* studies, and for immunogenicity and efficacy in a mouse model for visceral leishmaniasis. The aim of the current GHIT-funded LEISHDNAVAX project, which started in October 2017 and has an overall budget of approximately €3.1M, is to complete the preclinical development of the vaccine to assess its efficacy in a mouse model of cutaneous leishmaniasis.

The main objectives of the LEISHDNAVAX project are:

1. Preclinical evaluation of the vaccine candidate to study the protection against cutaneous leishmaniasis
2. Preclinical evaluation of the vaccine candidate to study its therapeutic potential against cutaneous leishmaniasis
3. GMP production and clinical batch release
4. Preparation of a phase I clinical trial to assess the safety and immunogenicity of the vaccine candidate in humans.

Recent achievements

The challenge mouse model for cutaneous leishmaniasis using luciferase-tagged parasite strains has been established at the Nagasaki University with the support of the team at LSHTM. With this tool in hands, prophylactic and therapeutic studies are ongoing to assess the efficacy of the vaccine candidate.

Meanwhile, five GMP Master Cell Banks, each carrying one of the five parental plasmids of MIDGE-vectors, have been produced and released. Accordingly, five feasibility studies of plasmid production have been conducted as the pre-requisite of large-scale plasmid production in high quality. These studies were concluded successfully.

Partners

- *Charité – Universitätsmedizin Berlin, Germany*
- *European Vaccine Initiative (EVI), Germany*
- *London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom*
- *Mologen AG, Germany*
- *University of Nagasaki, Japan*

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32. Endmann A et al, Vaccine. 2014;32:3460-7.

PREV_PKDL

Description

PREV_PKDL is a collaborative project funded by the European & Developing Countries Clinical Trials Partnership (EDCTP2) Programme supported by the European Union. The project started in April 2018 and has an overall budget of approximately €8 M.

The PREV_PKDL project aims at advancing the clinical development of ChAd63-KH vaccine for the prevention of post kala azar dermal leishmaniasis (PKDL). ChAd63-KH vaccine is a replication defective simian adenoviral vector expressing KH, a polyprotein comprising *L. donovani* KMP-11 and a synthetic HASPB that takes into account sequence diversity and repeated structures found in *L. donovani* field isolates. This vaccine has already been shown to be safe, well tolerated and able to induce a good immune response in healthy subjects[33] and is currently in a further safety study in Sudanese PKDL patients.

In the PREV_PKDL project ChAd63-KH will be evaluated in clinically cured visceral leishmaniasis (VL) patients in a safety and efficacy phase IIb clinical trial in Sudan powered to detect a reduction in PKDL incidence. Part of the clinical batch that will be used in this trial was previously manufactured with funds from the Wellcome Trust (https://wellcome.ac.uk/what-we-do/teams/innovations-team) and will be kindly donated to this project. The results of this trial will be decisive in the future development of ChAd63-KH.

Additionally, to better understand the disease as well as drug and vaccine responses, multidimensional, multiparameter phenotyping will be conducted on patient cohorts recruited across the countries of the Leishmaniasis East Africa Platform (LEAP; Ethiopia, Kenya, Sudan and Uganda). Launched in 2003 with the support of the Drugs for Neglected Diseases initiative (DNDi), LEAP brings together scientists and institutions in East Africa to develop clinical trial capacity to bring new treatment options to Leishmaniasis patients in this region. A major aim of PREV_PKDL is to support LEAP through the development of a flow cytometry network across LEAP. This capacity strengthening will help LEAP to develop as a major force for research and training on poverty-related neglected diseases in the East African Region.

Partners

- *European Vaccine Initiative (EVI), Germany*
- *University of York (UoY), United Kingdom*
- *Institute of Endemic Diseases (IEND), University of Khartoum, Sudan*
- *University of Gondar (UoG), Ethiopia*
- *Kenya Medical Research Institute (KEMRI), Kenya*
- *Makerere University (MU), Uganda*

Outreach and communication

Conference presentations:
Odile Leroy presented “Clinical development of a therapeutic vaccine for prevention of post kala azar dermal leishmaniasis” at the 9th EDCTP Forum on 17-21 September 201 in Lisbon, Portugal

Paul Kaye presented “Coupling deep phenotyping with human challenge to progress leishmaniasis vaccine development” at the EVI 20th anniversary symposium on 20-21 November 2018 in Heidelberg, Germany

Paul Kaye presented “Strategies for vaccine development 2018-2023” at the International Conference on Innovations for the Elimination and Control of Visceral Leishmaniasis (IEC-VL) on 29-30 November 2018 in New Delhi, India.

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· PREV-PKDL Group

Partner Profile

Prof Paul Kaye, PhD, FRCPath

Paul Kaye is Professor of Immunology at the University of York. He trained in zoology (BSc) and immunology (PhD) and has worked for over 30 years on the immunology and immunopathology of the neglected tropical disease leishmaniasis. He is internationally recognized for his research on macrophages and dendritic cells, contributing to a fundamental understanding of their biology in health and disease, and for his work on lymphoid tissue remodelling and granulomatous inflammation during chronic infection. Paul is a Wellcome Trust Senior Investigator and an elected Fellow of the UK Academy of Medical Sciences. He was awarded FRCPath by publication in 2004 and has published ~150 research articles and reviews, with many in leading international journals (e.g. Nature Medicine, Immunity, J. Clin. Invest., PNAS). Paul's research tackles leishmaniasis from a holistic viewpoint, rooted in the immunology of the host-parasite interaction, but employing tools and approaches taken from many disciplines, including mathematics, ecology, vector biology and neuroscience. He has extensive links with leishmaniasis-endemic countries and is currently leading on Phase II therapeutic vaccine trials in Sudan, developing a digital pathology platform with colleagues in Brazil, India and Sri Lanka and establishing a controlled human infection model for cutaneous leishmaniasis.

VIRAL VACCINES

Over the past years, EVI has become increasingly interested and engaged in the development of vaccines against viruses. EVI engaged in the development of a universal influenza vaccine, supported pre-clinical work on a measles vector-based dengue vaccine, and has recently broadened the portfolio to include a Zika vaccine, and is also actively involved in raising funds for the development of vaccines against a set of viruses causing diseases of poverty or emerging diseases.

Viruses are small infectious agents that can only replicate inside the living cells of other organisms. Although far less complex than other microorganisms, the development of vaccines against some viruses causing serious human disease nevertheless can present a formidable challenge. EVI is building on its expertise gained on malaria and other parasitic and bacterial diseases to support the preparedness for viral outbreak pathogens.

ZIKA VACCINES

Introduction

The Zika virus is a mosquito-borne flavivirus. The first recorded outbreak of Zika virus disease was reported from Micronesia in 2007, followed by a large outbreak of Zika virus infection in French Polynesia and other countries and territories in the Pacific in 2013. In 2015, Brazil reported a large outbreak of Zika virus infection, found to be associated with Guillain-Barré syndrome and microcephaly. To date, a total of 86 countries and territories have reported evidence of mosquito transmitted Zika infection[34].

Disease

Zika virus is transmitted through the bite of an infected Aedes mosquito, mainly Aedes aegypti in tropical regions. The same mosquito also transmits the viruses causing dengue, chikungunya and yellow fever. Zika virus is also transmitted from mother to fetus during pregnancy, through sexual contact, transfusion of blood and blood products, and organ transplantation. The incubation period (the time from exposure to symptoms) of Zika virus disease is estimated to be 3–14 days. Symptoms are similar to other arbovirus infections, and include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. These symptoms are usually mild and last for 2-7 days and often do not require any specific treatment. However, Zika virus infection during pregnancy is a cause of microcephaly and other congenital abnormalities in the developing fetus and newborn such as fetal loss, stillbirth, and preterm birth. Zika virus was shown to be a trigger of the Guillain-Barré syndrome neuropathy and myelitis, particularly in adults and older children. Zika virus infection can only be confirmed by laboratory tests of blood or other body fluids, such as urine or semen.

Epidemiology, burden & pandemic & epidemic preparedness

Zika virus is an emerging mosquito-borne flavivirus that adapted from an ancestral transmission cycle involving non-human primates and a broad spectrum of forest mosquito species as vectors to an urban cycle involving humans as reservoirs and the widely distributed Aedes mosquitoes as vectors[35]. Since the 1950s, Zika virus had only been reported as circulating sporadically in Africa and Southeast Asia. In 2007, Zika virus was isolated for the first time in the Pacific, on the Micronesian island of Yap[36]. Between October 2013 and April 2014, French Polynesia experienced the largest Zika outbreak ever reported at that time[37]. More than 32,000 patients were suspected for Zika virus infection. Between 2014 and 2015, Zika virus had spread to other Pacific islands, notably the Cook Islands and Easter Island (Chile). In March 2015, Brazil reported the autochthonous transmission of Zika virus[38] and declared an unprecedented outbreak six months later[39,40]. In February 2016, the WHO has declared the recent outbreak of the Zika virus a Public Health Emergency of International

34. https://www.who.int/news-room/fact-sheets/detail/zika-virus
35. 2015; 386: 243–44
36. Duffy MR et al, N Engl J Med 2009; 360: 2536–43.
37. Cao-Lormeau VM et al, Emerg Infect Dis 2013; 20: 1085–86.
38. Zanluca C et al, . Mem Inst Oswaldo Cruz 2015; 110: 569–72.
39. Dyer O, BMJ 2015; 351: h6983.
40. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome – 10 December 2015. Stockholm: ECDC; 2015.https://wwwnc.cdc.gov/travel/page/zika-travel-information
41. Petersen LR, et al. Zika Virus. N Engl J Med. 2016 doi: 10.1056/NEJMra1602113.

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. In 2018, approx. 90 countries, territories or subnational areas with evidence of vector-borne Zika virus transmission were reported[41].

Control measures & prevention

There is no specific treatment or vaccine available against Zika virus. 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. Preventive measures are centred on avoiding mosquito bites, reducing other forms of transmission (e.g. sexual transmission) and controlling the vector (mosquitos)[42]. Measures that can be challenging and have variable efficacy. 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[43].

Vaccine landscape

WHO, UNICEF and a working group of independent experts jointly developed a Zika virus vaccine target product profile (TPP) for use in an emergency, or in a future outbreak scenario[44,45,46]. Additionally, a Zika vaccine development technology roadmap was released by WHO that aims at providing a strategic framework for both outbreak and endemic use for vaccine researchers, funders and product developers[47].

According to WHO's Vaccine Pipeline Tracker[48], eleven Zika virus vaccine candidates have entered in phase I and phase II clinical trials. These candidates are based on whole inactivated virus, or on the prME viral antigen using DNA, mRNA, peptide technologies, as well as on recombinant viral vectors. The measles vector based platform technology used in ZIKAVAX is built upon one of the safest and most efficacious vaccines available, the live attenuated measles vaccine. It has been demonstrated to be safe, with an efficacy rate of approximately 93% after one administration and 97% after 2 administrations. The measles vaccine induces a life-long immunity by efficiently stimulating long-lasting B- and T-cells.

42. 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…
43. Vannice KS, et al. doi: 10.1016/j.vaccine.2016.10.034.
44. WHO. Zika virus vaccine product development. (2016, November). Retrieved from: http://www.who.int/immunization/research/development/zika/en/index2.html
45. http://www.who.int/immunization/research/development/WHO_UNICEF_Zikavac_TPP_Feb2017.pdf?ua=1
46. https://www.who.int/immunization/research/development/Zika_Vaccine_Development_Technology_Roadmap_after_consultation_April_2019.pdf?ua=1
47. https://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/
48. http://live.univ-lyon1.fr/webapp/website/website.html?id=3743907&pageId=275152 (accessed 29-05-2017)

ZIKAVAX

Description

ZIKAVAX (Fast track development of a Zika vaccine based on measles vector) is a collaborative project funded under the EU's H2020 Research and Innovation Programme and coordinated by EVI (grant agreement N° 732432). This four-year project was initiated in October 2016 and has an overall budget of approximately €5M. 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.

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[m].

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.

Recent achievements

Within ZIKAVAX, more than 40 different vaccine constructs were cloned and characterised in HEK293 cells. The antigen sequences were then 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, replicating recombinant vectors were generated by reverse genetics using a cell-based system developed by Institut Pasteur and were further characterised for antigen expression, growth characteristics and genetic stability. Based on the data, three constructs were selected for further immunogenicity and efficacy studies in mice. Immunogenicity and efficacy evaluation of the MV-Zika vaccine candidates in mice allowed the identification of a lead vaccine candidate. To further demonstrate preclinical immunogenicity and protective efficacy of the recombinant MV-Zika vaccine candidate(s) in non-human primates, CEA established a non-human primate challenge model for Zika virus infection. Results of the immunogenicity and efficacy studies of the lead vaccine candidate in NHPs are expected to be available in 2019.

Profiting from the knowledge acquired on manufacturing its MV-based Chikungunya vaccine candidate (MV-CHIK) currently in phase II clinical trial, Themis has adapted and optimised the upstream and downstream processes. The GMP manufacture of the selected MV-Zika vaccine candidate was performed with release of the drug product expected for 2019.

The preparation of a phase I clinical trial with the lead vaccine candidate was initiated and the clinical trial will be conducted in Europe in 2019/2020.

Partners

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

Outreach and communication

The ZIKAVAX consortium actively interacts 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.

CROSS-CUTTING ACTIVITIES

In addition to the different vaccine R&D projects that EVI supports and which have the objective to advance the development of vaccines for specific diseases, EVI also coordinates and promotes more "horizontal" projects. These projects address disease-overarching issues that are common and relevant for vaccine R&D in general and relate, for example, to issues such as vaccine formulation, animal models, vaccine manufacturing and other aspects.

FLUCOP

Description

Influenza vaccines have been widely used for many years to protect against infection by influenza viruses and to reduce sickness caused by the infection. Nevertheless, despite the clinical evidence existing concerning their ability to protect against influenza, substitute endpoints –i.e. correlates of protection- that could be used to assess the efficacy of influenza vaccines are still not fully understood.

FLUCOP aims to address this lack of knowledge by developing a toolbox of standardised and validated serological assays for human influenza vaccines, agreed and used by key parties in the public and private sectors. These tools are expected to have an important impact on influenza vaccine R&D and on the further definition of correlates of protection for these vaccines.

The FLUCOP project is supported by IMI and EFPIA, which together provide a total funding of €14M (half of which is provided in cash by IMI, the other half in kind by EFPIA). The five-year project started in March 2015, EVI is in charge of dissemination and communication.

