Report on the webinar
on the introduction of RTS,s/AS01 vaccine for Malaria

Convened by :
TDR, WHO and the OPT-SMC team

24 February 2022
13h-15h30 (GMT)

I. BACKGROUND AND OBJECTIVES OF THE WEBINAR

As a partner of ADP1, TDR in collaboration with the WHO and the OPT-SMC team are convening a series of workshops on the introduction of RTS,S/AS01 vaccine for malaria in order for countries involved in the Malaria vaccine implementation program to share their experiences with other countries of the sub-Saharan African region.

As of October 6th, 2021, WHO recommends the RTS,S/AS01 malaria vaccine for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO. Countries may now consider providing this vaccine seasonally, with a five-dose strategy in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks. Furthermore, WHO recommends that countries choosing the seasonal deployment of the vaccine to document their experience, including the vaccine effectiveness, feasibility, and occurrence of any adverse events, to feed into future guidance updates.

The current vaccination schedules include three primary doses to be administered before 9 months of age and a fourth dose at about 2 years of age. This involves three to four additional vaccination visits than are currently recommended in this age range. In areas of highly seasonal malaria transmission, seasonal deployment of booster doses, or of primary and booster doses, presents additional challenges.

TDR's malaria research focuses on helping low- and middle-income countries scale up their efforts to diagnose and treat malaria and prevent illness and deaths among the most vulnerable, including pregnant women and children. Researchers in African countries are receiving support for implementation research and training to help them improve malaria control.

In collaboration with national malaria control programmes of countries involved in SMC, the University of Thiès, MMV, and the LSHTM, TDR is working to strengthen capacity of national malaria programmes to conduct implementation research to optimize SMC delivery, to adapt to the local context and to improve impact, through the OPT-SMC project [2].

As a partner of the ADP, TDR also supported ADP-focus countries to strengthen their safety monitoring capacity through training in pharmacovigilance and implementation research on the use of digital tools for adverse event reporting. Two of the ADP focus countries, Malawi and Ghana, participated in the WHO-coordinated RTS,S malaria vaccine pilot programme.

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[1] *The Access and Delivery Partnership (ADP) works with low- and middle-income countries to ensure life-saving medicines and health technologies reach the people who need them. The ADP supports countries to strengthen and harmonize policies and systems and builds the capacities of key people and institutions to drive the necessary reforms for sustainable, country-led progress towards universal health coverage. (ADP is supported by the Government of Japan and led by the UNDP, in collaboration with the WHO, the TDR and PATH.)*
https://www.adphealth.org/

[2] https://www.smc-alliance.org/opt-smc-optimizing-smc-by-building-capacity-for-delivery-and-evaluation

Building upon TDR's work on malaria research on SMC, TDR's support to strengthen pharmacovigilance practices and tools in ADP-focus countries Ghana and Malawi, and as a partner of the ADP involved in implementation research to address barriers to the introduction of new health technologies, TDR will support the implementation of the latest WHO recommendation for the introduction of the RTS,S vaccine for malaria.

Target countries and participants

- Representative of all National Malaria Programs (NMPs), Expanded programmes of Immunization (EPI) and research institutions of ADP focus countries in Africa (Ghana, Senegal, Burkina Faso, Malawi, Tanzania)
- Representatives of all National Malaria Programs part of the OPT SMC project, EPI, and research institutions of the corresponding countries
- NMPs and EPI of other countries of sub-Saharan Africa with moderate to high *P.falciparum* transmission
- MOH representative of the countries for Heath/prevention
- In-country technical/financial partners

Objectives of the first webinar:

- to provide up to date information on the vaccine efficacy and safety as well as joint implementation of Seasonal Malaria Chemoprevention and RTS,S vaccine
- to foster exchanges between countries who piloted the introduction of the RTS,S malaria vaccine in routine child immunization services and countries who have not yet done so to better understand practical implementation challenges.
- To discuss availability plans of RTS,S malaria vaccine for the coming years

Expected outcomes:

