

Malaria vaccine implementation programme (MVIP)

Progress update

1. Background

In 2016, the World Health Organization (WHO) estimated that 216 million cases of malaria occurred worldwide (95% confidence interval [CI]: 196–263 million) leading to an estimated 445 000 deaths.¹ Children under the age of five in sub-Saharan Africa are especially vulnerable, accounting for approximately two thirds of all global deaths due to malaria. *Plasmodium falciparum* is the most prevalent malaria parasite in sub-Saharan Africa, accounting for 99% of estimated malaria cases in 2016.

African countries have made tremendous progress in the fight against malaria using core disease-prevention tools such as insecticide-treated mosquito nets, indoor spraying with insecticides and prompt diagnosis and treatment with antimalarial medicines. However, the rate of decline in malaria case incidence and mortality has stalled and even reversed in some regions. All current malaria control tools are only partially effective, and all are based on insecticides or drugs, which are increasingly threatened by resistance. In some areas, available tools are unable to drive down malaria further. New and complementary tools are needed to further drive down the disease burden with a view to achieving — ultimately — the vision of a world free of malaria.

2. The malaria vaccine RTS,S/AS01

The Phase 3 trial of RTS,S/AS01 was conducted over 5 years (2009–2014) in 7 sub-Saharan African countries: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania. The trial enrolled approximately 15 500 infants and young children in two target age groups:

- Older children received their first dose of the malaria vaccine between 5 and 17 months of age.
- Infants received the vaccine together with other routine childhood vaccines at 6, 10 and 14 weeks of age

Efficacy: Among children aged 5–17 months who received three doses of RTS,S administered at 1-month intervals, followed by a fourth dose 18 months later, the vaccine reduced malaria episodes by 39% (95% CI, 34–43), equivalent to preventing nearly 4 in 10 malaria cases.² In addition, the 4-dose vaccine schedule reduced severe malaria by 32% (95% CI 9–48) in this age group, with reductions also confirmed in malaria hospitalizations (37%, 95% CI, 24–49), all-cause hospitalization (15%, 95% CI 4–25) and severe anaemia (62%, 95% CI 27–81). In addition, blood transfusions were reduced by 29% (95% CI 4–47) in children randomized to receive four doses of RTS,S compared with those who received none.

¹ World Malaria Report 2017, World Health Organization, Geneva, 2017

² RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet*. 2015;386(9988):31–45.

Among children aged 5–17 months who did not receive a fourth dose of the vaccine, the protective benefit against severe malaria was lost, highlighting the importance of the fourth dose of this vaccine to maximise its benefits.

Impact: The impact of RTS,S/AS01 vaccination has been assessed by an estimation of cases averted in the Phase 3 clinical trial,² and by use of mathematical models to predict the impact of RTS,S/AS01 when administered through the routine EPI programme.³ The estimated number of cases averted by RTS,S/AS01 in the trial was the sum of differences in the number of cases between the control and the RTS,S/AS01 groups, expressed per 1000 participants vaccinated. Among participants in the 5–17 month age category who received a 3-dose schedule or a 4-dose schedule, the estimated numbers of cases of clinical malaria averted by study end (M2.5-SE) were 1363 (95% CI, 995–1797) and 1774 (95% CI, 1387–2186) per 1000 vaccinees, respectively. The largest numbers of cases averted per 1000 vaccinees were at sites with the greatest disease burden, reaching more than 6500 cases averted per 1000 children vaccinated with 4 doses.

A comparison of 4 mathematical models of the potential impact of RTS,S/AS01 was carried out.³ The models assumed that vaccine implementation was added to existing levels of malaria control interventions and treatment. With an assumed coverage of 90% for the first 3 doses, with 80% of these individuals receiving the fourth dose (72% coverage overall), all models predict a substantial additional public health impact of RTS,S/AS01 in settings with PfPR₂₋₁₀ between 10% and 65%.⁴ In these settings, median modelled estimates range from 200 to 700 deaths averted per 100 000 children vaccinated with a 4 dose schedule, and 10% to 28% of all malaria deaths averted in vaccinated children aged <5 years. Public health impact and cost-effectiveness tended to be greater at higher levels of transmission.