The long-term objectives of FLUCOP are to improve and standardise existing immunological assays for the definition of correlates of protection in future efficacy trials and to develop new assays to better evaluate influenza vaccine immunogenicity. To achieve these objectives, haemagglutination inhibition and virus neutralisation assays are being standardised by the consortium. Moreover, the understanding and application of cell-mediated immunity and NA assays as tools to evaluate the performance of influenza vaccines is being pushed forward and new technologies for the investigation of correlates of protection are being studied.

Recent achievements

Results of the first HI pilot study allowed defining optimal experimental conditions to be included in a consensus protocol that was then used in a second set of confirmatory experiments, in comparison to lab-specific protocols and reagents. Data from a first HI pilot study showed that the use of common protocols and reagents associated with the use of standards can significantly reduce the inter-lab variability of the HI assay. For VN assay, two distinct formats of the assay were selected for evaluation using the same approach as for HI assay. The pilot study for the short form VN assay has been completed, and the study for the long form assay is on-going. Also, the understanding and application of cell-mediated immunity could be advanced by the conduct of two pilot studies in which standardized protocols for flu-specific ELISpot and ICS assays were tested.

Partners

- *Abbott, 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*
- *Paul-Ehrlich-Institut, Bundesinstitut Für Impfstoffe Und Biomedizinische Arzneimittel, Germany*
- *QUINTEN, France*
- *Sanofi Pasteur, France*
- *Sclavo Vaccines Association, Italy*
- *Sequirus, US*
- *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 Perugia, Italy*
- *University of Surrey, United Kingdom*

Outreach and communication

Articles:

Impact of erythrocyte species on assays for influenza serology.
Trombetta CM, Ulivieri C, Cox RJ, Remarque EJ, Centi C, Perini D, Piccini G, Rossi S, Marchi S, Montomoli E.
J Prev Med Hyg. 2018 Mar 30;59(1):E1-E7. doi: 10.15167/2421-4248/jpmh2018.59.1.870

Antibody responses to influenza A/H1N1pdm09 virus after pandemic and seasonal influenza vaccination in healthcare workers: a five-year follow-up study.
Trieu MC, Jul-Larsen Å, Sævik M, Madsen A, Nøstbakken JK, Zhou F, Skrede S, Cox RJ.
Clin Infect Dis. 2018 Jun 9. doi: 10.1093/cid/ciy487

Impact of pre-existing immunity on the induction of functional cross-reactive anti-hemagglutinin stalk antibodies following vaccination with an AS03 adjuvanted pandemic H1N1 vaccine.
Tete SM, Jul-Larsen Å, Rostami S, Lunde THF, Søland H, Krammer F, Cox RJ.
Vaccine. 2018 Apr 12;36(16):2213-2219. doi: 10.1016/j.vaccine.2018.02.022.

Immune responses after live attenuated influenza vaccination.
Mohn KG, Smith I, Sjursen H, Cox RJ.
Hum Vaccin Immunother. 2018 Mar 4;14(3):571-578. doi: 10.1080/21645515.2017.1377376.

Conference presentations:

NIBSC presented "Standardisation of serology assays to evaluate immune responses to influenza vaccines" at the conference on Universal Influenza Vaccines 2018, 16-18 April 2018, Lausanne, Switzerland

VAC2VAC

Description

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 and immunochemical methods, cell-based assays and multiparametric assays & bioinformatics**. 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. For each type of vaccine, one or more vaccines are selected as product models (see table 1.1).

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.

Recent Achievements

Physicochemical methods

Mass spectrometry (LC-MS): assays for Leptospira and DTaP vaccines were successfully set up confirming suitability of MS for further analysis. A panel of physicochemical assays was applied to tetanus toxoid (TT) antigens from a number of manufacturers. From this panel, circular dichroism and fluorescence spectroscopy standout as promising candidate tests to assess structural conformation and stability of the TTs. In addition, LC-MS of the toxoid bulks showed that a purity profile can be generated. To facilitate these studies, tailor-made desorption protocols are being developed for human DTaP vaccines. Furthermore, the set up of enzymatic assays simulating antigen degradation by immune cells has started.

Immunochemical methods

Good progress has been made towards the overall objective. For veterinary rabies vaccine, the results obtained do indicate that a glycoprotein ELISA is a viable non-animal approach for potency testing of veterinary rabies vaccines and the industry partners will continue with in-house development of ELISA methods for rabies vaccine and will share progress with the VAC2VAC consortium. For TBEV, very good progress has been made for development of immunoassays for TBEV; Pfizer have joined the consortium and have developed a monoclonal antibody ELISA for TBEV; AGES have developed another ELISA method based on a monoclonal antibody that was selected after extensive characterisation of a panel of TBEV monoclonals; both ELISAs are proposed for a multicentre transferability study during year 4. For Clostridium chauvoei vaccine, an ELISA format has been developed and appears to be sufficiently sensitive for testing vaccine products. For IBV the characterisation and selection of mAbs is still ongoing.

Cell based assays

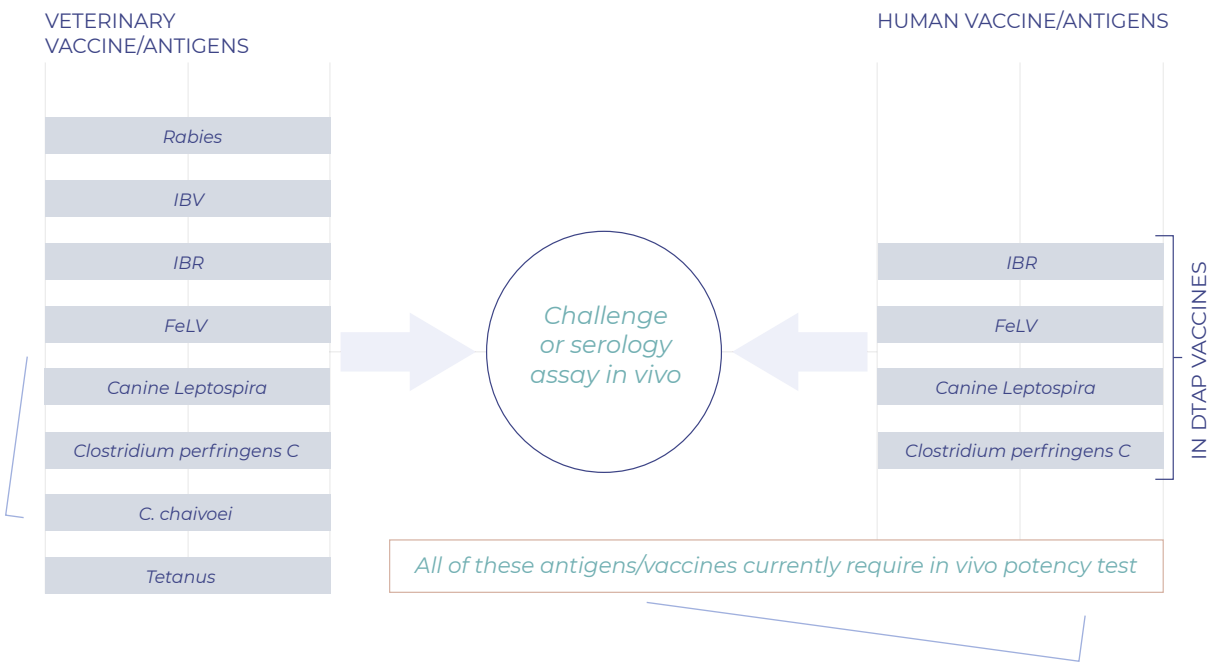
To replace the RPT for TBEV vaccine, the monocyte-activation test (MAT) using human peripheral blood mononuclear cells (h-PBMC) was optimized, validated and transferred to the respective industry partner.

The inflammasome activation assay has a biologically relevant read-out that could be useful for characterisation of intermediate alum-containing products. Cell-based assays to study IBV and Leptospira vaccines using antigen-presenting cells (APC) are under development. Innate immune fingerprinting: The FeLV vaccine component Quil-A was found to induce NF-κB- signaling in a dose-dependent and reproducible manner. For the IBR vaccine, no signal was detected using the entire bioassay library.

Human B-cell assay for consistency testing of DTaP antigens: It could be demonstrated that it is feasible to use PBMC isolated from buffy coats from healthy or freshly vaccinated donors for this ELISpot-based assay.
To assess toxoid processing and subsequent peptide presentation by APC, an in vitro co-culture assay of toxoid-primed human APC and tetanus- or diphtheria toxoid-specific CD4+ T cell hybridoma's is being set up. In addition, assays are under development to assay T cell activation induced by veterinary IBV and Leptospira vaccines.
In vitro safety test for bulk tetanus toxoid: a detection limit for tetanus toxin as low as 0.03 nM was reached and modifications to assay conditions will be tested to improve sensitivity of the assay and bring it close to what is detectable with in vivo assays. For veterinary C. perfringens C it was found that both A10 and THP-1 cell lines are susceptible to the C. perfringens C non-inactivated antigen in a concentration-dependent manner and with a sensitivity in the required range.

Multiparametric assays and bioinformatics
Characterization of Clostridium tetani seed strains was performed using DNA, RNA and protein analysis. Two DNA-based methods have been established and are ready to enter method validation. A mass spectrometry-based method for protein characterization was successfully set up and validation has started.
The development of an alternative pertussis vaccine safety test was initiated with the goal to obtain a fully quantitative readout. Preliminary data analysis demonstrates sufficient reproducibility and specificity to move on to detailed data analysis which is currently ongoing.
For the development of platform technology to study interaction of vaccines/adjuvants with APC, suitable cellular platforms were identified and robust protocols for obtaining and differentiating the cells to the desired phenotype are being developed. All vaccines were found to evoke specific responses in the used cells. In some cases, however, the final vaccine turned out to be toxic for the cells and material before absorption had to be used instead. Transcriptomics and proteomics analysis have been initiated for further characterization of the response.

Work on 'Pre-validation of selected methods'
The Method Template (MT) was finalised and disseminated to method developers as a guide to robust method development and reporting. It lists parameters and characteristics relating to method development and validation based on analytical target profiles. The MT is accompanied by a guidance document and score card, which will be used by the team as a decision tool, i.e. to select



Outreach and communication

Presentations at meetings:

		Date	Where
1	presentation at Annual INVITROM Symposium	22-22 March 2018	Utrecht, the Netherlands
2	presentation at 16th B Cell Forum	12-14 April 2018	Masserberg, Germany
3	presentation at DCVMN Workshops	7-10 May 2018	Hyderabad, India
4	Poster at IMI 10th Anniversary	27 June 2018	Brussels, Belgium
5	Poster at Avian Immunlogy Research Group Meeting	5-7 September	Oxford, UK
6	Poster at 6th European Veterinary Immunlogy workshop	7 September	Utrecht, Netherlands
7	4th meeting of WHO Network of CCs on Vaccine Standardization	13-14 September	Bejing, China
8	session (presentations and posters) dedicated to the Vac2Vac project at European Congress on Alternatives to Animal Testing	23-26 September 2018	Linz, Austria
9	Meeting with EDQM	27 September	Strasbourg, France
10	Presentation at the 2nd general meeting WHO-NCLNB	25-27 September	Rome, Italy
11	Presentation and poster at IABS Conference	16-17 October 2018	Bethesda, Maryland, US
12	Poster at I&I Utrecht Science symposium	29 October	Utrecht, Netherlands
13	Presentation at I&I PhD retreat	1-2 November	Leersum, Netherlands
14	Poster at Veterinary Science day	15 November	Bunnik, Netherlands
15	Poster at EVI 20th Anniversary Symposium	20-21 November	Heidelberg, Germany

Publications:

Recommendations of the VAC2VAC workshop on the design of multi-centre validation studies.
Marlies Halder, Hilde Depraetere, Frédérique Delannois, Arnoud Akkermans, Marie Emmanuelle Behr-Gross, Martijn Bruysters, Jean-François Dierick, Carmen Jungbäck,
Imke Kross, Bernard Metz, Jeroen Pennings, Peter Rigsby, Patrice Riou, Elisabeth Balks,
Alexandre Dobly, Odile Leroy, Catrina Stirling. Biologicals 52; 78-82, 2018. https://doi.org/10.1016/j.biologicals.2018.01.003

which method should undergo (pre-)validation, in case there are several methods available for the same purpose. With the workshop on the design of multi-centre validation studies organised by WP5 in 2017, the consortium started an open discussion with all stakeholders - vaccine manufacturers of major human and animal health companies, competent authorities, OMCLs, EDQM, etc. - signalling a common commitment by all parties to the 3Rs principles. The summary of the discussion and recommendations was published in Biologicals (https://doi.org/10.1016/j.biologicals.2018.01.003).

Work on 'Regulatory acceptance of the consistency approach'

Contacts with regulatory agencies and international organisations during year three confirmed that VAC2VAC approach receives global interest: in addition to the national regulatory authorities of the EU, North American authorities (FDA and Health Canada as SEAC Members) as well as USDA, EDQM (also SEAC member), interest was shown by WHO, OIE (The world organisation for Animal Health), the Bill and Melinda Gates Foundation, Human Society International (HIS) as well as by upcoming economies, particularly in Asia.

Partners

- *Biomedical Primate Research Centre (BPRC), The Netherlands*
- *Boehringer Ingelheim (BI), Germany*
- *College ter Beoordeling van Geneesmiddelen (CBG/MEB), The Netherlands*
- *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 (now part of BI)*
- *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*
- *Pfizer (Pfizer), Austria*
- *Sanofi Pasteur (SP), France*
- *Sciensano (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*

TRANSVAC2

Description

The main objective of TRANSVAC2 project is to unite and strengthen existing European and national vaccine development programmes by forming a sustainable European vaccine research infrastructure capable of addressing European societal health-related challenges and strengthening Europe's competitive position. In order to achieve this, TRANSVAC2 aims to reach the following specific objectives:

- Construct an efficient and coordinated research and innovation environment by integrating key infrastructures and related initiatives from Europe and beyond, focused around the sustainable vaccine infrastructure;
- Stimulate technological innovation and foster research within Europe by providing scientific and technical services (trans-national access - TNAs) to the vaccine R&D community;
- Strengthen and disseminate European vaccine expertise by offering classroom and laboratory training in vaccinology;
- Perform joint research activities (JRAs) that continuously enhance and improve the services offered by the infrastructure.
- Maximise engagement of the European vaccine industry, including large pharmaceutical companies and SMEs;
- Take an active role in policy development, providing evidence-based recommendations to legislators and regulatory bodies.

Recent achievements

Delivery platform, adjuvants and viral vectors

TRANSVAC2 provides highly-demanded and badly needed scientific and technical services (TNA) to European vaccine developers. It offers an integrated panel of services based on a "one-stop-shop" business model which has organised partner facilities into a single vaccine development pipeline, in which the different complementary units can work seamlessly with a harmonised and efficient work-flow.