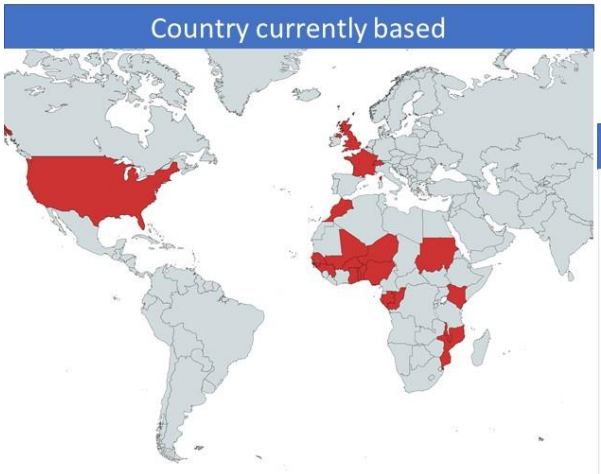
1. Strengthen technical and practical knowledge of NMPs and EIP on RTS,S malaria vaccine implementation
2. Fostered regional and national dialogue for the roll out of the use of the RTS,S vaccine

II. AGENDA of Webinar Feb 24,2022

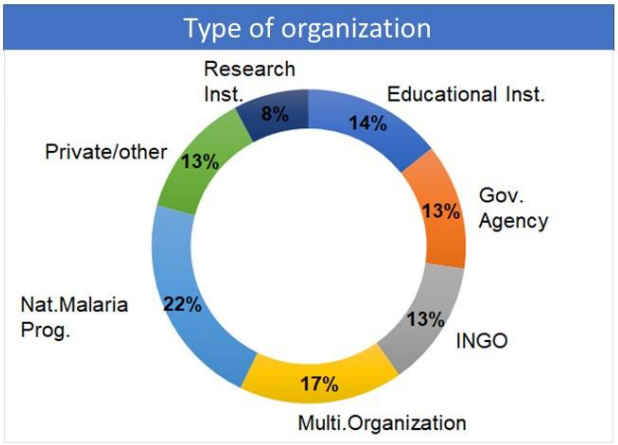
Chairperson: Prof. Oumar GAYE – UCAD, Senegal

Time (GMT)	Topic	Speakers
13:00-13:05	Welcome and objectives of the meeting	John REEDER (TDR)
Session 1. The evidence		
13:05-13:15	RTS.S evidence, including efficacy, safety, feasibility and impact -	Dr Mary HAMEL (WHO MVIP, IVB)
13:15-13:25	Efficacy and safety of combining the seasonal use of RTS,S malaria vaccine and Seasonal Malaria Chemoprevention (SMC)	Prof Alassane DICKO (MRTC, Mali)
13:25-13:35	Discussion (10 min)	All
Session 2. Lessons learned in terms of practical experience from pilot introduction of the RTS,S malaria vaccine in routine child immunization programmes in Ghana, Kenya and Malawi		
13:35-13:50	Kenya 'experience	Dr George GITHUKA (NMCP, Kenya) Dr Rose JALANG'O (NVIP, Kenya)
13:50-14:05	Ghana 'experience	Dr Kwame AMPONSA-ACHEANO (EPI, Ghana)
14:05-14:20	Malawi 'experience	Mr John SANDE (NMCP, Malawi) Mr Mtenje (EPI, Malawi)
14:20-14:30	Facilitators and barriers for differential uptake of RTS,S Doses 0-4: Evidence from child caregiver cohort from Ghana, Kenya, and Malawi	Dr Jessica PRICE (PATH)
14:30-15:00	Discussion	All
Session 3. Plans for vaccine deployment		
15:00-15:10	Next steps for the malaria vaccine for broader deployment	Dr Mgaywa MAGAFU (MVIP, AFRO)
15:10-15:25	Discussion	All
15:25-15:30	Overall conclusions	Prof Oumar GAYE (UCAD, Sénégal)
END OF MEETING		

III. ATTENDEES



# of Registrants	# of attendees
225	154



The audience was comprised of participants based in as various countries as Sudan, Congo Brazzaville, Mozambique, Niger, Benin, Mali, Nigeria, Senegal, Guinea, Gambia, France, Switzerland (see map above), a total of 22 countries mainly from Africa, Europe and North America.

22% of attendees were staff of national malaria control programs. Other participants were officials of other national health programs such as EPIs, representatives of Ministries of Health and Technical Working Groups, INGOs like PATH, research & academic institutions like Malaria Consortium, the Université Marien Ngouabi, Université Cheikh Anta Diop, LSHTM, as well as regional offices working to eliminate malaria and observers from other health sections (HIV, women and child health specialists).

