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A paradigm for Africa-centric vaccine development in Equatorial Guinea

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The Equatorial Guinea Malaria Vaccine Initiative (EGMVI) highlights how long-term African government and international energy industry investment, plus novel partnerships, can enable clinical development of vaccines in Africa, for Africa. We review achievements and challenges of this pioneering, award-winning, public–private partnership which offers a model for future Africa-centric clinical research and development (R&D).

The EGMVI: genesis of a novel partnership

In 2004, the Government of Equatorial Guinea (GEG) and a group of energy companies led by Marathon Oil and Noble Energy, among other local energy companies, began funding the comprehensive Bioko Island Malaria Control Program (BIMCP) through their corporate social responsibility (CSR) programs. Using long-lasting insecticide-treated bednets, indoor residual insecticide spraying, and case management, the BIMCP, implemented by the non-governmental organization (NGO) MCD Global Health in conjunction with the GEG Ministry of Health and Social Welfare (MHSW), reduced malaria prevalence in children aged 2–14 years on Bioko Island from 45% to 13.7% by 2012 [1]. The BIMCP has continued to limit malaria-related morbidity across Bioko Island; however, the overall malaria prevalence has plateaued since 2012, with no further significant reductions in recent years.

To strengthen the program, GEG and partnering energy companies agreed to an expanded strategy supporting development of *Plasmodium falciparum* (Pf) sporozoite (SPZ) vaccines against Pf malaria [2]. These vaccines, produced by Sanaria Inc., were designed to prevent infection rather than limit morbidity and thus could contribute to malaria elimination. Funding was agreed for development and licensure of an optimized Sanaria® PfSPZ vaccine regimen for incorporation into mass vaccination programs within the Bioko Island Malaria Elimination Project (BIMEP).

The components of the EGMVI were established between 2010 and 2012 to achieve this objective. The GEG, Sanaria, and MCD Global Health developed an extensive stakeholder network to support the work (Figure 1). Key components were trans-Africa partnerships between the GEG MHSW, which had never previously conducted a clinical trial, and two highly experienced African clinical research institutions, the Ifakara Health Institute (IHI), Tanzania and the Malaria Research and Training Center (MRTC), Bamako, Mali. Sanaria served as trial sponsor, under FDA oversight, and provided investigational products and expertise in malaria and clinical trials. The partnership enlisted the Swiss Tropical and Public Health Institute (Swiss TPH) to augment research capability, provide guidance, and establish clinical research laboratories to support the clinical trials, and the World Health Organization (WHO) to help establish a national ethical review committee. The EGMVI undertook extensive human and infrastructure capacity building before conducting clinical trials in Bagamoyo, Tanzania, and Bioko Island, while concurrently planning for malaria elimination on Bioko through integrated control efforts including vaccine deployment [3] under BIMEP.

Establishing the vaccine development partnership in Equatorial Guinea

The EGMVI started with a proposal by Sanaria to Marathon CSR. Presentations and discussions led to feasibility visits to Bioko by Sanaria and IHI. An advisory group of malaria researchers from Africa, the USA, and Europe guided the project's structure and direction. Presentations and path-finding discussions with the MHSW determined the enthusiasm and provided a framework for the work plan and site selection, while the other energy companies such as AMPCO, SONAGAS, and EG LNG, and the Ministry of Mines and Hydrocarbons, agreed to provide funding and establish legal partnerships. The Equatorial Guinea (EG) president approved the program, visited Sanaria (Figure 2), and met with Sanaria leadership in EG. These activities established core relationships and a realistic sense of project needs. Critical first steps were the creation of a national ethical review committee (CENGE), which received training from the WHO and the University of Maryland Baltimore School of Medicine; the formation of a clinical research team from seconded MHSW employees and new hires (trained in clinical trial methodologies by IHI and MRTC); and the establishment by IHI and Swiss TPH of a clinical laboratory meeting international standards. La Paz Hospital in Sipopo run by the MOHSW and a team of physicians and nurses from Israel agreed to serve as the study site. This state-of-the-art private facility provided clinical space for visits, vaccinations, and follow-up, a pharmacy for vaccine preparation, clinical laboratories for blood work and malaria diagnosis, and emergency care if needed.