In this context, 3 calls for trans-national access (TNA) have been completed in 2018. In total 27 applications were submitted (including 5 resubmissions) by 18 research institutions and 3 SMEs from 10 countries within Europe and 3 overseas. 25 services were granted to 14 projects (14 applicants) submitted by SMEs and research institutions from 9 countries within Europe and 1 from South America.

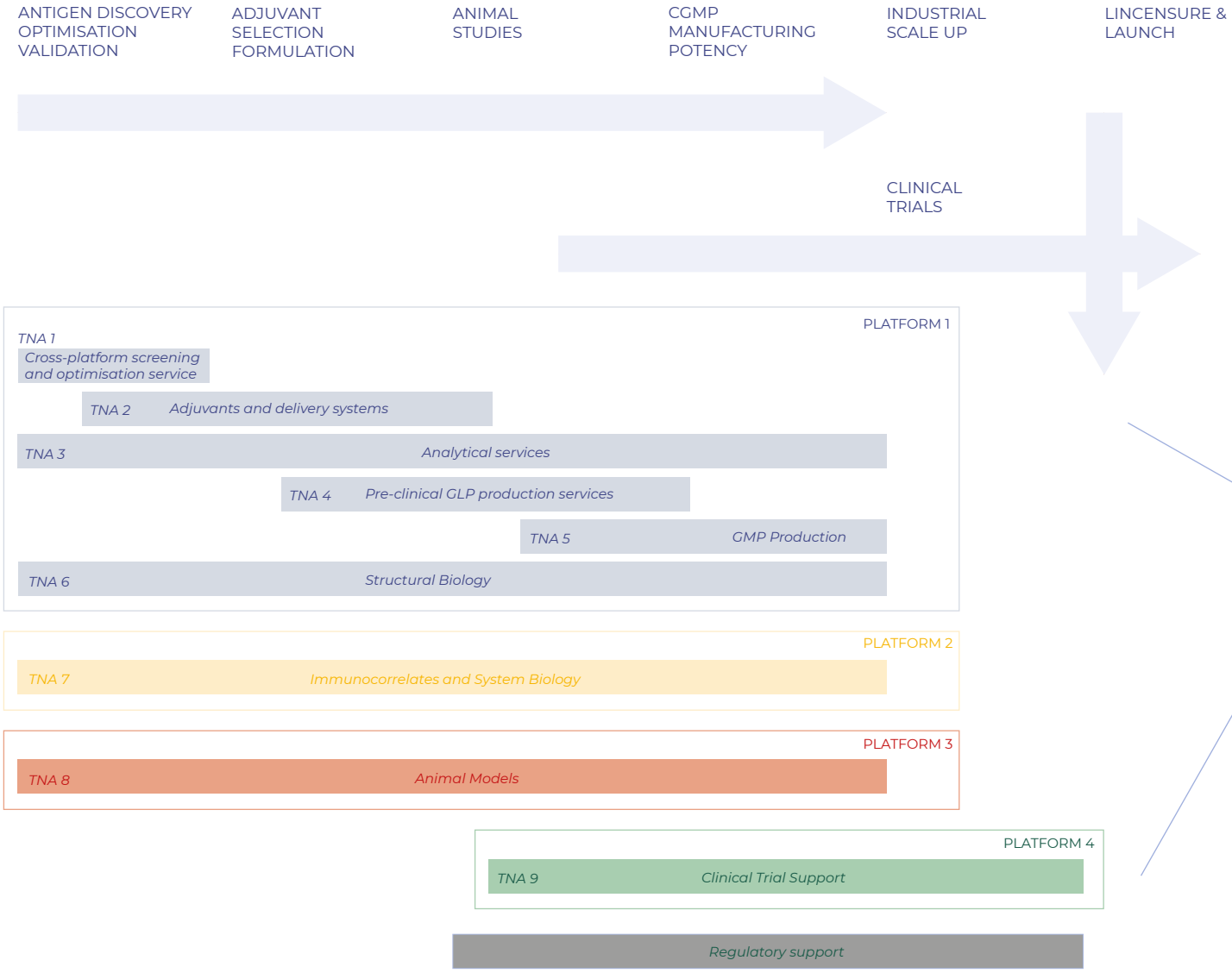
Platform 1 - Technology

This platform focuses on technologies for process development and GMP production. TRANSVAC2 will use a tiered system in which vaccine candidates will be tested using a diverse array of production systems including those based on bacterial, mammalian cells, and higher plant technologies. The platform provides centralised access to diverse production systems, analytical assays and process options, as well as expertise in GMP manufacture.

Both human and veterinary vaccines, for prophylactic and therapeutic applications, are being addressed by TRANSVAC2.

Platform 2 - Immunocorrelates and Systems Biology

The Systems Biology Platform offers a range of well-established services, including next-generation systems biology technologies for the analysis of innate and adaptive immune responses to vaccination. Approaches include "omics" technologies, including genomic, transcriptomic, proteomic and metabolomic analysis (complemented by computational biology to create databases), data pipelines, data visualisation tools, model building, and ultimately the capacity to simulate the necessary immune responses *in silico*.



Platform 3 - Animal models

It is a major challenge to ensure that data generated using animal models are relevant and informative for the development of human vaccines, as few scientifically-confirmed animal correlates-of-protection exist. The TRANSVAC2 Animal Platform offers a comprehensive and unprecedented panel of animal models and associated innovative techniques, primarily for monitoring immune responses to vaccines and experimental infection. TRANSVAC2 provides both valuable consultancy and acts as a service provider for vaccine researchers' animal study needs.

Platform 4 - Clinical Trials

Advanced consultancy can be provided on the planning and execution of clinical trials according to good clinical practice (GCP). This service covers a wide range of topics including trial design, methodologies, selection of sites, acquisition of funding, management, regulatory issues, and ethics.

Capacity strengthening, workshops, training

TRANSVAC aims to enhance the personal networks of the new generation of vaccine scientists through the project's training courses with the ultimate objective to establish a sustainable pan-European training platform for vaccine development. Consequently, two rounds of training modules in vaccinology at leading European centres, that can be combined to create customised international courses on vaccine R&D, have been set up and announced to the public in 2018.

Two calls for three training modules were launched in 2018, where 34 participants were selected: M1: Clinical vaccine development and biomanufacturing, M2: Human and Veterinary vaccine development, organized by University of Oxford (UK) and M3: Adjuvants and vaccine formulation provided by Vaccine Formulation Institute (UK).

Modules Nr	Training
M1	Clinical vaccine development and biomanufacturing
M2	Human and Veterinary vaccine development
M3	Adjuvants and Vaccine Formulation
M4	Validity and comparison of animal models
M5	Statistics for Vaccine Evaluation
M6	CyTOF
M7	Flow cytometry
M8	In vivo Imaging
M9	Key considerations and best practices for viral vaccine process development, scale-up and implementation at manufacturing scale including single use technologies
M10	Assay Development and Validation-Application of SPR Technologies in Vaccine development and manufacturing
M11	Process development and scale-up of recombinant protein vaccines
M12	Requirements for GMP production
M13	Systems biology of vaccinology
M14	Regulatory aspects of vaccine development

Harmonisation

TRANSVAC2 TNA activities are tightly interlinked with innovative joint research activities (JRAs) which, by improving the transnational services provided by TRANSVAC2, will directly strengthen, in an ongoing fashion, the value of the overall infrastructure by improving predictive assays, adjuvants, animal models, and systems biology. Research activities within all project platforms have been initiated (Technology, Immunocorrelates and Systems Biology, Animal Models and Clinical trial Support) and data generated within Platform Immunocorrelates and Systems Biology have been already presented at international scientific meetings.

Outreach and communication

TRANSVAC2's networking activities aim to strengthen cooperation among project participants, the scientific community, industry, and other key stakeholders such as funders, and policy and decision makers. In this context, a Board of Stakeholders (BoS) comprising representatives of policy and decision makers, industry associations and European infrastructures was established in August 2017. A first BoS workshop organized in June 2018 in Brussels was focused on identifying the gaps in existing European vaccine roadmaps (TRANSVAC and IPROVE). Based on the identified gaps, TRANSVAC2 is aiming to take an active role in policy development, providing evidence-based recommendations to legislators and regulatory bodies - a strategy will be proposed for updating the TRANSVAC roadmap that might support the development of a strategic business plan for a sustainable vaccine R&D infrastructure in Europe.

To learn more about TRANSVAC2 please watch a promotional movie (*https://www.youtube.com/watch?v=2sadifFegks*) and read about TRANSVAC2 successful story: (*http://ec.europa.eu/research/infocentre/article_en.cfm?&artid=49836&caller=FP*).
Spotlight news article MetaboNews in June 2018 Vol 8 - Issue 5 - *http://www.metabonews.ca/Jun2018/MetaboNews_Jun2018.pdf*

The project was presented (posters, presentations) and other promotional materials (flyers) were distributed at more than 20 scientific meetings (congresses, conferences and workshops):

Partner	Dissemination Activity	Venue
UNISI	Poster	33rd Congress of the International Society for Advancement of Cytometry, April 2018, Prague
SWR	Presentation	European Veterinary Vaccine workshop, May 2018, Edinburgh
EVI	Presentation	WHO/Wellcome Trust Meeting, May 2018
UNIL	Poster	Modern Vaccines Adjuvants & Delivery Systems, May 2018, Leiden
EVI	Presentation	IDMIT Symposium, and IDMIT Scientific Advisory Board, June 2018, Paris
UNIL	Presentation	HVA (European HIV Alliance) Annual Consortium Meeting, June 2018, Barcelona
EVI	Presentation and flyers	CTLS2018 (Core Technologies For Life Sciences), July 2018, Ghent
SWR	Exhibition, flyers	European Veterinary Virology Meeting, August 2018, Vienna
SWR	Flyers	European Veterinary Immunology Workshop, Sep 2018, Utrecht
VFI	poster	Virus-Like Particle & Nano-Particle Vaccines Meeting, September 2018, Bern
UNISI	Poster	5th European Congress of Immunology, September 2018, Amsterdam
UNISI	Poster	46° Congresso Nazionale della Società Italiana di Microbiologia, September 2018, Palermo
UOXF	Presentation	kick-off meeting for the Vax-Hub project, funded by EPSRC (UK Government funding)
EVI, UNISI	Presentation	ADITEC annual meeting, October 2018, Siena
EVI	Poster, flyers	Medical Infrastructure-Users Forum, October 2019, Paris
EVI	poster, flyers	The joint BioRN & Ci3 Annual Conference, October 2018, Darmstadt
EATRIS	flyers	World Vaccine Congress, October 2018, Lisbon

TRAINING

Training at EVI

Training scientists in vaccine research and development is part of EVI's mission. It is crucial in order 1) to sustain Europe's excellence in this field, and 2) to strengthen the public health and vaccine research capacities in Low- and Middle-Income Countries (LMICs). 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.

Within EVI's research projects, training is included as an integral part, and either offered as webinars, short modular training courses or long-term training of MSc and PhD students. The TRANSVAC2 Consortium has set up training modules at leading European centres that can be combined to create customised international courses on vaccine R&D. Two rounds of customised training courses are planned. Participants can select topics as needed in their field of vaccine development, and the various modules are harmonised to allow a logical continuation from one topic to the other. Within MMVC, training of three PhD students and two Master students within the African partner institutions is envisaged during the project lifetime, and training courses in immunology and vaccinology will be offered.

EVI is an associated partner of the "Leading International Vaccinology Education" (LIVE) Master programme and has 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.

LIVE

"Leading International Vaccinology Education" (LIVE), is an 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.[49]
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 PhD 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.

EDCTP/TDR Fellowships - Training at EVI

EVI is dedicated at strengthening public health and vaccine research capacities in the fight against diseases of poverty and emerging infectious diseases. In 2015, EVI therefore joined the EDCTP/TDR Clinical Research and Development Fellowship Scheme as a hosting institution providing training to researchers from Low- and Middle-Income Countries (LMICs) who are involved in clinical research projects.

The purpose of this fellowship scheme is to provide training to junior to mid-career researchers and key members of clinical trial research teams from LMICs to acquire specialist skills in clinical research and development through placements in pharmaceutical companies and PDPs. Fellows are expected to return to their home organisation for a minimum of two years after completion of the fellowship to transfer the skills acquired to their home institution. The training of scientists with an interest in activities in the scope of EDCTP or TDR is key in addressing public health challenges and developing and implementing appropriate solutions.

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. 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, preclinical and clinical development of vaccines, GMP manufacturing and regulatory aspects. In 2018, the two fellows were supervised by the EVI Executive Director, Odile Leroy, and mentored by Nicola Viebig, Chief Scientific Officer. The mentoring concept encourages the trainees to take personal responsibility of project tasks, offers assistance and stimulates individual creativity.

Since the beginning of EVI's involvement in the programme, three researchers from Burkina Faso and one researcher from Colombia with different educational background and working experiences were awarded with the EDCTP/TDR fellowship were hosted by EVI and spent one year at EVI in Heidelberg, Germany in 2016 and in 2017. In 2018, EVI hosted two young researchers, Fassiatou Tairou (UCAD, Senegal) and Moussa Niangaly (MRTC, Mali) who supported the EVI staff and acquired key competencies in vaccine development and project management.

After their return to their home institution, EVI maintains a close interaction and continues to mentor the trainees.

"We develop close relationships with the fellows during their one-year training and we continue to support and mentor the fellows after their return to facilitate their reintegration. We expect that after successful completion of this training programme, our fellows will contribute to promote high quality research in LMICs.", says Nicola Viebig.

In August 2018, Nicola Viebig was invited by the former trainee María del Mar Castro Noriega to CIDEIM in Cali, Colombia to visit the institution and to provide training on "Project management for clinical research: tracking study progress" to the scientists from CIDEIM and neighbouring institutions.

Following the positive experience in 2016-2018, EVI is happy to welcome one new trainee in 2019.

Fellows' profiles and their experience at EVI

Fassiatou Tairou

Fassia started her training at European Vaccine Initiative (EVI) on 8th January 2018. Native of Benin, she obtained a DIT (Diplôme d'Ingénieur des Travaux) in Radiology at "École Polytechnique d'Abomey-Calavi" of National University of Benin in 2003, followed by a Master degree (MSc) in Epidemiology from Laval University in Quebec in 2006. From 2008 to 2011, she acted as research officer at the National Institute of Public Health of Quebec on several topics including climate change and health impact of uranium mines. Since 2013, she works as epidemiologist on malaria research studies.