IV. MALARIA VACCINE STATUS

A. RTS.S evidence: efficacy, safety, feasibility, and impact

Speaker: Dr Mary HAMEL (WHO MVIP, IVB)

The RTS,S development phases since 1984 and the number of phases undergone over the years, include the following important developments:

- 2015: the European Medical Agency's (EMA) positive scientific opinion about the benefits of the vaccine as outweighing its risks.
- 2016: WHO recommendation, on the advice of the SAGE, to undertake an important pilot implementation program to watch the safety and the impact of the vaccine in the routine use. The feasibility of reaching children with a new vaccine schedule was also to be monitored.
- 2019: after national regulatory approval of the vaccine in Ghana, Kenya and Malawi the vaccine was launched by their respective Ministries of Health (MOH) and introduced in the countries' immunization programs. This was part of a large partnership involving the three countries' MOHs, WHO, UNICEF, PATH, evaluation partners commissioned by WHO in each country, funders (GAVI, The Global Fund, Unitaid), external monitors, reference laboratories and partners in qualitative studies commissioned by PATH.

Most of this pilot vaccine implementation was also the period of Covid-19 pandemic which affected all the 3 implementing countries. Yet, disruption to the program was minimized which avoided the restart or the reschedule of the program and allowed a high coverage. This also showed EPI's resilience and commitment to face challenges due to Covid-19.
There were 3 major findings:

1. feasibility to deliver as the malaria vaccination schedule was inserted in the existing immunization program,
2. safety ensured after more than 2.7 million doses delivered to over 920.000 children,
3. impact proven by the substantial reduction in eligible for vaccine children of hospitalization due to severe malaria or malaria infection.

In 2021, after two years of implementation, the information and the evidence gathered in the three countries, led to WHO recommending for a broader dissemination of the vaccine on October 6. Subsequently to this, the GAVI Vaccine Alliance met in December and the board made the decision to fund the RTS,S malaria vaccine roll-out.

B. Seasonal Malaria Vaccination with RTS,S/AS01

Speaker: Prof Alassane DICKO (MRTC, Mali)

The University of Bamako in collaboration with the Institute of Health Science in Burkina Faso have been fighting against seasonal malaria (SM) with chemoprevention, through their Seasonal Malaria Chemoprevention programme (SMCP), implemented in 2012.
In 2020, 33,5 million children had been reached in the Sahel and Sub-Sahel regions. Although the therapy was rated highly efficient (88% effective within the first 28 days), there was still room for an additional tool such as a malaria vaccine, to achieve better results. The compilation of data showed that, compared to all the other prevailing diseases, malaria was still the primary cause of both hospital admission and death, even in SMC use environment.
It was observed that the SMC alone was efficient for a few months before its effects declined. But after provision of a booster dose, it would rise again. So, to achieve maximum impact, the

following pattern was adopted: the vaccine was given at the beginning of the malaria transmission season (MTS) and a booster at the beginning of each MTS.
In 2017, a randomized, controlled trial to assess whether seasonal vaccination with RTS,S/AS01E was noninferior to chemoprevention in preventing uncomplicated malaria and whether the two interventions combined were superior to either one alone in preventing uncomplicated malaria and severe malaria-related outcomes (https://pubmed.ncbi.nlm.nih.gov/34432975). The study was carried out on 2 groups of 3,000 children each, divided in groups receiving (i) SMC; (2) RTS,S combined with Placebo SMC and (3) RTS,S combined with SMC. The data, collected over the next three years related to rates of malaria incidence, hospital admissions and deaths. Administration of RTS,S/AS01E was noninferior to chemoprevention in preventing uncomplicated malaria. The combination of these interventions resulted in a substantially lower incidence of uncomplicated malaria, severe malaria, and death from malaria than either intervention alone.