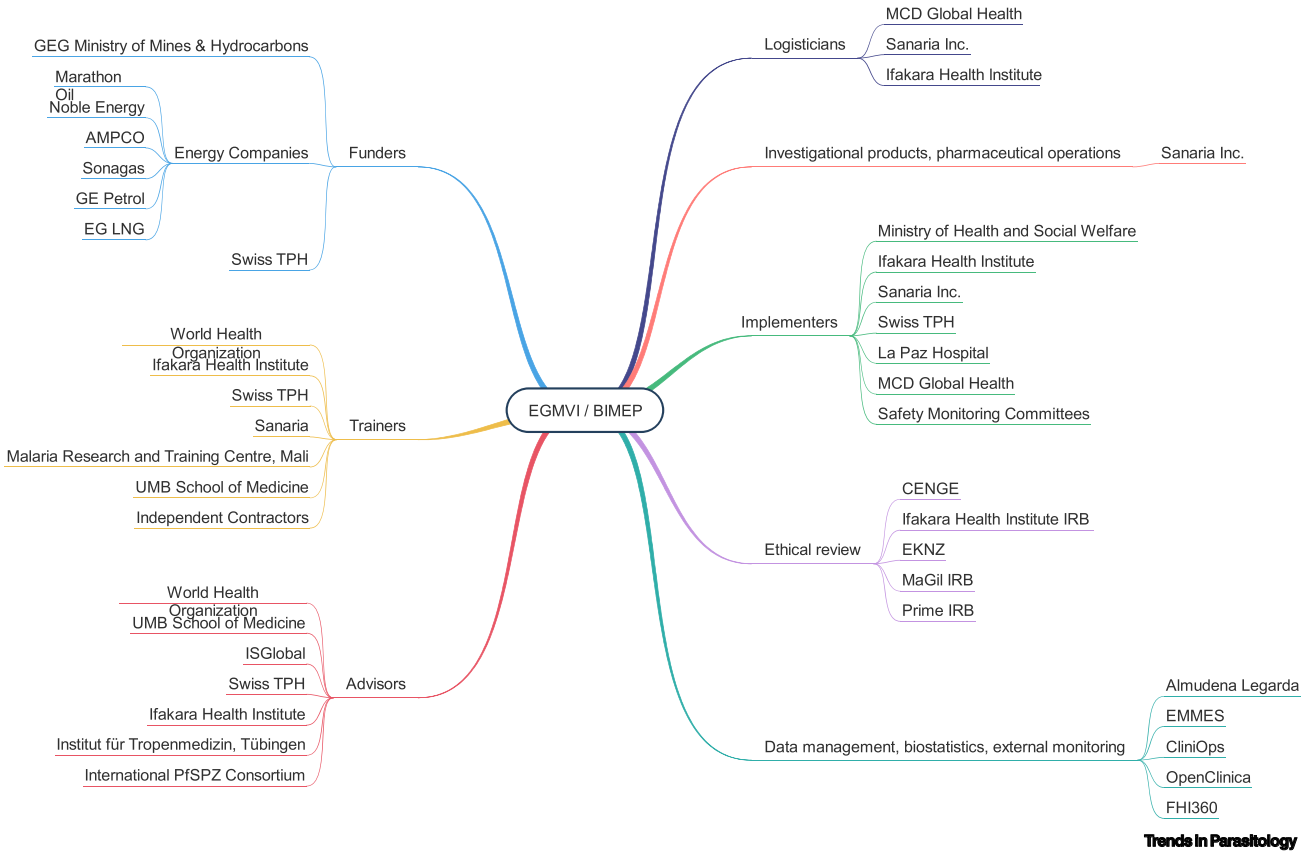

Figure 1. Stakeholders in the Equatorial Guinea Malaria Vaccine Initiative (EGMVI). The EGMVI partnership is represented by the different groups of stakeholders. The project was supported by a unique group of funders composed of the Equatorial Guinea (EG) government (GEG) and private-sector energy companies via their corporate social responsibility programs, with specific funding gaps plugged by Swiss TPH. The project took clinical research from scratch to Phase 2 vaccine trials, and the complexity and ambition required steering from a wide selection of advisors, trainers, and implementers, ensuring that checks and balances were in place at all steps. Likewise, the fledgling EG national ethics committee received back-up from coreviews by established IRBs while remaining the IRB of record. Logistics divided naturally into the expertise areas of MCD running all ground activities, Sanaria leading all vaccine activities and IHI covering all clinical activities. Abbreviations: BIMEP, Bioko Island Malaria Elimination Project; CENGE, National Ethics Committee of Equatorial Guinea; EKNZ, Ethics Committee of Northwestern and Central Switzerland; IRB, Institutional Review Board; MCD, Medical Care Development; Swiss TPH, Swiss Tropical and Public Health Institute; UMB, University of Maryland, Baltimore.

The EGMVI clinical program

The first clinical trial was conducted by IHI in Bagamoyo, Tanzania, to foster confidence and trust in the project and partners. This trial, BSPZV2, a randomized, double-blind, placebo-controlled trial (RCT), established the safety of PfSPZ vaccine (radiation-attenuated PfSPZ) in Tanzanian adults, children, and infants, and also showed that SPZ doses above a threshold size led to diminished vaccine efficacy (VE) against controlled human malaria infection (CHMI) [4,5]. A group of four IHI-Tanzanian clinical trialists then moved to Malabo to conduct the first RCT in EG, EGSPZV1, which retested PfSPZ Vaccine. A Tanzanian principal investigator (PI) worked closely with the lead Equatoguinean investigator-in-training, with similar Tanzanian mentorship provided in nursing, clinical trial coordination, documentation management, quality assurance, and laboratory science. EGSPZV1, conducted in 23 healthy malaria-exposed adults and completed in 2015, also demonstrated safety and tolerability [6]. EGSPZV2 was an age de-escalation trial of PfSPZ vaccine that assessed safety and tolerability in 6-month-old babies to 61-year-olds [7], mirroring BSPZV2 in Tanzania and expanding the safety assessment to subjects >50 years of age. EGSPZV2 also assessed VE against CHMI and was the first direct comparison of PfSPZ vaccine and PfSPZ-CVac (chemo-attenuated PfSPZ) VE [8]. EGSPZV3 identified the most efficacious of several PfSPZ vaccine regimens to transition to Phase 3 testing, and investigated the value of multi-dose priming and a delayed boost [9]. By addressing new research questions, EGSPZV2 and EGSPZV3 centrally positioned the EGMVI team in PfSPZ vaccine development. They also provided sufficient mentorship to transfer PI responsibilities to an Equatoguinean investigator, who subsequently led a malaria incidence study to determine sample size for the anticipated