"I'm very grateful to be placed at EVI through WHO/TDR Clinical Development Fellowship. This meaningful experience allowed me to work in multicultural research environment, to acquire new skills in clinical research project management and to enhance my knowledges in clinical research development from antigen discovery to early stage phases. The skills and experiences gained during my training at EVI are useful for my professional career and will be transferred to my colleagues to reinforce the capacity of my department. Many thanks to EVI staff for their commitment to the training and their availability for scientific and personal support, this facilitated my integration to the team and therefore the training. Sincere thanks to WHO/TDR for giving me the opportunity of this fellowship."

Moussa Niangaly

Moussa started his fellowship at EVI on 4th January 2018. A native of Mali, Moussa received a Medical Doctorate in July 2009, from the University of Sciences Techniques and Technologies of Bamako/Faculty of Medicine and Dentistry including training in Good Clinical Practice, introduction of clinical research, clinic research ethics aspects and site coordinator. Subsequently, he started working at the Malaria Research and Training Center (MRTC) as clinical investigator in a Malaria in Pregnancy consortium project funded by the European and Developing Countries' Clinical Trials Partnership. In May 2011, he moved to the National Institute of Health (NIH)/Laboratory of Immunogenetics (LIG) program- in collaboration with MRTC, where he had been assigned a field coordinator position, for the study "A longitudinal Systems Biological Analysis of Naturally Acquired Malaria Immunity in Kalifabougou, Mali. All of his above clinical research activities aimed to improve malaria management and control in Mali. After completion of his EDCTP/TDR Clinical Research and Development fellowship at EVI, Moussa returned to MRTC as Clinical Investigator, where he is coordinating a malaria vaccine clinical research project.

"The fellowship at EVI has been an excellent experience in hands-on training, networking and working in multicultural settings. The training gave me an important knowledge in product development including pre-clinical and early clinical phases' studies. My daily activities including interaction with different project partners (sponsors, funders, clinical trial teams and ethics committees) provided me in-depth understanding of clinical development questions and project life cycle management.
The training program at EVI allowed me to get additional lab training at the Department of Infectious Diseases, Parasitology (Heidelberg University Hospital, Heidelberg, Germany).

The practical competencies from the "hands-on training" will improve my daily clinical research work and reinforce the capacity building at my home institution.

All my gratitude goes to EVI's staff for their commitment to my training and for supporting my strong professional and personal experiences. Thanks to WHO/TDR for giving me this training opportunity.

As part of my re-entry, I am implementing a clinical research project management strategy including the development of general data protection policy, to improve ethics aspect of clinical studies at MRTC."

ADVOCACY AND INTERNATIONAL FORA

The year 2018 was an important year for global health advocacy, as many funders and policy makers are in the process of preparing, or revising their global health strategies, or are preparing new long-term funding programmes such as the EU framework programme for research and innovation, for example. In this context, EVI participated in many workshops, symposia and other events with the goal to further mobilise support for R&D for global health products and participated in consultations and surveys to ensure that these topics remain high on the agenda. To this end, EVI also arranged many bilateral meetings with funders and policy makers on national and international level were relevant topics were discussed. Major events that were attended by EVI during 2018 are listed below.

ADVOCACY

Shigella and ETEC Funders Workshop, 18 January 2018, London UK

The objective of this meeting –organised by the Gates Foundation- was to create a forum for the international funding community to discuss and develop a transparent approach for sharing new, emerging data and to outline a strategic vision and prioritization for decision-making processes with global partners funding the development of enterotoxigenic *E coli* (ETEC) and Shigella vaccines. EVI was represented by Stefan Jungbluth.

EU Advocacy on Global Health R&D: Strategy workshop, 27 February 2018, Brussels, Belgium

This workshop, organised by DSW, brought together different stakeholders engaged in global health advocacy to exchange information and to discuss and align future advocacy activities for global health R&D on EU level. Stefan Jungbluth participated in this event for EVI.

Third Global Vaccine and Immunization Research Forum (GVIRF), 20-22 March 2019, Bangkok, Thailand

The GVIRF is a unique Forum in the field of vaccines & immunization. It is the central discussion platform of all research aspects related to the Global Vaccine Action Plan (GVAP), which was developed in the context of the Decade of Vaccines Collaboration and endorsed by the 2012 World Health Assembly. The GVIRF is co-hosted by WHO, the National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation. Gathering leading experts from public health, academia, government, civil society and private sector, the forum is held every second year.

Presentation of report on NTD research in Germany, 10 April 2018, Berlin, Germany

For the definition of the future support to NTD research, the BMBF had commissioned this report to map the landscape of German actors in the NTD R&D field. Presentation of the report was followed by discussion with representatives of different ministries from the German federal government. EVI was represented in this meeting by Stefan Jungbluth

Kick-off event for the development of a global health strategy of the German Federal Government, 6 June 2018, Berlin, Germany

The German Ministry of Health invited to this event to discuss the outline of the future global health strategy of the German federal government. Contributions to this strategy from stakeholders from civil society, science, politics and industry who had been consulted were presented and discussed with the audience. Stefan Jungbluth participated in this event for EVI.

2018 WHO Product Development for Vaccines Advisory Committee (PDVAC) Meeting, 26-28 June 2018, Geneva, Switzerland

On 26-28 June, WHO's Product Development for Vaccines Advisory Committee (PDVAC) was convened for its 5th annual meeting. Over two days, progress was discussed in vaccine and monoclonal antibody development for the 10 previously prioritized pathogen areas (Human Immunodeficiency Virus, (HIV), Tuberculosis (TB), Malaria, Influenza, Respiratory syncytial virus (RSV), Group B Streptococcus (GBS), Group A Streptococcus (GAS), Herpes Simplex Virus (HSV), Enterotoxigenic E.coli (ETEC) and Shigella spp), and also for three new pathogens with candidates in, or approaching, clinical development (Neisseria gonorrhoeae (GC), Chikungunya (CHIKV) and Non-Typhoidal Salmonella (NTS)). Several cross-cutting topics were considered, such as the potential role of vaccines in addressing antimicrobial resistance (AMR) and two new vaccine product development initiatives, namely Total Systems Effectiveness (TSE) and the Vaccine Innovation Prioritization Strategy (VIPS), were presented. The third day consisted of a closed session with the PDVAC members to deliberate over recommendations.

Passion for Global Health. From Rights to Strategies, 10 October, Berlin, Germany

The meeting was organised by VENRO, the umbrella organisation of development non-governmental organisations in Germany. Goal of the conference was to give specific recommendations to the German federal government to their new global health strategy. The meeting was attended by Stefan Jungbluth from EVI who was also a panel member in one of its parallel events, a role play workshop on "Availability. Accessibility. Affordability".

INTERNATIONAL FORA ATTENDED

7th MIM Pan-African Malaria Conference, 15-20 April 2018 in Dakar, Senegal

The Multilateral Initiative on Malaria (MIM) was established in 1997 with a mission to strengthen and sustain through collaborative research and training, the capacity of malaria-endemic countries in Africa to carry out research that is required to develop and improve tools for malaria control and to strengthen the research-control interphase. The conference aimed to bring together scientists from different backgrounds and with varied interests, to encourage discussion of the latest findings in malaria research. EVI was represented by Fassiatou Tairou, Moussa Niangaly and Nicola Viebig.

The Role of Research and Development in the Fight against Poverty-related and Neglected Diseases, 18 April, Berlin, Germany

This parliamentary event was co-organised by EVI and had the objective to discuss the role of R&D in the fight against poverty-related and neglected diseases and to mobilise further support from parliament for this area. Representatives of several PDP, Members of the German Parliament and other stakeholders took part in this meeting in which Stefan Jungbluth participated for EVI.

International Symposium on Zika Virus Research, 04-06 June 2018, Marseille, France

The symposium provided an overview of the current status of Zika research – covering from basic to clinical research, epidemiology, environmental studies and social sciences – and an opportunity to present the latest results from research conducted by the EU funded Zika consortia. This event was organised by the EU-funded ZIKAlliance project in collaboration with three other EU-funded Zika projects (ZikaPLAN, ZIKAction, and ZIKAVAX) and the European Society for Virology. EVI was represented by Nicola Viebig.

Swiss TPH Summer Symposium 2018 "Clinical Research in Resource Limited Settings: Mission Impossible or Role Model for Future Drug Development?", 28 June 2018, Basel, Switzerland

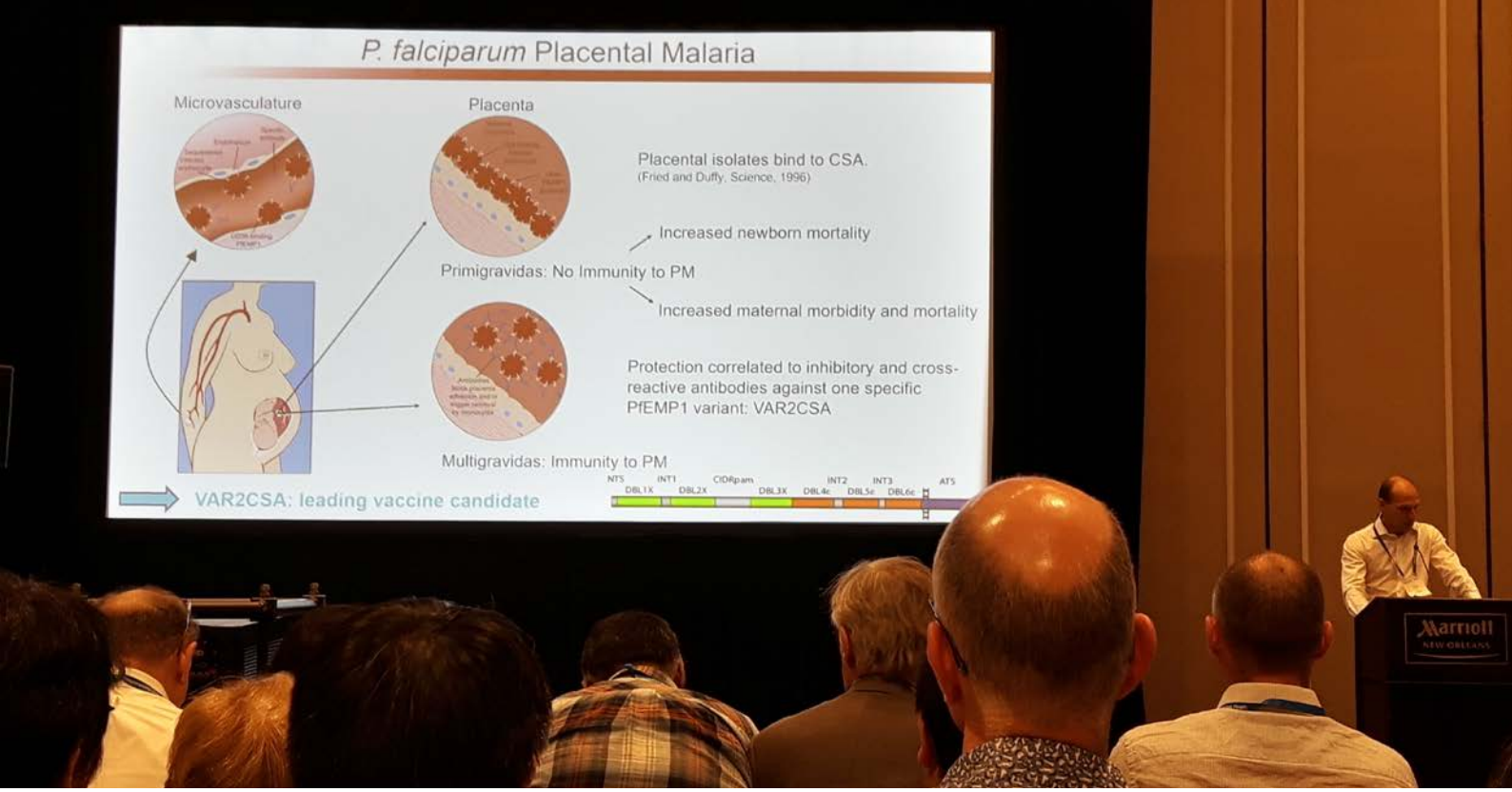
The Swiss TPH traditionally organises two symposia a year. The summer symposium 2018 invited clinical research and drug development specialists to discuss future approaches to drug development. Topics included cost explosion of drug development, impact of GCP-guideline amendment 2016, clinical trials in low resource settings, the Biotech approach to clinical development, the Pharma view on clinical development, learnings from R&D in low resource settings, alternative business models and partnerships. EVI was represented by Flavia D'Alessio and Sophie Houard.

Ninth EDCTP Forum, 17-21 September 2018, Lisbon, Portugal

The EDCTP Fora provided an international platform for the presentation and discussion of R&D to address poverty-related infectious diseases in sub-Saharan Africa and for networking of the players involved. This forum was the ninth in a row and again attracted a large and diverse audience from the research community, health care providers, governments, civil society and other stakeholders. EVI was represented by Stefan Jungbluth, Nicola Viebig, Sophie Houard and Odile Leroy who presented "Clinical development of a therapeutic vaccine for prevention of post kala azar dermal leishmaniasis"

American Society of Tropical Medicine and Hygiene (ASTMH) 67th Annual Meeting, 28 October – 01 November 2018, New Orleans, USA

The ASTMH Annual Meeting draws tropical medicine and global health professionals representing academia, government, non-profits, philanthropy, NGOs, industry, military and private practice. The meeting is designed for researchers, professors, government and public health officials, military personnel, travel clinic physicians, practicing physicians in tropical medicine, students and all health care providers working in the fields of tropical medicine, hygiene and global health. The Annual Meeting is a five-day educational conference that includes four pre-meeting courses and draws approximately 4,800 attendees from more than 100 countries. EVI was represented by Nicola Viebig.



Joint Japan-Spain symposium on medical research, 7 November 2018, Madrid, Spain

The symposium was celebrated on the occasion of the 150th anniversary of the Japan-Spain Diplomatic Relations Programme. Presentations from government representatives from both countries were followed by presentations from several biomedical researchers. The meeting was attended by Stefan Jungbluth from EVI.