V. PILOT COUNTRIES: SHARING OF EXPERIENCE

A. KENYA

Speakers: Dr. George GITHUKA (NMCP, Kenya)
Dr. Rose JALANG'O (NVIP, Kenya)

The distribution of malaria transmission in Kenya is quite varied with some regions being endemic (+ 20%) and other parts registering low risks. The endemic regions where prevalence is 13% were the ones selected for the malaria vaccine pilot to be implemented.
In the framework of the Kenya Malaria Strategy for 2019-2023, malaria research began as operational research, and all-inclusive process bringing together, all the way from the Senior MOH officials to the level of the county, through the involved organizations and working groups at all levels. They collaborated and compiled the needed evidence for decision-making, which led to the formal application of Kenya to participate in the malaria vaccine pilot.
Steps taken before participating in the MVIP include:

- Advocacy for the malaria vaccine: an important tool which was put forward especially as center stage in the World Malaria Day commemoration
- Discussions at the districts level in order to select both the counties of implementation for the vaccine and comparator counties
- Close collaboration and strong commitment of malaria control coordinators and EPI coordinators which led to the successful implementation of the malaria vaccine program
- Strong engagement of the Health Promotion Officers (HPO) at the country level

Before the introduction of the vaccine, the following steps were taken to secure successful implementation:

- Approval of the vaccine from the National Regulatory Authority
- Writing a vaccine introduction plan comprising budget of implementation that includes all the elements of Immunization: vaccine supply and forecasting for the selected areas
- Areas concerned were making sure their data capturing systems/Digital health tools were in place
- Availability of training and communication/information materials
- Ensuring stakeholders' engagement at senior levels of MOH and county leadership of the regions at stake
- Engagement of the political leadership, technical leadership and the community

Advocacy also allowed the adherence and support to the introduction of the vaccine from the Health Care Workers (HCW) and professional associations such as the Kenya Pediatric Association, the faith-based associations, the academic community like the University of Nairobi, etc.

Implementation Phase

Malaria vaccine program, led by the MOH's National Vaccination and Immunization Program (NVIP), was introduced in September 2019, and integrated into the routine schedule as an additional tool alongside the existing ones in controlling malaria. The schedule for the 4 doses is 6, 7, 9 and 24 months, integrated with other childhood interventions. The western part of the country, where malaria burden is the highest, was selected for the pilot: 26 sub-counties of 8 counties were identified. The vaccine is administered in all immunizing health facilities that include public, private, and faith-based health facilities. The collaboration between the NVIP and the NMCP was key, since the MV was introduced as an additional tool to the existing interventions.

Positive points before and during implementation include:

- AEFI surveillance was one of the components strengthened before the introduction of RTS,S. The implementation phase was an opportunity to train the HCW on AEFI reporting and monitoring, through the development of guidelines and printing of tools
- Some health benefits gained to introduce a 4-dose schedule to the health systems, e.g. second year platform strengthening as the second dose of measles rubella (MR) is given at 18 months and RTS,S fourth dose at 2 years, some of the children who had missed their MR who come for their 2 years' RTS,S are provided with the missed MR dose
- Strengthening of other childhood interventions like Vitamin A or deworming which are co-administered with other doses

Challenges that slowed our pace of implementation include:

- the HCW who went on strike at some point, or
- Covid-19 pandemic that resulted in health facilities turned into isolation units, fear of healthcare workers to visit health facilities.

However, we managed to catch up doses missed through intensification of routine immunization activities.

The lessons learned from this experience can be summarized as follows:

- Introduction of the malaria vaccine through the existing EPI infrastructure is doable and practical, because the equipment and the same HCW administering the other vaccines are availed for the RTS,S malaria vaccine
- Coordination with NMCP is secured as RTS,S and the other interventions are complementary
- Community engagement during pre-introduction of the vaccine is key to have their acceptance
- Supportive supervision is key in identifying and coping with challenges during implementation
- Community Health Volunteers' role is important, especially in creating demand in the community and in sustaining/reducing drop off cases
- Post-launch advocacy is critical in reminding caregivers that RTS,S is needed as much as the other vaccines provided in the region

The next steps are:

- Scale up of the program to the comparator regions
- Updating the introduction plan and budgets
- Proceeding with the same pre-introduction activities in order to secure smooth implementation and high impact.
- Utilize lessons learnt in the initial sub counties to scale up to the comparator areas.
- Continued collaboration between National Malaria Control Program and Immunization Program.

B. GHANA

Speaker: Dr Kwame AMPONSA-ACHEANO (EPI, Ghana)

MVIP started on May 1, 2019 with a target population of 176,000 children under 1 year of age, from 42 districts. Comparator districts were 39. The launch of the MVIP, first at national level and then regional, involved senior health managers and many stakeholders including the National House of Chiefs and Queens who are important stakeholders in terms of health care delivery at the local level. Besides the media, at various points in time before implementation, there was involvement of professional associations, the Parliament, the Academy of Arts and Sciences, etc. RTS,S was integrated into the routine immunization program (RIP) at ages 6, 7, 9 and 24 months and provided along other vaccines.