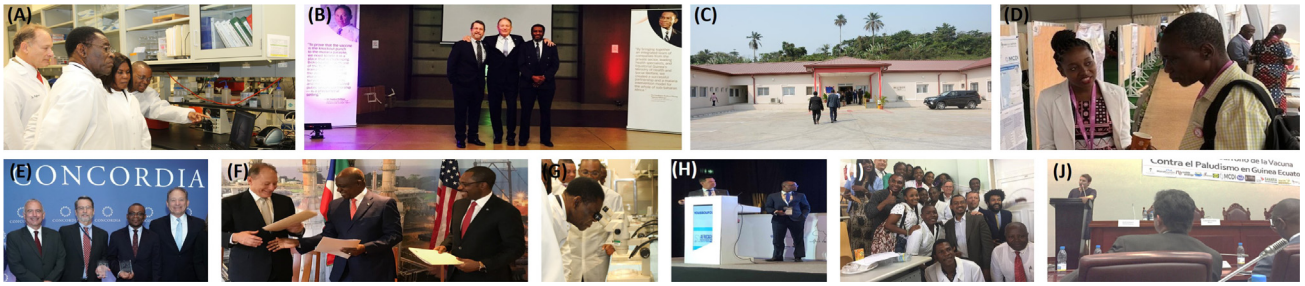

Figure 2. Images from the Equatorial Guinea Malaria Vaccine Initiative. (A) Presidential visit to Sanaria (L–R: Dr S.L. Hoffman, CEO Sanaria Inc., His Excellency T. Obiang, President of Republic of Equatorial Guinea, Mrs C. Mangue de Obiang, First Lady of Equatorial Guinea, His Excellency M. Ondo'o Ayekaba, Minister of Health and Social Welfare); (B) Celebration of 10 years of the BIMCP in Djibloho EG (L–R: Dr C. Schwabe, CEO, MCD Global Health, Dr S.L. Hoffman, Dr S. Abdulla, former Director IHI); (C) Clinical Laboratory and Hospital in Baney; (D) Ms E. Eburo, PhD student, at the 7th MIM Pan African Malaria Conference; (E) BIMEP team receiving the Concordia P3 Award (L–R: Mr P. Sanders, former General Manager Marathon Oil, EG; Dr C. Schwabe, His Excellency M. Ondo'o Ayekaba, Dr S.L. Hoffman); (F) Signing of agreement between Sanaria and GEG (L–R: Dr S.L. Hoffman, His Excellency S. Nguema Owono, Former Minister of Health and Social Welfare, GEG, His Excellency G.M. Obiang Lima former Minister of Mines and Hydrocarbons, GEG); (G) His Excellency President T. Obiang examines mosquitoes through a microscope at Sanaria; (H) Dr C. Maas (Former Marathon CSR) and HE M. Ondo'o Ayekaba presenting the BIMEP progress at the African Business Health Forum in Addis Ababa; (I) Students and presenters from the EGMVI team following presentations at the National University of Equatorial Guinea School of Medicine in Bata; (J) Professor C. Daubenberger at the International PfSPZ Consortium meeting in Sipopo.

Phase 3 trial [10]. A second trial was also conducted in Tanzania, BSPZV3, assessing the safety, immunogenicity, and VE of PfSPZ vaccine in persons living with HIV [11].

This body of work included additional training (a 2-week course in clinical trials held at IHI for Equatoguineans, including Good Clinical Practices, Human Subject Protections, and Advanced Cardiac Life Support), presentations at international conferences, and opportunities for individualized education programs. A government building was refurbished to serve as a clinical trial center, and a new combined hospital, pharmacy and laboratory building in Baney was equipped with state-of-the-art diagnostic and research capabilities including PCR and microscopy, hematology, biochemistry, mass spectrometry, facilities for processing and storage of clinical specimens, a liquid nitrogen generating plant, and an incinerator.

Closure of EGMVI

Despite completing five vaccine trials and an incidence study, and creating a clinical trial registry to support Phase 3 testing, the EGMVI ended before achieving its long-term goal of eliminating malaria from Bioko Island using Sanaria's PfSPZ vaccine in an integrated strategy. What happened?

Research on a more potent, less expensive vaccine became reality. Sanaria and collaborators developed a third-generation PfSPZ vaccine (PfSPZ-LARC2 Vaccine), based on a genetically attenuated late liver-stage-arresting replication competent (LARC) parasite [12] that is expected to be more protective at ~20% of the dose of the PfSPZ vaccine. While EGMVI funders had agreed to pursue a Phase 3 trial of PfSPZ vaccine, Sanaria was unconvinced that this was appropriate given the new, likely superior vaccine candidate, and there was no willingness by the GEG and the energy companies to pivot at this late stage to a vaccine candidate untested in humans with an extended timeline to licensure.