German Center for Infection Research (DZIF) Annual Meeting, 03 – 04 December 2018, Heidelberg, Germany

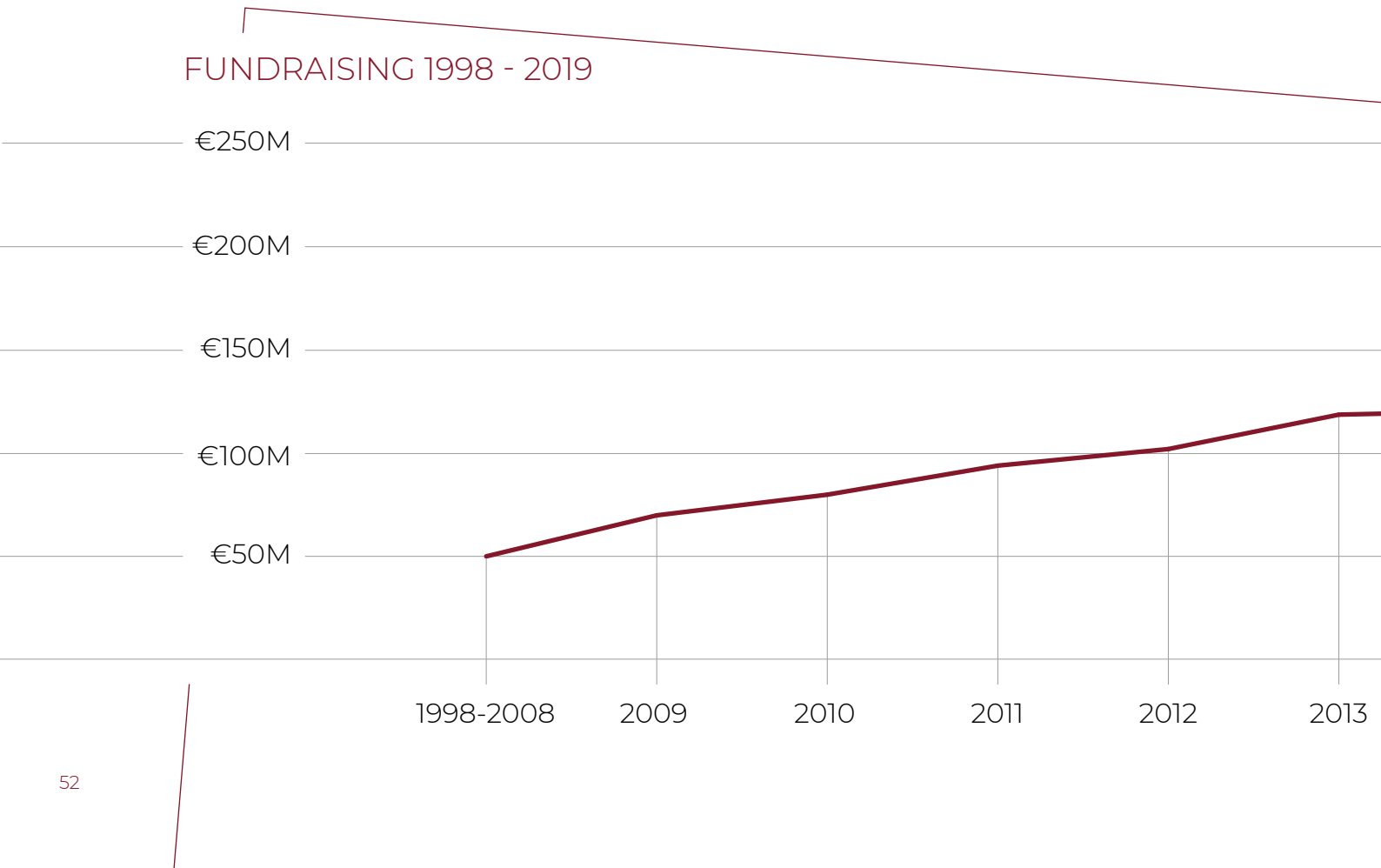
The German Federal Ministry for Education and Research (BMBF) established the German Centre for Infection Research (Deutsche Zentrum für Infektionsforschung, DZIF), bringing together universities, university medical centres, Leibniz and Max Planck institutes, Helmholtz centres and other government research establishments with strong profiles in the field of infectious diseases to tackle the most urgent infectiology challenges with an integrative approach. The DZIF Annual Meeting provided the opportunity for networking inside the DZIF and with other health research centres. The conference was attended by Nicola Viebig from EVI.

Financial performance report 2018

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 of adequate and affordable vaccines.

Fundraising

In the course of 2018, EVI made major impact through fundraising efforts while growing the portfolio with two new EDCTP projects starting during the year (PREV-PKDL & MMVC). These projects where the result of the primary efforts for fundraising during 2017. EVI is pleased that the Wellcome Trust is providing support in kind (worth 130 thousand Euro) for the PREV_PKDL project through donation of vaccine vials for the safety cohort of the phase II clinical trial planned in Sudan. In 2018 the efforts for fundraising yielded even greater result with new project starting in 2019 as described below.



With the project starting in 2019 we are proud to introduce the joint coordination with University of Tokyo for the project of developing vaccine against Nipah. The project is funded by CEPI and will include a total investment of 31 Million US Dollars over 5 years. The project is the single largest project in the portfolio history of EVI. Likewise, EVI will start a new pilot programme called "lump-sum funding scheme" with the European Union for the development of a Shigella vaccine at a total amount of 8.5 Million Euros. Another project for Shigella is in development at the time of writing this annual report.
In addition to this EVI is honoured to start yet another project funded by Japanese GHIT for a blood stage malaria vaccine. The project is estimated to take two years and is net worth 95 Million Japanese Yen.

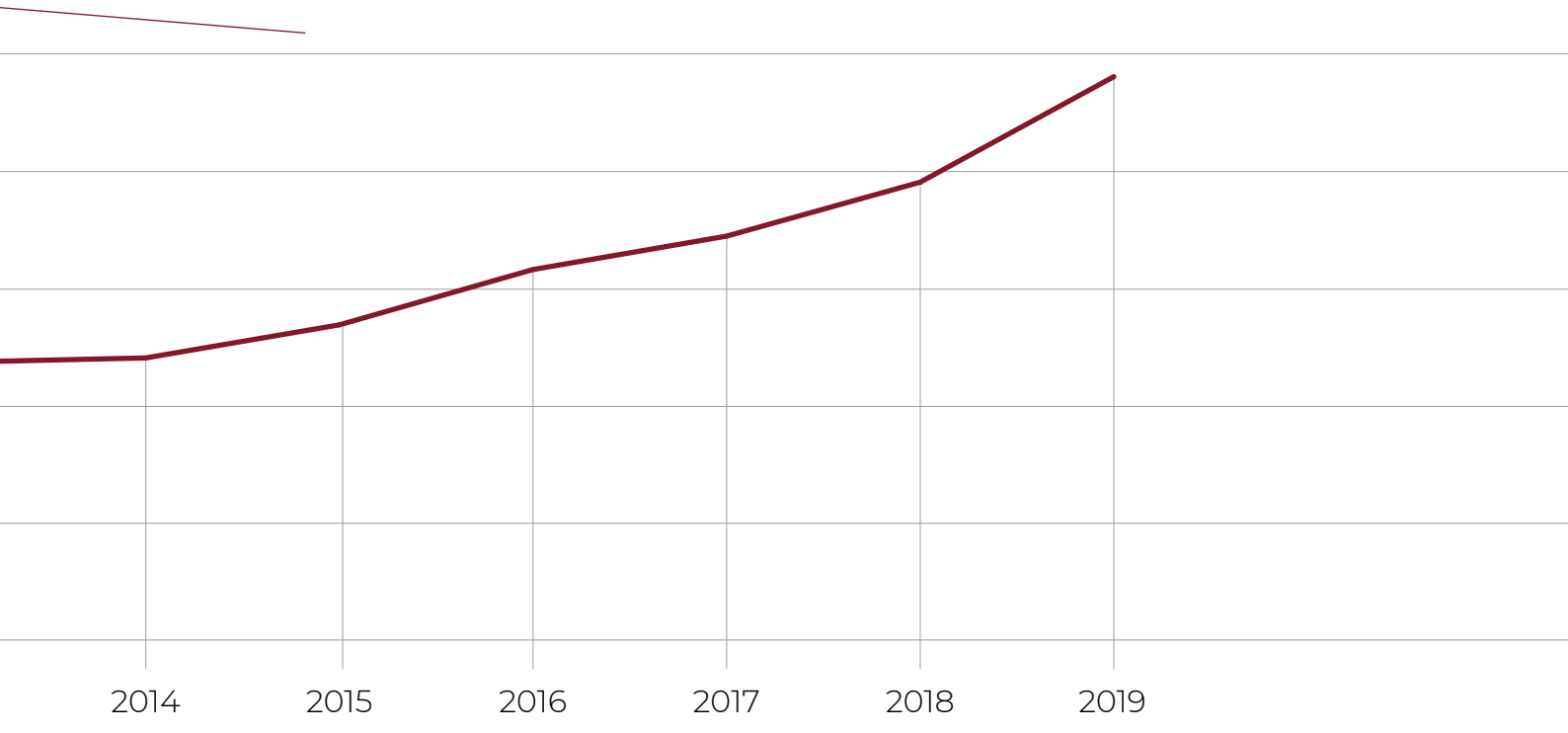
Furthermore, EVI appreciates to participate in an infrastructure project called SENET funded by the European Union. In the course of this project EVI is cooperating with partners not only in Europe but also in China. Lastly EVI is taking part in a portfolio project funded by the WHO together with our partner Duke University, USA. So even if not visible in the numbers for the financial report for 2018, we are expecting a major financial impact in 2019. Since the start of EVI fundraising at EVI has grown close to 200 Million Euro and including in the time as EMVI since 1998 it arises to close to a quarter of a billion Euros for the development of vaccines against poverty related diseases.

Thus, the financial performance is strong and is expected to grow further in the coming years.

Portfolio funding

EVI's project portfolio as of 31 December 2018 consists of eight active projects in the broad field of translational vaccine R&D, transnational access services, capacity building and of course vaccine development in general through clinical trials. Two projects were contractually concluded in 2018, six new projects are secured and will start beginning of 2019. By mid-2019 EVI will run 13 active projects in total. As always, EVI appreciates the establishment of new partnerships and valuates highly the continued support by its long-term partners.

EVI's activities over the current reporting period were covering a broad portfolio of EU, EDCTP IMI and GHIT projects and will, as mentioned above, see the introduction of CEPI and WHO as funding agencies in 2019.
Since 2009, almost 90% of all fundraising has gone uncut to GMP production, clinical development and direct support for the scientific institutions. On top of this comes the work of EVI staff on the projects which thereafter leaves an only small percentage for general management. Furthermore, EVI has successfully diversified its funding sources in order to reduce its financial risks and continues through R&D innovations to target new business opportunities globally.



EVI has likewise managed to diversify its collaborations and fundraising efforts with partner organisations from all over the world. In 2019 EVI will once again expand its operations, now including new cooperating countries such as China and Bangladesh, in addition to the already currently running collaboration projects, and EVI is further spending all efforts to include new partners, organizations and countries in the quest to combat diseases of poverty and emerging diseases.

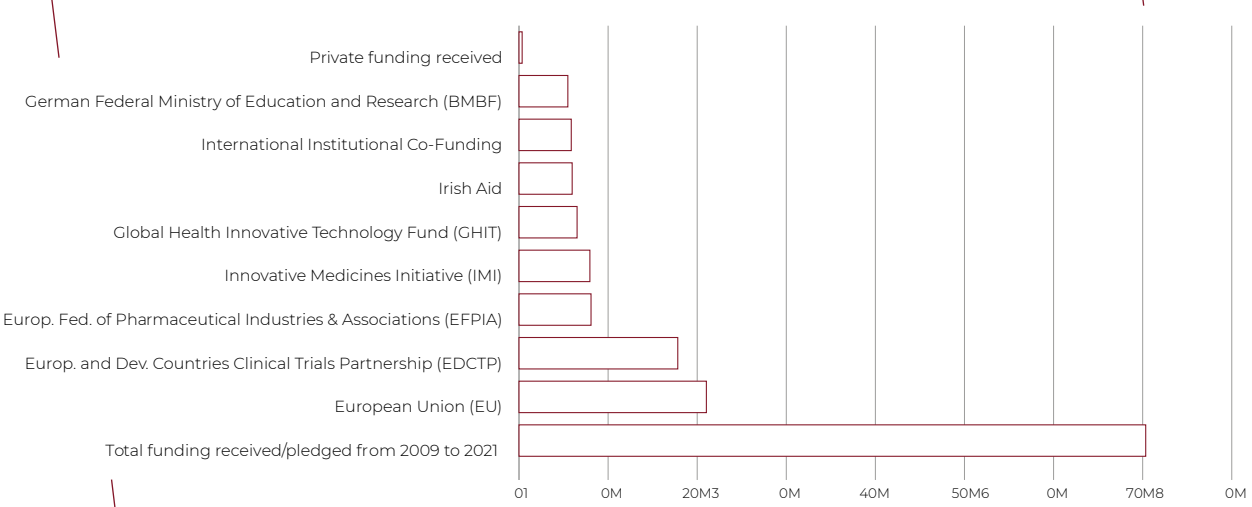
This is reflected by EVI's collaborations with partners from all seven continents of the world.

Diseases know no boundaries, and although the diseases, that the work of EVI is involved with, are linked to poverty, the EVI mission is not restricted to offering poverty-stricken populations a safer life, stronger opportunities and economies of scale and scope. Indeed, the impact of global migration and global warming brings an unprecedented challenge to combat diseases of poverty before they spread and affect even more people. In addition to its work in the field of vaccine development, EVI recognises the importance to combat climate changes, as this has a profound negative impact on the spread of terrible diseases previously confined to geographic areas but now in the risk of spreading globally.

Financial efficiency

Between 2009 and 2018 every single euro of invested EVI funds has leveraged through matched co-funding and in-kind contributions approximately €5.50 of R&D value. For EVI the key factor is synergy in all actions and processes to optimize the output. The donors to EVI have every right to expect an added value to their investments and EVI makes every effort to meet their expectations, which historically proven are delivered. Yet one substantial challenge, that EVI is facing, is the high expectations for good governance and high-quality administration against the lack of funding opportunities for the same. Advocacy is therefore paramount to explain the strong linkage between good governance and high-quality administration on the one side and the efficient and successful project implementation connected to it, as it has been done by EVI in the last 20 years and for which EVI aims to continue for many more years to come.
The investments to build the above-mentioned significant increase in portfolio and focus on project awarded funding rather than portfolio core funding, has meant that EVI has utilised a large part of its core resources leading to a deficit in the profit and loss by 198 thousand Euro. In 2019 EVI expects to reduce this deficit significantly through the extension of rationalization measures and to reach the break-even point again in 2020.