Safety: No fatal adverse events were assessed as causally related to RTS,S/AS01 vaccination. In the 5–17 month age category, from the first dose to the trial end, serious adverse events (SAEs) were slightly less frequent in the RTS,S/AS01 groups than in the control group. In this age group, febrile convulsions were an identified risk in RTS,S/AS01 recipients in the 7 days following vaccination. In the same age group, meningitis was identified as a potential risk, with more cases of meningitis in RTS,S/AS01 recipients, compared to the control group (relative risk (RR) 8.0 (95% Confidence Interval (CI) 1.1-60.3)). Unplanned, exploratory analyses in children in the 5-17 month age category revealed more cerebral malaria cases in the RTS,S/AS01 group and, for both age categories, more deaths in vaccinated girls compared to the control group. A relationship between the RTS,S vaccine and these findings has not been established. The pilot evaluations and a Phase IV study (further explained below) have been designed to provide further information.

3. WHO position

In January 2016, WHO published its position paper for RTS,S/AS01, adopting the joint recommendation by the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC).⁵ WHO recommends pilot implementation of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational

³ Penny MA, et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *Lancet* ([http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(15\)00725-4.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)00725-4.pdf), accessed January 2016).

⁴ Prevalence of infection as measured by cross-sectional surveys in those aged 2–10 years. Prevalence of infection in children is a commonly used measure of malaria parasite transmission.

⁵ Weekly Epidemiological Record No4, 2016, 91, 33-52, Malaria vaccine: WHO Position paper.

level, covering moderate-to-high transmission settings, in order to generate critical evidence to enable decision-making about potential wider scale use.

These pilot implementations should be done with phased designs and in the context of ongoing high coverage of other proven malaria control measures. A highly critical issue is the extent to which the protection demonstrated in children aged 5–17 months in the Phase 3 trial can be replicated in the context of routine health systems, particularly in view of the need for a 4-dose schedule that requires new immunization contacts. Other questions that should be addressed as part of pilot implementations include the extent to which RTS,S/AS01 vaccination impacts all-cause mortality (including gender-specific mortality), which could not be adequately assessed in the Phase 3 trial owing to the very low overall mortality in the trial; and whether the excess cases of meningitis and cerebral malaria identified during the Phase 3 trial are causally related to RTS,S/AS01 vaccination.

Based on the efficacy data from the Phase 3 trial, WHO does not recommend the use of the RTS,S vaccine in the younger (6–12 weeks) age category, as the vaccine efficacy was found to be low in this age category.

4. Regulatory review of RTS,S/AS01

The European Medicines Agency (EMA), under a process known as Article 58, has reviewed data on the quality, safety and efficacy of RTS,S/AS01 and issued a positive scientific opinion in July 2015. The positive opinion means that the quality of the vaccine and its risk/benefit profile is favourable from a regulatory perspective. In its assessment, the EMA applies the same rigorous standards as for medicines to be marketed within the EU. The EMA's assessment is being updated as new data become available and has remained valid since the original issuance.

As a prerequisite for vaccine implementation in pilot countries, RTS,S/AS01 must be authorized for use by the respective National Regulatory Authorities (see status update in subsequent sections).

5. Malaria Vaccine Implementation Programme

The Malaria Vaccine Implementation Programme (MVIP) was established by WHO to coordinate and support the introduction of the vaccine in selected areas of Africa through country-led routine immunization programmes and to evaluate the outstanding questions related to the public health use of the vaccine. The MVIP consists of three components:

- **Vaccine introduction:** National immunization programmes in Ghana, Kenya, and Malawi will lead the pilot introduction of the malaria vaccine in areas with moderate to high malaria transmission. The aim is to reach approximately 360 000 children per year in the selected areas.
- **Pilot evaluation:** A master protocol has been developed and will be implemented by country-based research partners to evaluate: (1) the programmatic feasibility of delivering RTS,S/AS01 with new immunization contacts, including the fourth dose in the second year of life; (2) the vaccine's impact on mortality and (3) the vaccine's safety in the context of routine immunization, with an emphasis on meningitis and cerebral malaria.
- **GSK Phase 4 study:** The GSK-sponsored observational Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA to further assess vaccine safety, effectiveness and impact in routine use. The WHO-led pilot evaluation has been designed to complement the GSK Phase 4 study.

Evidence and experience from the MVP will be provided to SAGE and MPAC to inform recommendations on the vaccine's potential use on a wider scale in Africa.