Concurrently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic struck. Funding for the vaccine arm of BIMEP was diverted to support MHSW efforts to protect the EG population. The EGMVI clinical research team and clinical laboratories were tasked by the MHSW with providing EG with pandemic-response capacity. The clinicians became front-line caregivers and managed quarantine programs, while the malaria laboratory, by February 2020, established molecular diagnosis of SARS-CoV-2 using qPCR, becoming among the first African laboratories certified by WHO for SARS-CoV-2 detection.

BIMEP has consequently returned to a mosquito-control-based approach along with improved primary healthcare delivery, but the option remains to reinstate a clinical research program aiming to deploy a malaria vaccine that prevents infection in >90% of individuals, consistent with Sanaria's and the WHO's strategic goals for malaria vaccines [13].

Legacy of the EGMVI partnership

The EGMVI collaboration was highly successful in training a cadre of EG clinical and laboratory scientists and in developing clinical trials' capacity, including a clinical research laboratory and study facilities, a credible ethical review process (CENGE), importation of investigational products, effective methods for recruitment and screening of research participants, and conduct of multiple clinical trials that met EG's needs as well as the global community's strict criteria for regulatory approvals, all 'firsts' for the country. To do so, the EGMVI established a unique South–South collaboration with highly experienced investigators from Tanzania, and funded and conducted six

clinical trials in Tanzania and EG. EGMVI staff gave the first MHSW presentations at international conferences, and the project supported successful completion of six master's degrees by five staff members, one PhD nearing completion, and acquisition of samples and data for future collaborative projects. Central to this was a period of initially stable private-sector funding.

The EGMVI advanced significantly the development of PfSPZ vaccines against malaria (Table 1). This included demonstration of vaccine safety in 6-month-old babies to 61-year-olds, the first direct comparison of two PfSPZ vaccine candidates, optimization and down-selection of a PfSPZ vaccine regimen for potential Phase 3 development, and the demonstration of vaccine safety in persons living with HIV and creating a clinical trials registry.

In 2019, the EGMVI partnership was independently recognized when the BIMEP received the P3 Impact Award from the US Department of State, University of Virginia Darden School of Business, and Concordia[i] for its unique development model composed of African government and private-sector funders, collaborating research institutions in Africa and Europe, key South–South partnerships, a private sector biotech company, and an NGO (Figure 2).

A paradigm for future vaccine development partnerships

The EGMVI exemplifies how African country-led and -funded partnerships can lead vaccine R&D on the continent, building on the legacy of partnerships such as the African Malaria Network Trust (AMANET) and the European and Developing Countries Clinical Trials Partnership (EDCTP). Neither of these have been led or funded by African governments. With malaria on the increase [14], the WHO has recommended that the use of the PfCSP-based RTS,S and R21 malaria vaccines be deployed for use in children [14]. It is clear that, to reach malaria elimination, parasite infection-preventing vaccines are required that can be administered to all population demographics, including at-risk groups such as HIV+ and pregnant individuals, and deployed in diverse epidemiological settings [13]. While such vaccines are likely to be successful only when included within the greater malaria-elimination tool box alongside vector control,