Figure: Distribution of funds received by or pledged to EVI as coordinator since 2009 (as of 31/12/2018) in %



Concerning the deployment of funds and activities in 2018, EVI has continued to focus on streamlining and improving its processes to maximise the usage of funds in its portfolio of projects and to minimise administrative expenses by expanding the usage of our enterprise resource planning (ERP) software – SAP Business ByDesign. Implementation of SAP and electronical resource management has led to further significant improvements in terms of information availability, quality and administrative cost savings. With the aim to minimise management costs while maintaining or improving quality, through reviewing and optimising the administrative processes EVI has succeeded in keeping the share of management costs low.

It is EVI's opinion, that donations and funding should be used for supporting EVI's vision and mission; other cost factors, which do not generate a direct added value for the true beneficiaries – the people – should be minimised. Therefore, EVI is always striving for a maximum utilisation of funds for the benefit of vaccine development and the children and adults urgently in need of vaccines against poverty related diseases. This strategy has led EVI to limit its management costs to below 7% of total costs per calendar year. Consequently, a minimum of 93% of funds could be invested into the projects. Facing increased global controlling and reporting requirements, EVI envisages that administration costs may rise beyond this threshold in the future and keep a close eye on the costs by targeted budgeting.

The management percentage represents a share of the total incurred costs, which are indirectly contributing to the progress of the science or the projects. It includes costs such as rent, utility, payroll management, general secretariat work, audit costs, tax management etc., which are essential for the work of the EVI secretariat and as such for the administration of the projects. The costs are total management costs less overhead coverage from active projects (absorption of management costs).

No organisation can exist without these costs and they are the foundation for the projects to exist on. The percentage is calculated as the share of executive management costs in relation to the total costs of the organisation. Other costs earmarked to improve EVI's administrative capacities in project management are consolidated as core initiative costs, which include EVI staff training, external communication and advocacy, as well as the cost coverage of EVI's governing and scientific advisory bodies. These costs represent amongst others the efforts in creating new consortia across the world, the creation of new innovative projects with our partners, which form innovative science as defined in our name being an "initiative", and the development of the capacities at EVI to perform in these projects. The core initiative costs were equal to 4.08% of the total costs.

This results after subtraction of management and core initiative costs in a net investment of 89.45% of EVI's total funds directly on project development.

Figure: Realised and forecasted EVI income and expenses

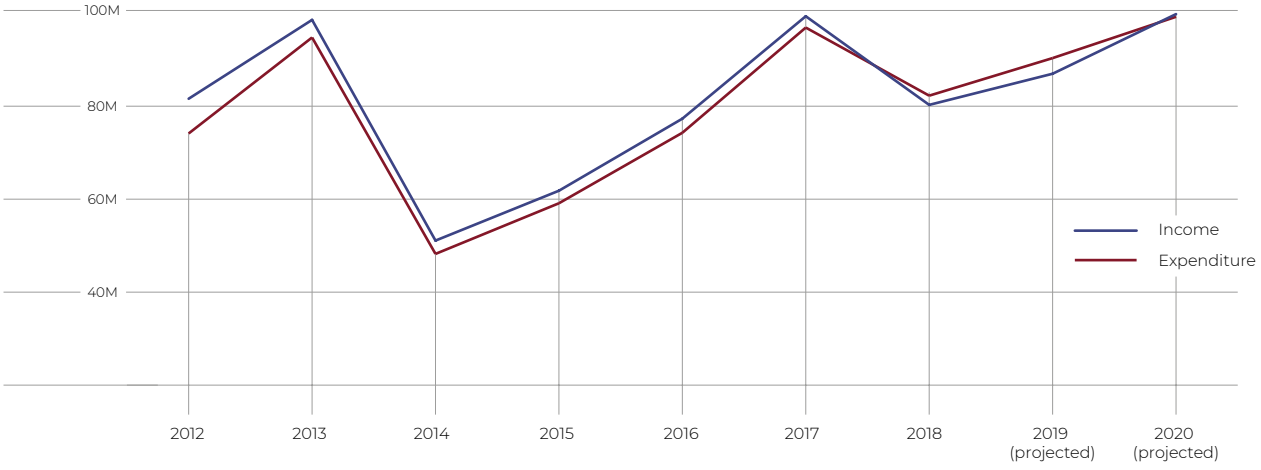


Table: Development of management costs (in % of total costs)

Management percentage (excluding core initiative costs)

Year	Upper threshold	Result	Direct investment percentage of each euro donated
2016	7%	6.27%	93.73%
2017	7%	1.33%	98.77%
2018	7%	6.47%	93.53%

Key ratios

EVI's current EU financial viability status in terms of key ratios is "good", which is the highest achievable grade in terms of sustainability, solvency, liquidity and profitability according to EU standards. EVI is supported by major organisations in Europe and is a financially strong organisation that appropriately incorporates possible risks and liabilities in its financial planning. EVI demonstrates 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.

In 2018 EVI have seen a decrease in equity ratio incurred due to an annual deficit of 198 thousand Euros and an increase in cash and cash equivalents by the end of the year.

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 2018, 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 2018.

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 & GDPR.

All information with regards to grants received by EVI in 2018, 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 2018. 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, eliminate the possibilities of duplications of transaction accountings and are regularly reviewed by certified external auditors. EVI confirms that all tax affairs are following requirements of the jurisdiction of where EVI or its staff members have been tax registered in 2018, namely Germany, Denmark and Belgium.

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

The positive change of cash position despite a deficit in the profit and loss result for 2018 is due to receipt of major advance payments to project beneficiaries of EVI.

Figure: EVI equity ratio 2012-2018

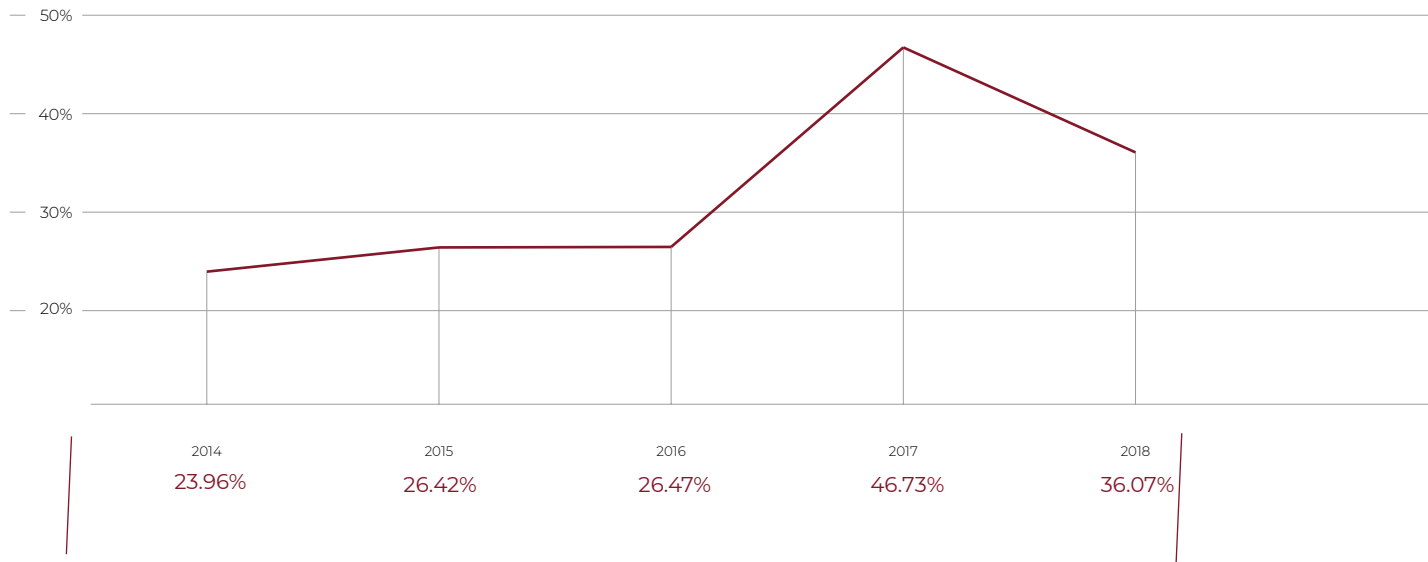


Table: EVI liquidity ratios 2018

Cash ratio (Cash + Cash equivalents) / Current liabilities)	1.55
Quick ratio (Cash + Cash equivalents + Accounts receivables) / Current liabilities)	1.56
Current ratio (Current assets / Current liabilities)	1.56

As explained in the initial presentation, almost 90% of all funds from fundraising over the years from 2009 are used uncut on GMP productions, clinical development and funding for scientific institutions, which can cause major changes in liquid funds from year to year as shown above and in the IFRS statement. However, for other for-profit entities this might be interpreted negatively but in the case of EVI it signifies the funding of projects and vaccine development as an expression of scientific progress.

Management and auditing

EVI has taken 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 Board 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 and Denmark 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 2018 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.

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

	2018	2017
Net Income (result from ordinary operations)	**(198,459.21)**	243,864.57
Fixed Asset Depreciation and Retirement	**7,673.89**	9,575.00
Increase/(Decrease) of accruals	**892,578.51**	(1,223,526.53)
Increase/(Decrease) in accounts receivable (net)	**(5,309,418.30)**	(827,253.79)
Increase/(Decrease) in other receivable (net)	**(1,443.03)**	17,427.97
Increase/(Decrease) in accounts payable	**5,477,300.31**	(826,178.20)
Increase/(Decrease) in other payables	**(3,658.45)**	361,136.10
CF from operating activities	**864,573.72**	(2,244,954.88)
Fixed Asset Investments	**(3,893.89)**	0.00
CF from Investment activities	**(3,893.89)**	0.00
CF from financing activities	**3.00**	3.00
Change of Liquid funds	**860,682.85**	(2,732,658.30)

We formally sign and approve the EVI annual financial report for the year ending 31 December 2017 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: / / 2018

Sten Larsen Finnsson,
EVI Finance & HR Director

Date: / / 2018

Hilde Depraetere,
EVI Executive Director

Date: / /2018

Clemens Kocken,
Chair of EVI-EEIG

Financial presentation 2018

Table 1: Statement of financial position as of 31 December 2018

	Notes	EUR 2018	EUR 2017
Current assets			
Cash and cash equivalents:			
Cash and banks - key accounts		**5,635,110.66**	2,992,427.83
Time deposits		**-**	1,782,000.00
Total cash and cash equivalents		**5,635,110.66**	4,774,427.83
Current accounts and receivables:			
Trade receivables		**-**	1,042
Other receivables		**12,709.61**	539.664,85
Prepaid expenses		**8,666.55**	6,245.25
Total current accounts and receivables		**21,376.16**	546.952,10
TOTAL CURRENT ASSETS		**5,656,486.82**	5,321,379.93
Non-current assets			
Tangible fixed assets, net	2	**11,624.00**	15,404.00
Total non-current assets		**11,624.00**	15,404.00
Total assets		**5,668,110.82**	5.336.783,93
Current liabilities			
Liability to banks		**-**	11.36
Creditors	3	**121,990.82**	208,804.23
Accrued expenses	4	**1,647,984.76**	755,406.25
Other liabilities	5	**25,418.08**	29,530.85
Deferred income	6	**1,840,011.85**	2,111,866.72
TOTAL CURRENT LIABILITIES		**3,635,405.51**	3,105,619.41
Equity of organisation			
Operating result		**(198,459.21)**	243,864.57
Unrestricted operating funds		**2,231,164.52**	1,987,299.95
Total equity of the organisation		**2,032,705.31**	2,231,164.52
TOTAL EQUITY AND LIABILITIES		**5,668,110.82**	5.336.783,93

Table 2: Statement of comprehensive income for the year as of 31 December 2018

	Notes	EUR 2018	EUR 2017
Income	7		
Turnover from sales		**812.03**	500.00
Public institutional funding:	7		
Governmental & international organisations		**2,415,705.47**	3,865,682.22
EU & IMI grants		**3,305,080.47**	5,906,243.02
EDCTP		**2,134,617.52**	0.00
Total public institutional funding	7	**7,855,403.46**	**9,771,925.24**
Other income net		**24,578.41**	13,915.62
TOTAL INCOME		**7,880,793.90**	9,786,340.86
Social mission expenditure			
Research & vaccine development expenditure:	8		
EVI vaccine development projects		**1,781,955.96**	3,246,732.63
EU-funded research and vaccine development projects		**1,434,371.41**	4,967,535.60
IMI funded research and vaccine development projects		**1,876,302.71**	937,168.59
EDCTP-funded research and vaccine development projects		**2,134,617.52**	0.00
Advocacy & communications expenses		**107,551.41**	55,657.56
TOTAL SOCIAL MISSION EXPENDITURE		**7,334,799.01**	9,207,094.38
Supportive social mission expenditure	8		
Training, quality assurance and project development		**11,053.25**	19,851.61
Fundraising		**178,840.98**	138,281.15
Governance		**32,194.02**	51,849.58
TOTAL SUPPORTIVE SOCIAL MISSION EXPENDITURE		**222,088.25**	209,982.34
Non-social mission expenditure	8		
General executive administration		**522,365.85**	126,641.59
TOTAL NON-SOCIAL MISSION EXPENDITURE		**522,365.85**	126,641.59
TOTAL EXPENDITURE		**8,079,253.11**	9,543,718.31
Operating surplus / (deficit)		**(198,459.21)**	245,106.57
Other income (expenses)			
Financial income, net	7	**-**	1,242.02
Total other income (expenses), net		**-**	1,242.02
Net surplus/ (deficit) for the year prior to allocations		**(198,459.21)**	243,864.57
Allocation / (release) to restricted operating funds in equity		**-**	-
Allocation / (release) to unrestricted operating funds in equity		**198,459.21**	(243,864.57)
NET SURPLUS FOR THE YEAR AFTER ALLOCATIONS		**-**	-

Table 3: Funds flow statement for the year ended 31 December 2018 (with 2017 comparative figures)

Funds flow from operations	EUR 2018	EUR 2017
Net surplus(deficit) for the year	**(198,459.21)**	243,864.57
Depreciation of fixed assets	**7,673.89**	9,575.00
Increase (decrease) in provisions	**(4,124.13)**	(62,639.24)
(Increase) Decrease in other receivables	**527,997.24**	(516,210.53)
(Increase) Decrease in prepaid expenses	**(2,421.30)**	8,147.12
Increase (decrease) in creditors	**(86,813.41)**	(880,718.81)
Increase (decrease) in accrued expenses	**892,578.51**	(1,223,526.53)
Increase (decrease) in deferred income	**(271,854.87)**	(311,149.88)
FUNDS FLOW FROM OPERATIONS	**864,576.72**	(2,732,658.30)
Funds flow from investing activities	**2018**	2017
(Increase) Decrease of investments in tangible fixed assets	**(3,893.89)**	(9,575.00)
FUNDS FLOW FROM INVESTING ACTIVITIES	**(3,893.89)**	(9,575.00)
Funds flow from financing activities	**2018**	2017
Cash increase (decrease)	**860,682.83**	(2,732,658.30)
Cash and cash equivalents – beginning of year	**4,774,427.83**	7,507,086.13
CASH AND CASH EQUIVALENTS – END OF YEAR	**5,635,110.66**	4,774,427.83