5.1. Malaria vaccine implementation

The malaria vaccine introduction is country-led. RTS,S/AS01 will be implemented by the Ministry of Health through the national immunization programme in selected areas characterized by medium-to-high malaria transmission. Immunization authorities in the 3 pilot countries will specify the exact vaccination schedule, based on WHO recommendations. A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age followed by doses 2 and 3 at approximately monthly intervals and the fourth dose near the child's second birthday. RTS,S/AS01 can be co-administered with other vaccines in the national immunization programme.

Close collaboration with the national malaria control programme will ensure that existing WHO-recommended prevention tools, such as long-lasting insecticidal nets (LLINs) and artemisinin-based combination therapies (ACTs), continue to be deployed on a wide scale.

5.2. Pilot evaluation

While it is critical that the MVP represents routine vaccine implementation through the national immunization programmes, the evaluation components must be conducted in a scientifically rigorous manner to generate answers to the remaining questions. For this reason, RTS,S/AS01 will be introduced in some areas at the beginning of the programme with other areas, initially without RTS,S/AS01 introduction, acting as comparison. The division into vaccine implementation or comparison areas will be randomized in order to generate the strongest possible evidence on the impact and safety of the vaccine. Identical monitoring systems will be established in both implementation and comparison areas to record impact and safety outcomes through observational and cross sectional studies. Surveillance systems will be established and cross-sectional surveys conducted at time periods to allow evaluation of key variables more than 1 year following the administration of the fourth vaccine dose in a sufficiently large number of children to meet sample size needs.

A master protocol for the pilot evaluations was developed by WHO and received approval by the WHO Research Ethics Review Committee in February 2018. Country-based research partners will be contracted to implement country-specific protocols. The subsequent sections provide further information about the three evaluation components.

5.2.1. Feasibility evaluation

The operational feasibility of providing RTS,S/AS01 at the recommended four-dose schedule will be evaluated in the context of routine health service delivery. The primary objective of the feasibility evaluation will be to estimate the coverage of RTS,S/AS01 in the implementation areas, defined as the proportion of children aged 12-23 months who had received 3 doses of RTS,S/AS01 by 12 months of age, and the proportion of children aged 27-38 months who had received their fourth dose of RTS,S/AS01 by 27 months of age. Secondary feasibility objectives will measure, in implementation and comparison areas, the coverage of recommended EPI vaccines; the coverage and utilization of ITN/LLIN and IRS; changes in malaria diagnosis and treatment practices; and the patterns of health-seeking behaviour for febrile children. In addition to ongoing monitoring of

facility-based administrative uptake and coverage data, three cross-sectional household surveys will be conducted in each pilot country over the course of the programme.

As for most new vaccine introductions, a New Vaccine Post-Introduction Evaluation (PIE) will be conducted approximately 6 to 12 months after introduction of RTS,S/AS01 to evaluate programmatic performance.

In addition, a qualitative study will explore a range of factors (socio-economic, cultural, demographic, systemic and health-related) that may impact on how the vaccine is delivered and received at district and local level. Using Qualitative Longitudinal (QL) methods, the study will run alongside and track the introduction of the vaccine, following health care professionals as they promote and deliver the new vaccine, and following households as they receive it. In particular, it will track a panel of households with eligible children over time, as the programme is introduced and established. In this way, the study will shed light on the factors that influence the sustained engagement of families in the vaccine programme, and what (if any) impact the introduction of the vaccine has on their health-related practices and understandings.

Finally, the Programme will collect economic data to estimate the incremental cost of adding RTS,S/AS01 to the routine schedule, its budgetary impact and to provide updated estimates of the vaccine's impact and cost-effectiveness.

5.2.2. Impact evaluation

The second evaluation component aims to estimate the impact of RTS,S/AS01 on all-cause mortality in children aged 5-39 months, malaria mortality, and rate of hospitalization with malaria (as an indicator of severe malaria) and the gender-specific effect of RTS,S/AS01 on all cause child mortality. Data will be captured at the community level through resident Village Reporters (VR) specially trained to document and report deaths in the target age group. Trained VR supervisors will conduct Verbal Autopsies, using WHO-recommended methods.

Malaria mortality and the rate of hospitalization with malaria will be captured at sentinel hospitals on all children in the relevant age group presenting to the hospital. The randomized vaccine introduction will enable a comparison of the rate of these events between the areas that have introduced RTS,S/AS01 and those which have not yet introduced the vaccine.