Main data include :

- All the 1,017,067 doses deployed were administered.
- Improvement was recorded over time in terms of coverage, as shown below.:
    - From 66% coverage for year 1, figures show a 72% coverage for D1
    - From 62% coverage to 69% for D2
    - From 51% coverage to 67% for D3

However, as mentioned earlier D4 had a very dropout rate that slowly eased over time. Thus from 22% in 2020 figures attained 41% in 2021.
About dropouts for doses 1-2 and 1-3, there are signs of stability as figures of cohort are maintained, and only the segment 1-4 remains high. But even then, 71% of those due for D4 have turned up thus bringing the dropout rate 29%.
Trends in vaccination coverage for RTS,S 1-4 as compared with other vaccines provided at the same time, show peaks of D1-3 reaching up to MR1's and D4 starting to really catch up, though there is still room to improve. Efforts are being carried out for that purpose.

The implementation of RTS,S was an opportunity to update and/or improve certain aspects related to program functioning :

- Routine vaccination in the implementing regions and districts has dramatically improved with the introduction of the RTS,S.
- Daily performance review meetings and feedback were maintained over time.
- Expansion of the scope of monitoring and supervision using electronic tools.
- Development of numerous HCW guides, e.g., interactive quizzes, videos on eligibility criteria, key messages to reduce missed opportunities, use WhatsApp platform to answer questions & queries, refresher trainings, etc.
- Targeted support from partners, especially WHO & PATH, for defaulters tracing, home visits, mop-up activities and community education.

- Refresher training on malaria vaccine implementation and RIP.
- RTS,S logistics also served to support provision of the other vaccines of the RIP (motorbikes, computers, cold chain, etc.);
- Targeted support to districts in needs to get to hard-to-reach population;
- Improvement of Vaccine Safety Surveillance (VSS) through cascade trainings down to sub-districts.

The main challenges include:

- Wave of anti-vaccination campaign at the beginning affected the launching but was overcome with time.
- Misapplication of eligibility criteria led to miss opportunities, which translated gaps in HCW's education.
- Because RTS,S was being implemented in specified regions, a lot of attritions was noticed among trained staff moving to other parts of the country. This implied continually renewing of staff.
- Very low AEFI reporting.
- Supervision at lower levels was challenged by irregularity caused by HCW overwhelmed with activities, especially during Covid-19 pandemic.
- Issues of data gaps and irregular feedback across health administrative levels.
- High dropout rates for the 4th dose due to the long interval between dose 3 and dose 4;
- 4th dose being provided in the 3rd year of life which was a big challenge but is gradually easing now

Main observations are:

- High level of commitment and support easing implementation.
- Vaccine acceptance despite initial hiccups caused by the anti-vaccine campaigns.
- Lots of inter- and intra- sectoral collaboration, especially MCP in the periphery.
- Regular joint malaria vaccine committee meeting held (every 2 weeks).
- Sustained performance during Covid-19 pandemic after a short period of stockout.
- Good uptake rate for a new vaccine: 88% of implementing districts achieved at least 60% coverage.
- Maintenance of dropout rates at less than 10% for doses 1 and 3 especially.
- Finally: euphoria in Ghana generated by WHO recommendation for a wider use of the vaccine.

The next steps include:

- TWG meeting to decide on expansion of RTS,S to other areas
- PRM with MVIP districts will include competitor districts in order to draw strategies of improving D4 uptakes
- Target monitoring of low performing districts
- Expansion of comparator districts to 39 by end of 2029
- Budget Plan being developed before its presentation to MOH for decision
- Communication: key messages for the rollout considering the lessons learned from pilot areas.

C. MALAWI

Speakers: Mr John SANDE (NMCP, Malawi)

Mr Mtenje (EPI, Malawi)

Malawi is an endemic country with malaria transmission throughout the year and seasonal peaks from November to April. Malaria's illustration in Malawi is as follows:

- It's the leading cause of death among children under 5.
- As of 2017, malaria prevalence was 24% after a small decrease from 43% was recorded.
- ITNs are distributed in the communities, but their use among children under 5 accounts for 68%.
- Preventive treatment for pregnant women is provided.
- Around 2019, estimates reported about 3,9 million cases and 6,000 deaths.