Table 1. Summary of clinical studies completed during the EGMVI

Studies[a]	Outcomes
EGSPZV1: Assessed safety, tolerability, and immunogenicity of PfSPZ vaccine in Equatoguinean adults [6].	In the first clinical trial in EG, 33 adult volunteers were injected with three doses of PfSPZ vaccine or normal saline placebo. There were no safety issues and the vaccine was well tolerated and stimulated specific antibody responses. Immunogenicity was comparable to that found in Mali.
BSPZV2: Assessed safety and tolerability of PfSPZ vaccine in 18–45-, 11–17-, 6–10-, and 1–5-year-olds, and 6–11-month-olds using an age-de-escalation design [4,5].	93 volunteers aged 6 months to 45 years received three doses of PfSPZ vaccine or normal saline placebo. The vaccine was safe, well tolerated and stimulated specific antibody and T cell responses. The highest vaccine efficacy (VE) against controlled human malaria infection (CHMI) was at the lower of two vaccine doses tested.
EGSPZV2a: Assessed safety and tolerability of PfSPZ vaccine in 18–61, 11–17, 6–10-, and 1–5-year-olds, and 6–11-month-olds using an age de-escalation/dose escalation design [7].	104 participants aged 6 months to 61 years were administered three doses of PfSPZ vaccine (80) or normal saline placebo (24). PfSPZ vaccine was safe, well tolerated and stimulated specific antibody responses.
EGSPZV2b: Assessed comparative immunogenicity and VE against CHMI in EG adults immunized with PfSPZ vaccine or PfSPZ-CVac (chloroquine) [8].	38 adult volunteers completed the first head-to-head comparison of PfSPZ vaccine and PfSPZ-CVac (chloroquine) for safety, tolerability and VE against CHMI. PfSPZ-CVac had higher VE than PfSPZ vaccine at a 27-fold lower dose of PfSPZ.
EGSPZV3: Assessed VE of different PfSPZ vaccine regimens, including multi-dose priming and a delayed boost [9].	96 adult volunteers received one of the four different dose regimens of PfSPZ vaccine or a normal saline placebo. PfSPZ vaccine administered at 1, 8, and 29 days provided the best protection against homologous CHMI.
BSPZV3: Assessed safety and VE of PfSPZ vaccine administered to HIV-negative and HIV-positive Tanzanian adults [11].	Nine HIV- and 12 HIV+ participants were injected with five doses of PfSPZ vaccine or normal saline placebo. PfSPZ vaccine was safe and well tolerated and protective against CHMI in HIV– but not HIV+ participants.
EGMALEP: Assessed malaria incidence in the Malabo area to support sample size design for a planned Phase 3 trial of the best PfSPZ vaccine regimen from EGSPZV3 [10].	58 episodes of Pf infection were recorded in 240 individuals aged 6 months to 45 years during a 24-week study with diagnostic blood samples taken every 2 weeks following parasite clearance.
EGRESPAR: Assessed population health status in the Malabo area and created a participant registry in preparation for a Phase 3 trial (manuscript submitted).	6493 individuals from 1807 of 2325 visited households completed household questionnaires, with 2021 continuing to screening and 1378 placed in a registry. In addition to malaria, cases of Loa loa, hepatitis B and C, and HIV were recorded.

[a]All studies were randomized, double-blind, placebo-controlled clinical trials except EGMALEP and EGRESPAR.

diagnosis and treatment, mass drug administration, and surveillance [3], their further development to reach the high bar of >90% protection against infection for >12 months needs the sustained efforts of teams and partnerships such at the EGMVI. It is time for philanthropists, donor institutions, governments, and investors across the continent to sustainably support African-centric malaria vaccine R&D.

Acknowledgments

The trial was funded by a public–private partnership, the Equatorial Guinea Malaria Vaccine Initiative (EGMVI), composed of the Government of Equatorial Guinea (EG) Ministries of Mines and Hydrocarbons, and Health and Social Welfare, Marathon EG Production Limited, Noble Energy, Atlantic Methanol Production Company (AMPCO), and EG LNG, with additional funding through Swiss TPH. Only Sanaria has a direct or indirect financial interest in the development of PfSPZ vaccines. This whole program would not have been possible without the many participants who took part and the members of Safety Monitoring Committees who voluntarily provided their time, expertise, and advice.

Declaration of interests

S.L.H. holds numerous patents related to PfSPZ vaccines. S.L.H. is founder of Sanaria Inc. and co-owner with two family members. P.F.B., T.L.R., and S.L.H. are employees of Sanaria Inc., which manufactures PfSPZ vaccines.

Resources

[i]www.concordia.net/organization/bioko-island-malaria-elimination-program/

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