5.2.3. Safety evaluation

In addition to strengthened routine pharmacovigilance, safety data will be captured in up to 24 sentinel hospitals across the three pilot countries by means of systematic, prospective, monitoring of all paediatric admissions, paying particular attention to meningitis and cerebral malaria.

Data collected in the pilot evaluations will be complemented by data collected by GSK in Phase IV post-approval studies. The observational Phase IV studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA and aim to monitor vaccine safety, effectiveness and impact in routine use. In addition to enhanced hospitalization surveillance, the Phase IV study will include active surveillance through home visits and continuous monitoring of outpatient visits and hospitalisations at health care facilities in a subset of implementing and comparison areas.

Safety data from routine pharmacovigilance, the pilot evaluations and the Phase IV studies will be reviewed regularly by a Data Safety and Monitoring Board (DSMB) to identify, assess causality and monitor any accumulating safety signals.

6. Country selection

WHO initiated the country selection process by issuing a call for expressions of interest addressed to Ministries of Health in Sub-Saharan Africa in December 2015. Of the ten countries that expressed interest, three were selected for the Programme based on pre-specified criteria. Key among these criteria was the desire to engage in the MVIP by national stakeholders – particularly the Ministry of Health – and well-functioning malaria and immunization programmes. Other criteria included: good coverage of recommended malaria control interventions and childhood vaccinations; moderate-to-high malaria transmission despite good implementation of WHO-recommended malaria interventions; a sufficient number of infants living in the malaria-transmission areas where the vaccine will be introduced; strong implementation research or evaluation experience in the country; and capacity to assess safety outcomes. Participation in the Phase 3 RTS,S/AS01 trial was an additional element considered during the country selection process.

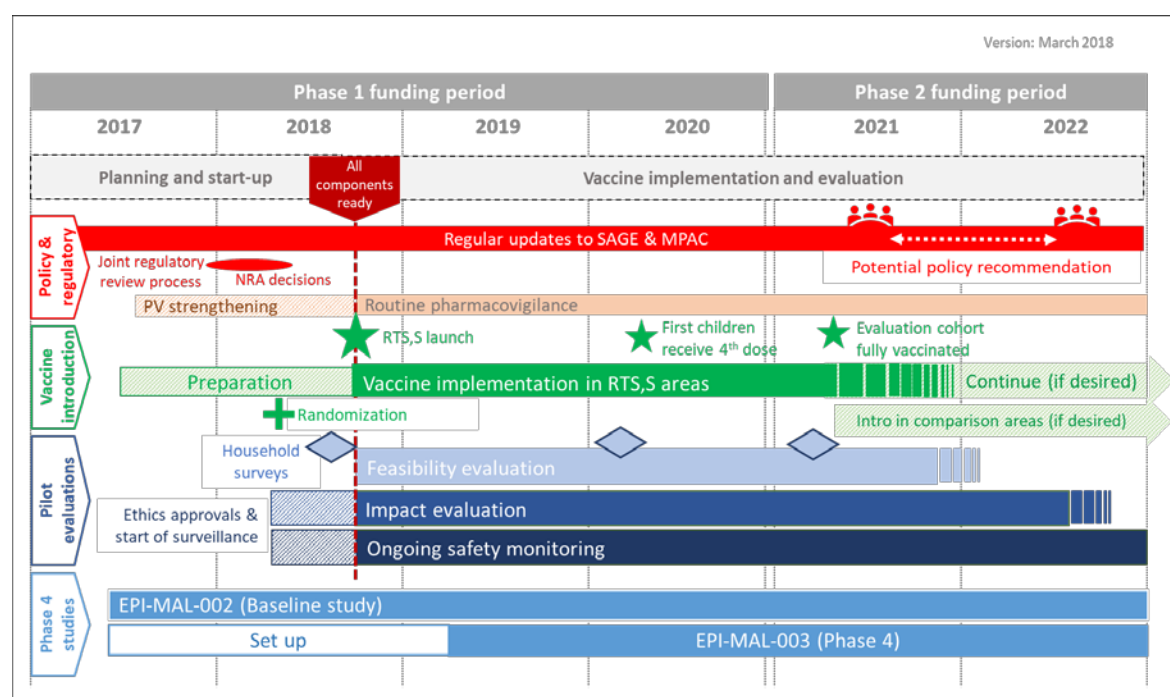
The selection of Ghana, Kenya and Malawi to participate in the MVIP was made public on 24 April 2017, just ahead of World Malaria Day and during African Vaccination Week.⁶

7. Programme timeline

The MVIP will be implemented over approximately 6 years from 2017 to 2022. RTS,S/AS01 introduction is anticipated in 2018 in the first country, upon confirmation of readiness of all relevant components (see Figure 1).