Though there was no 'launch campaign' as it is usually done for new vaccines, the MOH commitment was very strong from the start. Planning and coordination involvement from EPI and NMCP were equally strong.
Malawi was the first country to introduce malaria vaccine in April 2019, with the collaboration of the EPI program, the Health Education Services Unit and partners like WHO and PATH. A National Task Force (NTF) and a Malaria Vaccine Coordination Group (MVCG) composed of partners like governance structures, MOH, EPI, NMCP, were put in place to handle not only the phase of preparing the application for Malawi to participate in the pilot phase, but also the selection and randomization process of districts selection, as well as planning and coordinating the introduction.
However, in Malawi, no launch was done for the malaria vaccine, as it was done for the other vaccines: it was integrated straight away into the routine system. People came to accept it over time and were bringing their children for vaccination.
The introduction, scheduled at age 5, 6, 7 and 22 months, was done in 11 districts with pilot and control clusters each. 907.919 doses were administered between April 2019 and September 2021.

Lessons learned include:

- Adherence tool longer than for vaccines introduced with a preamble launching. It took time to get the people participate.
- Interference of Covid-19 led us to combine both administration of malaria vaccine and Covid-19 vaccines.
- Education Services' important role in social mobilization and community engagement for the creation of demand.
- Caregivers of the communities along with opinion and local/religious leaders were also very important actors.
- Work with the civil society, especially the women groups, to mobilize and encourage caregivers.
- Strong social mobilization impacted the improvement of D4 uptakes.
- Supportive supervision and stakeholders' engagement were key
- Tools provision to HCW: it was noticed the first year that there were gaps that needed to be filled in the information/training of HCW. Once well-equipped they were able to pass on the right information to caregivers and communities
- Meetings to share information and experience were gathering all the districts and included management teams and districts' representatives.

Major challenges observed relate to:

- Assessment of data quality

- Cases of missed doses which required from interveners to create occasions of catching them up

The upcoming steps mainly consist in activities related to coordination and governance for the wider use of the vaccine that we have been granted.

VI. FACILITATORS AND BARRIERS FOR DIFFERENTIAL UPTAKES OF RTS,S D 1-4

Speaker: Dr Jessica PRICE (PATH)

A study was conducted in all three pilot countries to explore reasons why children received 0, 3 or 4 RTS,S doses. The purpose of the sampling strategy was to select a cohort of children caregivers from 9 communities in the 3 pilot countries: on basis of the following criteria : All had vaccine-eligible age children and were all living in areas where the vaccine was being given. Three interviews were conducted at key points in time over the 2-year dose schedule: interview n°1, shortly after D1 or D2 should have been received; interview n°2: in between D3 and D4; interview n°3: soon after D4 could have been received. The study was done on 198 caregivers who were interviewed at least once during the study.

Results show that RTS,S success and trust grew over time, no matter how many doses a child received. In general, caregivers trust their country's health care services and vaccines including the RTS,S vaccine. Despite initial concerns about RTS,S vaccine, this general trust led caregivers to accept the first dose. The gain of personal experience with RTS,S and its side effects being similar to other vaccines increased caregivers' trust in the RTS,S vaccine. The pattern of increasing trust seemed to be linked to the interview focus in round 2 and 3, and drives the will to complete the RTS,S schedule. Nearly all the caregivers who completed their children's 4 doses said they personally witnessed the benefits of the vaccination. This was similar for caregivers whose children received fewer doses for various reasons. These reasons for an incomplete vaccination included complacency, information need, personal circumstances, clinic services barriers and refusal/hesitancy. The lesson learned from the 34 cases who received the first 3 doses but missed the fourth is that 19 were due to complacency, 8 to information need, 2 to service barrier and 1 to personal barrier. Some of these complacency cases had to do with fear of vaccine, personal circumstances, lack of important information. Others were due to lack of persistence/commitment, over dependency on the health system to take care of the child, caring for other life demands, and lack of conscience of their role in taking their children for preventive services. These various aspects of complacency require different responses, mainly including the increase of information provision to caregivers on what steps to take if a dose is missed or delayed.

Eleven cases were recorded where children had received not a single dose. Most of these 'zero dose' were attributed to countries' specific challenges. Examples include a) in Ghana: ¾ refusals due to rumors and fears spread by anti RTS,S social media, b) in Kenya: 2 due to HCW strike and stockout, and c) in Malawi: 4 due to either critical information gaps possibly consequent to the skipped launching OR to challenges of errors in recording.