Statement of changes in equity for the year ended 31 December 2018 (EUR)

Internally generated funds as of 31 December 2017	Opening balance	Allocation	Internal fund transfers	Closing balance
Paid-in capital	-	-	-	-
Surplus for the year	-	243,864.57	(243,864.57)	-
Restricted operating funds	1,987,299.95	-	-	1,987,299.95
Unrestricted operating funds	-	-	243,864.57	243,864.57
CAPITAL OF THE ORGANISATION	1,987,299.95	243,864.57	-	2,231,164.52
Internally generated funds as of 31 December 2018				
Paid-in capital	-	-	-	-
Surplus (deficit) for the year	-	(198,459.21)	198,459.21	-
Restricted operating funds	1,987,299.95	-	-	1,987,299.95
Unrestricted operating funds	243,864.57	-	(198,459.21)	45,405.36
CAPITAL OF THE ORGANISATION	2,231,164.52	(198,459.21)	-	2,032,705.31

Notes to the financial statement for the year 2018

Note 1 - Significant Accounting Policies

e. 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. Since July 2016, EVI introduced SAP Business by Design as the new accounting tool with fully integrated features from the previously used accounting system 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. For the year of 2018 several improvements have been made to SAP and paperwork was transferred to electronic methods and integrated to SAP.

f. 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. The EVI accounting method is accrual based, with consideration of projects governed by external guidelines. One major basis of accounting that should be mentioned is that EVI recognizes the accounting treatment prescribed by International Accounting Standard (IAS) 20, namely to recognise income through grants received at the time and up to the amount of expenditures allocated hereto, the residual amount of the grants received 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 are 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.
f. Negative amounts are shown within brackets as required by standard.

g. 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.

h. Funding parties in 2018

EVI is currently funded by Governmental agencies (GHIT) and the European Union in addition to the EDCTP and IMI whom are EU financed.

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.

i. 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 grant received and the cumulative expenses incurred is accounted for as a 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.

j. 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.

k. Payables

All payables of EVI are attributed to the financial statement in the cost-relevant year on the basis of accrual-based accounting. Payables are identified, evaluated and approved by the relevant project leaders for proof of deliverables and milestones. The Finance Unit then posts them accordingly to the respective accounts.

l. Social mission expenditure

Social mission expenditures are expenses made with direct effect on targets, as defined within the statutory purposes of EVI, its vision and mission.

Expenditures and grants allocated for R&D and other scientific 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 unspent at the year end, it is included under current liabilities. Expenses paid before year end for the following period are recorded as deferred expenses under current assets.

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

m. Investment income and interest receivable

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

n. 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.

o. Funds accounting

Funds held by EVI are either:

- Core innovation 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

p. 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 and non-productive hour by employees, which are segmented in defined dimensions in detail, and are posted to the accounting system as such.

q. 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 and part of projects subcontracted to partners and current expenditures required to achieve the objectives for the year. Budget rewvisions 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.

r. Tangible fixed assets

Tangible fixed assets are separately presented in the financial statement at historic acquisition costs as well as the amount of accumulated depreciation. Depreciation is accounted by straight-line method of depreciation over the duration of useful live of the specific items. The duration of useful lives is based on the German list of depreciation for wear and tear (Absetzung für Abnutzung (AfA))

s. 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.

t. Provisions and accruals

A provision and accrual 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. Amount and time of the settlement however bear a certain degree of uncertainty.

Provisions and accruals are measured according to the management's best estimates of the expenditure required to settle that obligation on the date of annual closure.

u. Equity

Funds held by EVI as equity:
Equity is utilised as a strategic reserve for the funding of all activities of EVI in line with its statutory purposes, its vision and mission. EVI does not pay out any dividends or similar benefits to its shareholders as stipulated by the statutes of the organisation.

v. 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 DKK/EUR. Monetary and non-monetary assets and liabilities denominated in foreign currencies at the statement of financial position date are translated to Euros in accordance with the provisions of the German GAAP. Foreign exchange differences arising on translation are recognised in the statement of comprehensive income. EVI has, for the year 2018, made use of the following currencies: EUR, DKK, INR, USD, JPY, GBP and XOF.

w. 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 statement of comprehensive income and statement of financial position 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 audit to Prentis & Co, Cambridge, UK. Prentis & Co visited EVI offices December 2018 as part of conducting the internal audit for 2018 during the period from October until December.

Note - 2 Tangible fixed assets (EUR)

Net carrying amount 31/12/2017	
Beginning of the period 1.1.2017	24,979.00
Additions	-
Disposals	-
End of the period 31.12.2017	24,979.00
Accrued amortization 2017	-
Accumulated amortization 2017	9,575.00
END OF THE PERIOD 31.12.2017	15,404.00
Net carrying amount 31/12/2018	
Beginning of the period 1.1.2018	15,404.00
Additions	3,893.89
Disposals	-
END OF THE PERIOD 31.12.2018	19,297.89
Accrued amortization 2018	-
Accumulated amortization 2018	7,673.89
END OF THE PERIOD 31.12.2018	11,624.00

Note - 3 Creditors

	EUR 2018	EUR 2017
Creditors for grant linked payments	**106,852.92**	190,246.16
Other creditors	**15,137.90**	18,558.07
TOTAL	**121,990.82**	208,804.23

Note - 4 Accrued expenses

	EUR 2018	EUR 2017
Accrued paid leave	**89,219.34**	63,928.17
Accrued payables (grants linked)	**1,365,128.71**	566,518.81
Accrued direct costs	**38,936.71**	50,025.82
Accrued indirect costs	**154,700.00**	71,203.08
Accrued other expenses	**-**	3,730.37
TOTAL	**1,647,984.76**	755,406.25

Note - 5 Other Liabilities (EUR)

Carrying period as per 31/12/2017	
Tax provisions	23,078.91
Social charges provisions	3,537.68
Other provisions	2,914.26
TOTAL PROVISIONS 31.12.2017	29,530.85
Carrying period as per 31/12/2018	
Tax liabilities	18,497.15
Social charges liabilities	5,383.18
Other liabilities	1,537.75
TOTAL LIABILITIES 31.12.2018	25,418.08

Note - 6 Deferred income

Cumulative donations committed to EVI as of 31 December 2018 and current deferred income

DONORS	Contract Currency	Total commitments in currency	Total commitments in Euro	Deferred liabilities 31-12-2017	Incoming payments	Outgoing transactions	Remains as deferred liabilities 31-12-2018
GHIT - JP	JPY	757,115,556.00	5,797,209.46	492,043.41	1,062,195.61	1,424,250.18	**129,988.84**
EU - FP7	EUR	16,229,077.00	16,229,077.00	(526,216.77)	464,882.50	(61,334.27)	**-**
EU - H2020	EUR	15,518,071.00	15,518,071.00	560,370.70	2,459,731.72	2,200,298.77	**819,803.65**
EDCTP	EUR	8,674,445.17	8,674,445.17	-	2,909,804.16	2,134,617.52	**775,186.64**
IMI	EUR	8,000,000.00	8,000,000.00	181,333.52	1,810,001.91	1,876,302.71	**115,032.72**
EVI reserve funds	EUR	3,321,642.18	3,321,642.18	878,119.09	-	878,119.09	**-**
TOTAL			57,540,444.81	1,585,649.95	8,706,615.90	8,452,254.00	**1,840,011.85**

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

Donator/Grant	Type	Balance 31/12 2017	Incoming payments	Outgoing transactions	Balance 31/12 2018
EVI Reserve Funds	Core	878,119.09	-	878,119.09	**-**
JP GHIT /LEISHDNAVAX	Restricted	76,663.11	-	(8,892.42)	**85,555.53**
JP GHIT /SEmalvac	Restricted	(122,123.77)	-	(122,123.77)	**-**
JP GHIT /Semalvac2	Restricted	537,504.07	1,062,195.61	1,555,266.37	**44,433.31**
EU EDUFLUVAC	Restricted	(253,515.68)	300,715.84	47,200.16	**-**
EU TRANSVAC 2	Restricted	311,798.52	-	211,493.91	**100,304.61**
EU MultiMalVax	Restricted	(272,701.09)	164,166.66	(108,534.43)	**-**
EU ZIKAVAX	Restricted	248,572.18	2,459,731.72	1,988,804.86	**719,499.04**
IMI FLUCOP	Restricted	28,859.59	-	26,078.54	**2,781.05**
IMI VAC2VAC	Restricted	152,473.93	1,810,001.91	1,850,224.17	**112,251.67**
EDCTP PREV-PKDL	Restricted	-	2,784,129.77	2,101,530.19	**682,599.58**
EDCTP MMVC	Restricted	-	125,674.39	33,087.33	**92,587.06**
EVI Equity Reserves	Core	2,231,164.52	-	198,459.21	**2,032,705.31**
Total core		3,109,283.61	-	1,076,578.30	**2,032,705.31**
Total restricted		707,530.86	8,706,615.90	7,574,134.91	**1,840,011.85**
TOTAL EVI FUNDS AVAILABLE		3,816,814.47	8,706,615.90	8,650,713.21	**3,872,717.16**

Note - 7 Income / realised (EUR)

Funding used per project (restricted and unrestricted)

	GHIT	EU	IMI	EDCTP
GHIT/EVI vaccine development projects	1,709,335.94	-	-	-
Supportive EVI vaccine development costs	-	-	-	-
EU research & development projects	-	1,434,371.41	-	-
Supportive EU project development costs	-	-	-	-
IMI research & development projects	-	-	1,876,302.71	-
Supportive IMI project development costs	-	-	-	-
EDCTP research & development projects	-	-	-	2,134,617.52
Supportive EDCTP project development costs	-	-	-	-
Executive administration	-	-	-	-
Internal allocations	-	-	-	-
TOTAL INCOME	1,709,335.94	1,232,204.32	1,876,302.71	2,134,617.52

	Reserve funds	Total Income pr. Activity	Unfunded deficit	Total Income
GHIT/EVI vaccine development projects	72,620.02	1,781,955.96	-	1,781,955.96
Supportive EVI development costs	288,021.17	288,021.17	-	288,021.17
EU R&D projects	-	1,434,371.41	-	1,434,371.41
Supportive EU development costs	18,180.38	18,180.38	-	18,180.38
IMI R&D projects	-	1,876,302.71	-	1,876,302.71
Supportive IMI development costs	10,825.82	10,825.82	-	10,825.82
EDCTP R&D projects	-	2,134,617.52	-	2,134,617.52
Supportive EDCTP development costs	12,612.29	12,612.29	-	12,612.29
Executive administration	522,365.85	522,365.85	-	522,365.85
Internal allocations	-	-	(198,459.21)	(198,459.21)
TOTAL INCOME	924,625.53	8,079,253.11	(198,459.21)	7,880,793.90

Note - 8 Social & non-social mission expenditure	Notes	EUR 2018	EUR 2017
GHIT/EVI VACCINE DEVELOPMENT PROJECTS			
AMA1-DiCo	(a)	**75,213.11**	-
MVDvax	(a)	**-**	34,487.56
SEmalvac	(a)	**(2,593.09)**	54,284.50
SEmalvac 2	(a)	**1,514,831.53**	543,057.10
LEISHDNAVAX	(a)	**194,504.41**	2,614,903.47
Supportive vaccine development costs	(a)	**288,021.17**	226,901.39
TOTAL GHIT/EVI VACCINE DEVELOPMENT PROJECTS		**2,069,977.13**	3,473,634.02
EU funded research and development projects			
MULTIMALVAX		**-**	72,193.13
PLACMALVAC		**-**	149,707.62
EDUFLUVAC		**463,938.50**	1,302,865.67
ZIKAVAX		**758,939.00**	44,570.15
TRANSVAC 2		**211,493.91**	3,398,199.03
Supportive project development costs		**18,180.38**	26,032.44
TOTAL EU FUNDED RESEARCH AND DEVELOPMENT PROJECTS		**1,452,551.79**	4,993,568.04
IMI funded research and development projects			
VAC2VAC		**1,850,224.17**	919,554.66
FLUCOP		**26,078.54**	17,613.93
Supportive project development costs		**10,825.82**	1,401.93
Total IMI funded research and development projects		**1,887,128.53**	938,570.52
EDCTP funded research & development projects			
PREV-PKDL		**2,101,530.19**	-
MMVC		**33,087.33**	-
Supportive project development costs		**12,612.29**	11,304.14
TOTAL EDCTP FUNDED RESEARCH & DEVELOPMENT PROJECTS		**2,147,229.81**	11,304.14
Executive administration			
Executive administrative management cost [50]		**522,365.85**	126,641.59
TOTAL EXECUTIVE ADMINISTRATION		**522,365.85**	126,641.59
TOTAL OF ALL PROJECTS RELATED EXPENDITURE	(b)	**8,079,253.11**	9,543,718.31

50 The management percentage represents a share of the total incurred costs, which are indirectly contributing to the progress of the science or the projects. It includes costs such as rent, utility, payroll management, general secretariat work, audit costs, tax management etc., which are essential for the work of the EVI secretariat and as such for the administration of the projects. The costs are total management costs less overhead coverage from active projects (absorption of management costs).