Data on programmatic feasibility, vaccine safety, and impact will accumulate over time. Regular updates will be provided to SAGE and MPAC to ultimately inform recommendations on the vaccine's potential use on a wider scale in Africa.

Figure 1. MVIP timeline



⁶ Pilot country announcement by WHO AFRO (April 2017) <http://www.afro.who.int/news/historic-launch-malaria-vaccine-pilots-africa>

8. Financial support

Financing for the MVIP up until 2020 has been mobilized through an unprecedented collaboration between three major global health funding bodies: Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaids. WHO is providing additional in-kind contributions and PATH's activities are also supported by the Bill & Melinda Gates Foundation. GSK is contributing through the provision of vaccine doses free of charge for the MVIP and is covering the costs of the Phase IV studies.

9. Programme coordination and oversight

The Programme is jointly coordinated by the Global Malaria Programme (GMP), the Immunization, Vaccines & Biologicals (IVB) department and the WHO Regional Office for Africa, collaborating closely with other WHO departments and country offices, ministries of health in pilot countries and PATH. Relevant activities are coordinated with the vaccine manufacturer, GSK, based on a MVIP Collaboration Agreement signed between WHO, PATH and GSK in October 2017.

The malaria vaccine introduction is led by pilot countries' Ministry of Health through the national immunization programme, with technical support provided by WHO as appropriate.

A MVIP Programme Advisory Group (PAG) has been established to regularly review progress and to provide technical advice and recommendations to WHO on Programme-specific issues (see PAG membership in Annex 1).

To safeguard the well-being of children participating in the MVIP a Programme-specific Data Safety and Monitoring Board (DSMB) has been set up (see DSMB membership in Annex 2). The DSMB will regularly review relevant safety data from the pilot evaluation, the GSK-sponsored Phase IV studies and routine pharmacovigilance across the three countries and provide advice and recommendations to WHO.

Regular MVIP updates will continue to be provided to the Global Advisory Committee on Vaccine Safety (GACVS), the Regional Immunization Technical Advisory Group in Africa (RITAG), as well as SAGE and MPAC.

10. Current status of the malaria vaccine implementation programme

Following the WHO recommendation for pilot implementation in January 2016, a team at WHO with support from PATH has taken the lead in developing a funding proposal to prospective donors in view of securing the required resources for the MVIP. Funding commitments from Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Malaria and Tuberculosis and Unitaids were secured by the end of 2016 and donor agreements fully signed by the end of 2017. Various preparatory activities have taken place since 2016 as further described in the following section.

10.1. Regulatory review by national authorities

The use of RTS,S/AS01 in the MVIP will require approval by national regulatory authorities (NRA) of the three pilot countries prior to vaccine introduction. A joint regulatory review by the three NRAs, convened under the African Vaccine Regulatory Forum (AVAREF), took place in February 2018. The joint review was based on the EMA assessment reports leading to the positive scientific opinion in accordance with Article 58. Timelines for the post-review steps leading to special authorization of the vaccine by national agencies have been agreed upon.

10.2. Preparation for vaccine introduction

In-country stakeholders in all three countries have provided recommendations on the most suitable sub-national areas for the pilot, based on a review of available data and guiding criteria set by WHO. The selection process is currently being finalized.

The national immunization programmes of the three countries have developed RTS,S/AS01 vaccine introduction plans and budgets. These plans specify how the four doses of RTS,S/AS01 will be included into the national immunization schedule and outline strategies and activities to ensure successful introduction, covering communication, social mobilization, health worker training, vaccine supply, cold chain and logistics, adaptation of monitoring tools, and strengthening of routine pharmacovigilance, amongst other topics. While similar planning approaches have been used as for other new vaccine introductions, particular attention was given to the inclusion of relevant stakeholders from the national malaria control programme. The plans are currently being finalized with technical support from WHO and PATH.

10.3. Supply planning

As part of the MVIP Collaboration Agreement, GSK has committed to supply sufficient quantities of the RTS,S/AS01 vaccine, free of charge to the Programme, to allow sound implementation of the MVIP, up to a maximum of 10 million doses. Operational planning with UNICEF as the delivery partner is ongoing.

10.4. Preparation for pilot evaluations

A master protocol for the malaria vaccine pilot evaluation was developed by the WHO MVIP team with inputs from external experts. The protocol received final approval from the WHO Research Ethics Review Committee (ERC) in February 2018. Adaptation into country-specific protocols by the local research partners is expected in the coming months.

On 18 May 2017, WHO released a Request for Proposals (RFP) to identify suitable research partners to conduct the evaluations. A lead bidder consortium of partners has been identified for each pilot country and contracts are currently being finalized.

10.5. Readiness for MVIP start

Various elements need to be in place before vaccine introduction and pilot evaluations can begin in each country. The WHO MVIP team is actively supporting the components within its remit (i.e. support for vaccine introduction; support for pilot evaluation set-up, etc.) while monitoring closely the aspects outside of its control and their impact on timelines, such as the special approval by national regulators for use of the vaccine, competing priorities for the national Immunization Programmes, etc. At present, the first vaccine introduction is expected to occur in 2018.

11. Framework for Policy Decision

In 2015, the Joint Technical Expert Group on Malaria Vaccines (JTEG) recommended that WHO should monitor emerging findings from pilot implementation, so that countrywide introduction may be recommended *“if concerns about safety have been resolved, and if favorable implementation data become available, including high coverage of the fourth dose”*. However, neither JTEG nor SAGE/MPAC did specify how the collected data would be used to inform a policy recommendation,

e.g. what coverage levels may be considered favorable and whether demonstration of impact on mortality is required for a policy recommendation.

The WHO MVIP team therefore proposed to develop a framework for policy decision on RTS,S/AS01 that describes how data collected through the MVIP would be used to inform policy. Both SAGE and MPAC were in favor of development of such a framework.

SAGE will be updated on the status of framework development during its meeting in April 2018 and a separate background document on this topic has been provided.

12. More information

Further information on the MVIP is available on the WHO web site:

<http://www.who.int/malaria/media/malaria-vaccine-implementation-ga/en/>

Annex 1: Malaria Vaccine Implementation Programme Advisory Group (PAG) membership

The role of the Programme Advisory Group is to provide technical advice and recommendations to WHO on issues concerning the Malaria Vaccine Implementation Programme.

Membership as of March 2018

Professor Nick Andrews, Public Health England, United Kingdom

Dr Dominique A. Caugant, WHO Collaborating Centre on Meningococci, National Institute of Public Health, Norway

Dr Corine Karema, Swiss Tropical and Public Health Institute and University of Basel, Switzerland

Dr Eusebio Macete, Manhica Health Research Centre (CISM), Mozambique

Professor Kim Mulholland, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom and MCRI, Australia

Professor Francine Ntoumi, Fondation Congolaise pour la Recherche Médicale (FORM), Republic of the Congo

Ms Adelaide Eleanor Shearley, Maternal and Child Health Integrated Programme (MCHIP), Zimbabwe

Professor Peter Smith, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom

Professor Frederick Were, University of Nairobi, Kenya

Annex 2: Malaria Vaccine Implementation Programme Data Safety and Monitoring Board (DSMB) membership

The role of the Data Safety and Monitoring Board (DSMB) is to safeguard the well-being of children participating in the Malaria Vaccine Implementation Programme and to provide advice and recommendations on issues concerning the safety of RTS,S/AS01 in the MVIP to WHO.

Membership as of March 2018

Dr Esperança Sevene, Eduardo Mondlane University, Mozambique

Prof. Alexander Doodoo, Ghana Standards Authority, Ghana

Dr Jane Achan, MRC Unit -The Gambia

Professor Charles Newton, KEMRI-Wellcome Trust Research Programme, Kenya

Professor Larry Moulton, The Johns Hopkins University, USA*

Professor Katherine O'Brien, Johns Hopkins Bloomberg School of Public Health, USA

Dr Cynthia Whitney, NCRID, U.S. Centers for Disease Control and Prevention (CDC), USA.