(a) Breakdown of R&D coordination expenditure per activity

	EUR 2018	EUR 2017
1 - Project development	**245,954.34**	168,960.73
2 - Process development	**44,712.64**	705.54
3 - Production	**80,446.83**	1,192.77
4 - Clinical trials	**1,597,916.74**	3,212,881.72
5 - Other support services	**-**	-
6 - International collaboration	**113,558.87**	88,067.93
7 - Quality Assurance	**-**	1,825.33
TOTAL	**2,082,589.42**	3,473,634.02

(b) Breakdown R&D coordination expenditure for pre-clinical and clinical activities costs per purpose in 2018 – value of above €5,000

Projects	Partners
AMA1-DiCo	Inserm – Final project payment
SEmalvac 2	2 African & Japanese Partners, statistician and monitoring contractors
LEISHDNAVAX	4 European and Japanese partners
VAC2VAC	13 European Partners
EDUFLUVAC	5 European Partners
ZIKAVAX	3 European Partners
PREV-PKDL	5 African & European Partners

(c) Presentation of EVI expenditures per nature of expenses

	EUR 2018	EUR 2017
Payables – GHIT/EVI program related	**1,560,742.99**	3,164,761.52
Payables - EDCTP program related	**1,978,246.22**	-
Payables - EU program related	**1,015,505.88**	4,896,042.79
Payables - IMI program related	**1,662,604.67**	-
Salary cost (also includes in-house consultants)	**1,036,138.52**	1,035,804.54
Contract service expenses	**77,592.55**	91,273.92
Facility & equipment maintenance expenses:	**83,465.15**	76,439.74
Equipment, hardware & software	**7,673.89**	9,575.00
Travel & meetings expenses:	**170,738.98**	116,717.88
Other Direct expenses:	**332,286.09**	(11,303.22)
Indirect Business expenses:	**133,496.41**	159,584.97
Governance expenses:	**20,761.76**	4,408.29
EU ESAC, SAC, SC expenses:	**-**	412.88
TOTAL EXPENSES	**8,079,253.11**	9,543,718.31

Note 9 - EVI stock of vaccine and adjuvant vials (non-accounted stock value)

Inventory ID	Name	Product type	Description	Batch number	Stock 01/01/18	Changes 2018	Quantity 31/12/18
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	1222	(0)	1222
NOVALABS	EVIy003	Adjuvant	Alhydrogel Line B	EVIy002	1390	(0)	1390
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line A	EVIc001	1737	(0)	1737
NOVALABS	EVIc001	Adjuvant	Alhydrogel Line B	EVIc001	1805	(0)	1805

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 December 31, 2018.

Management's Responsibility for the Financial Presentation

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

Auditor's Responsibility

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

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

We have issued a separate audit opinion on the German GAAP financial statements as at December 31, 2018 of European Vaccine Initiative EWIV, Heidelberg, dated April 5, 2019.

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 December 31, 2018 in accordance with IFRS as endorsed by the EU relevant to preparing such Financial Presentation.

Heidelberg, 30 April, 2019

FALK GmbH & Co KG
Wirtschaftsprüfungsgesellschaft
Steuerberatungsgesellschaft

(Meyer)
Wirtschaftsprüfer

(Ahrens)
Wirtschaftsprüfer

GOVERNANCE

as of 31 December 2018

EVI Board

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.

Members of the EVI Board

Wolfgang Herzog
Heidelberg University
(2014)

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

Corine Kruiswijk
Institute for Translational Vaccinology, Bilthoven
(June 2016)

Clemens Kocken
Biomedical Primate Research Centre, Rijswijk, The Netherlands
(March 2011)
Chair (December 2013)

Claude Leclerc,
Institut Pasteur, Paris
(November 2014)

Samuel McConkey,
Royal College of Surgeons in Ireland, Dublin (June 2016)

David Salisbury
Jenner Vaccine Foundation, Oxford
(March 2012)

Marita Troye-Blomberg
Wenner Gren Institute, Stockholm University, Vice Chair (August 2009) (Former Chair)

EVI Board of Stakeholders (BoS)

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

Members of the EVI BoS

Suresh Jadhav
Serum Institute of India, Pune, India

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

Jean-Paul H. Prieels
MaSTherCell, Belgium

Sodiomon Bienvenu
Sirima, Chairman, Groupe de Recherche Action en Santé, Ouagadougou, Burkina Faso

Charles de Taisne,
Consultant, France

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

Members of the EVI SAC

James Searl Robertson
Independent,
United Kingdom,
SAC Chairperson

Michael Lanzer
Universitäts Klinikum
Heidelberg, Germany,
SAC Vice-Chairperson

Nancy Le Cam
Bouveret, Moderna,
USA

Dominique Mazier
Université Pierre et Marie
Curie, France

Johan Vekemans
World Health Organization
Switzerland

Diana Boraschi
National Research Council,
Naples, Italy

Nadia Tornieporth
University of Applied
Sciences & Arts
Hannover, Germany

Francine Ntoumi,
Université Marien
Ngouabi, Republic of
Congo

Nathalie Garçon
BIOASTER Technology
Research Institute,
France

EVI Scientific Advisory Committee (SAC)

The independent Scientific Advisory Committee makes recommendations to the EVI Board on scientific direction and technologies as well as on the choice of applications for funding. The EVI SAC consists of experts in infectious diseases, immunology, regulatory and vaccine research and development.

FRMC

The FRMC provides independent advice to the EVI Board on the financial reporting and on the financial risks associated with the different EVI projects. The FRMC makes recommendations to the EVI Board with regards to financial managerial decisions.

Members of EVI Finance and Risk Management Committee (FRMC)

Clemens Kocken
(Biomedical Primate
Research Centre,
Rijswijk, The
Netherlands)

Terry McWade
(Chair of FRMC)

Martin Trillsch
(legal Counsel,
University Clinical
Centre, Heidelberg,
Germany

Secretariat

Members of EVI Secretariat

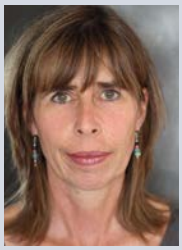
Odile Leroy
Executive Director

Flavia D'Alessio
Project Manager

Hilde Depraetere
Senior Project Manager

Sandra Hauenstein
Accounting Assistant

Nicolas Havelange
Production Director, Consultant



Sophie Houard
Director of Vaccine Development

Stefan Jungbluth
Head of Business Development

Thorsten Kohaut
Chief Financial Officer

Sten Finnsson
Finance & HR, Director

Nicola Viebig
Chief Scientific Officer

Monika Ślęzak
Project Manager

ACKNOWLEDGMENTS

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- **Danida**, Denmark's development cooperation, Denmark
- **Department of Foreign Affairs**, Irish Aid, Ireland
- **Dutch Ministry of Foreign Affairs**, Directorate-General for International Cooperation (DGIS), The Netherlands
- **Dutch Research Council**, The Netherlands
- **European and Developing Countries Clinical Trials Partnership (EDCTP)**, The Netherlands, with co-funding from EU Member States and other countries
- **European Union (EU)**, Belgium
- **Federal Ministry of Education and Research (BMBF) through KfW**, Germany
- **Global Health Innovative Technologies (GHIT) Fund**, Japan
- **Innovative Medicines Initiative (IMI)**, Belgium
- **Nobelpharma Co., Ltd.**, Japan
- **Swedish Ministry of Foreign Affairs**, Swedish International Development Cooperation Agency (Sida), Sweden
- **World Health Organization - Special Programme for Research and Training in Tropical Diseases (WHO-TDR)**, Switzerland
- Minor donations and support though marketing and communications
  - **All4Cloud**
  - **SAP**
- Co-funding was kindly provided by the following organisations:
  - **NIH – NIAID**, United States of America
  - **Research Institute for Microbial Diseases (RIMD)**, Japan
  - **Centre National de Recherche et de Formation sur le Paludisme (CNRFP)**, Burkina Faso
  - **University of Copenhagen**, Denmark
  - **Danish National Advanced Technology Foundation**, Denmark
  - **Inserm**, France
  - **Institut National de la Transfusion Sanguine (INTS)**, France
  - **Centre National de la Recherche Scientifique (CNRS)**, France
  - **Austrian Federal Ministry of Science and Research**, Austria
  - **University of Oxford**, United Kingdom
  - **Sanofi Pasteur (SP)**, France
  - **Zoetis Belgium SA (Zoetis)**, Belgium
  - **Merial**, France
  - **Boehringer Ingelheim (BI)**, Germany
  - **Intervet International B.V.,** also known as MSD Animal Health (MSD), Netherlands
  - **GSK Biologicals (GSKBio)**, Belgium
  - **Wellcome Trust**, United Kingdom

LIST OF ABBREVIATIONS

3D7	Plasmodium falciparum clone 3D7
ADCI	Antibody-Dependent Cellular Inhibition
AS01B	GSK Biologicals' Adjuvant System AS01B
AS02A	GSK Biologicals' Adjuvant System AS02A
ASTMH	American Society for Tropical Medicine and Hygiene
BF	Burkina Faso
BI	Boehringer Ingelheim
BK-SE36	Plasmodium falciparum serine repeat antigen-5 formulated with aluminium hydroxyl gel
BMBF	German Federal Ministry of Education and Research
BoS	Board of Stakeholders
BPRC	Biomedical Primate Research Centre
CDC	Center for Diesease Control and Prevention
CEA	Commissariat à l'énergie atomique et aux énergies alternatives
CEPI	Coalition for Epidemic Preparedness Innovations
CF	Cash Flow
ChAd	Chimpanzee Adenovirus
CHMI	Controlled Human Malaria Infection
CI	Confidence Intervals
CIC	Centre d'investigation clinique
CIDEIM	Centro Internacional de Entrenamiento e Investigaciones Medicas
CL	Cutaneous Leishmaniasis
CMO	Contract Manufacturing Organisation
CMP	Centre for Medical Parasitology (CMP), University of Copenhagen
CNRFP	Centre national de recherche et de formation sur le paludisme
CPA	Cysteine proteinases A
CPB	Cysteine proteinases B
CpG	Cytosine triphosphate deoxynucleotide phosphodiester link to Guanine triphosphate deoxynucleotide DNA
CSA	Chondroitin Sulfate A
CSP	Circumsporozoite Protein
CSP R21	adjuvanted Circumsporozoite Protein particle (R21)
DALY	Disability-Adjusted Life Years
DBL	Duffy-Binding-Like
DGIS	Directorate General for International Cooperation at Ministry of Foreign Affairs, The Netherlands
DNA	Deoxyribonucleic Acid
DNDi	Drugs for Neglected Diseases initiative
DSMB	Data Safety Monitoring Board
DSW	Deutsche Stiftung Weltbevölkerung
E. coli	Escherichia coli
EDCTP	European and Developing Countries' Clinical Trials Partnership
EDQM	European Directorate for the Quality of Medicines & HealthCare
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
EMVI	European Malaria Vaccine Initiative
EPI	Expanded Programme on Immunization
ERA	European research area
ERP	Enterprise Resource Planning
EU	European Union
EUR	Euro (currency of European Union)
EVI	European Vaccine Initiative
F-CRIN	French Clinical Research Infrastructure Network
Fraunhofer IME	Fraunhofer Institute for Molecular Biology and Applied Ecology
FRMC	Financial Risk Management Committee
GAAP	German General Accepted Accounting Principles
GBP	British Pound
GCP	Good Clinical Practice
GHIT	Global Health Innovation Technology
GHRP	Good Health Research Practice
GIA	Growth Inhibition Assay
GLA	Glucopyranosyl Lipid A Adjuvant-Stable Emulsion
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HA	Haemagglutinin
HAI	Haemagglutination- Inhibition Assay
HGB	Handelsgesetzbuch - German Commercial Code
HASPB	Hydrophilic acylated surface protein B
HTF	Danish National Advanced Technology Foundation
IAS	International Accounting Standard
IB	Investigator's Brochure
iBET	Instituto de Biologia Experimental e Tecnológica
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
Inserm	Institut national de la santé et de la recherche médicale
Intravacc	Institute for Translational Vaccinology
INTS	Institut national de transfusion sanguine, France
IPP	Institut Pasteur Paris
IPTp	Intermittent Preventive Treatment during Pregnancy
IR	Ireland
IRD	Institut de recherche pour le développement
IRSS	Institut de Recherche en Sciences de la Santé
ISA	International Standards on Auditing
JPY	Yapanese yen
JRAs	Joint Research Activities
kDa	Kilodalton
KEMRI	Kenya Medical Research Institute
KfW	Kreditanstalt für Wiederaufbau

KHRC	Kintampo Health Research Centre
Kmp11	Kinetoplastid membrane protein 11
LEAP	Leishmaniasis East Africa Platform
LMIC	Low- and Middle-Income Countries
LMIV	Laboratory of Malaria Immunology and Vaccinology
LSHTM	London School of Hygiene & Tropical Medicine
LSQ	Liposome-QS21 formulation
Matrix M	Adjuvant by Novavax, in which matrix complexes are formed by a specific mixture of Quillaja saponin, cholesterol and phospholipids
MCL	Mucocutaneous Leishmaniasis
MERS	Middle East Respiratory Syndrom
ME-TRAP	Multiple Epitope Thrombospondin-Related Adhesion Protein
MHRA	Medicine and Healthcare Products Regulatory Agency
MIDGE	Minimalistic Immunogenically Defined Gene Expression
MMVC	Multi-Stage Malaria Vaccine Consortium: field efficacy testing of a multi-stage malaria vaccin
MN	MicroNeutralisation virus assay
MPL	Monophosphoryl Lipid A
MRC	Medical Research Council, Gambia
MRTC	Malaria Research and Training Center
MSc	Master of Science
MSP	Merozoite Surface Protein
MTA	Material Transfer Agreement
MultiMalVax	Multi-stage Malaria Vaccine
MV	Measles Vector
MVA	Modified Vaccinia Virus Ankara
MV-CHIK	MV-based Chikungunya
MVI	Malaria Vaccine Initiative
MVVC	Malaria Vectored Vaccines Consortium
MVVC 2	Malaria Vectored Vaccines Consortium 2
NA	Neuraminidase
NEKKEN	Institute of Tropical Medicine Nagasaki University
NGO	Non-governmental organisation
NHP	Non-Human Primate
NIBSC	National Institute for Biological Standards and Control
NIH/NIAID	National Institutes of Health / National Institute of Allergy and Infectious Diseases
ODN	Oligodeoxynucleotides
OMCL	Official Medicines Control Laboratories
P27A	Fragment P27A of PFF0165c malaria protein
PAMCPH	Recombinant VAR2CSA protein as a vaccine candidate for pregnancy-associated malaria
PBMC	Peripheral Blood Mononuclear Cells
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
PKDL	Post Kala-azar Dermal Leishmaniasis
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
PRIMVAC	Recombinant VAR2CSA DBL1-2 Vaccine Candidate
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
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
SMEs	Small and Medium Enterprises
SN	Senegal
Swiss TPH	Swiss Tropical and Public Health Institute
TLR	Toll-Like Receptor
TRANSVAC	European Network of Vaccine Research and Development
TSA	Thiol-specific antioxidant protein
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
USD	US Dollar
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
VL	Visceral Leishmaniasis (also known as kala-azar)
VLP	Virus-like Particle
WBVR	Wageningen Bioveterinary Research
WP	Work Package
WHO	World Health Organization
XOF	Currency of Communauté Financière Africaine (BCEAO)
ZIKAVAX	Fast track development of a Zika vaccine based on measles vector

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