Recommendations worth mentioning include taking advantage of caregivers' trust in their HCS systems & vaccines as early as possible, and using RTS,S launching to address caregivers' questions and concerns which usually relate to rumors and misinformation. HCS need to find a way of sending reminders to parents for completion of vaccination schedule, with a special campaign for D4. Education and training about the need, the number, and the timing of vaccines requires to be continued.

VII. NEXT STEPS FOR THE MALARIA VACCINE BROADER DEPLOYMENT

Speaker: Dr Mgaywa MAGAFU (MVIP, AFRO)

Important steps are being undertaken for the expansion and the introduction of the vaccine into other areas and countries. WHO welcomes the historic investment by Gavi in the first malaria vaccine programme. On December 2, 2021, GAVI board met and approved an initial investment of US$ 155.7 million for 2022-2025. GAVI is currently designing a Malaria Vaccine Support Program including the development of application guidelines for the eligible countries. Patterns to be followed in the process of selection will be shared in due time.

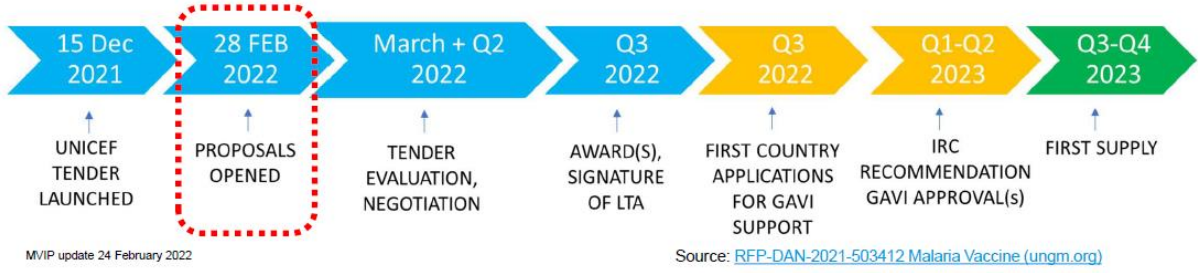
It is worth noting here that for ethical reasons, continued vaccination in the 3 pilot countries will be supported, expanding it to the other geographical areas.

UNICEF is seeking comprehensive and innovative proposals from developers and manufacturers of Malaria Vaccine for the sustained and uninterrupted supply of affordable Malaria Vaccine of assured quality, starting from January 2023 through December 2026, with possibility to extend the tender period by up to two additional years, through 2028.

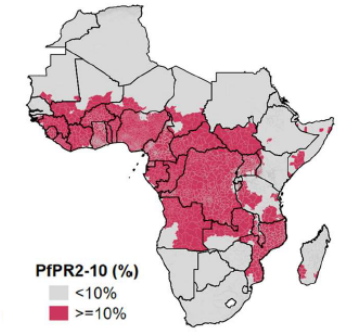
- Bidders requested to submit proposal for maximum available annual quantities

• All developers of Malaria Vaccines anticipating entering the Malaria Vaccine market during the tender period encouraged to submit their comprehensive proposals

• UNICEF will consider innovative approaches to contracting, such as volume-based commitments as well as any risk-sharing mechanisms for pricing proposed, provided they help achieve the objectives of this solicitation process.



WHO is coordinating the development of a Framework for vaccine supply through a transparent and participatory process that is built on ethical principles. This is important due to the initial limited supply of vaccine. An expert advisory group, with strong representation from the African continent has been convened to draft the Framework. The Framework aims to offer guidance globally on the allocation of malaria vaccines between countries, and to offer high-level guidance nationally on the prioritization of areas for vaccination within countries (while respecting sovereign decision-making) while supply is limited. The expectation is that once finalized, all relevant stakeholders will adhere to the Framework, including malaria endemic countries, Gavi in its application guidance and processes for accessing and providing support; UNICEF in its procurement; the manufacturer(s), and other partners as they consider their financial and technical support to countries.



Plasmodium falciparum parasite prevalence ($PfPR_{2-10}$) estimates, 2019

MVIP update 24 February 2022

Demand

- Expected to be high
- Could exceed 80-100 million doses/year (based on Gavi's latest forecast)

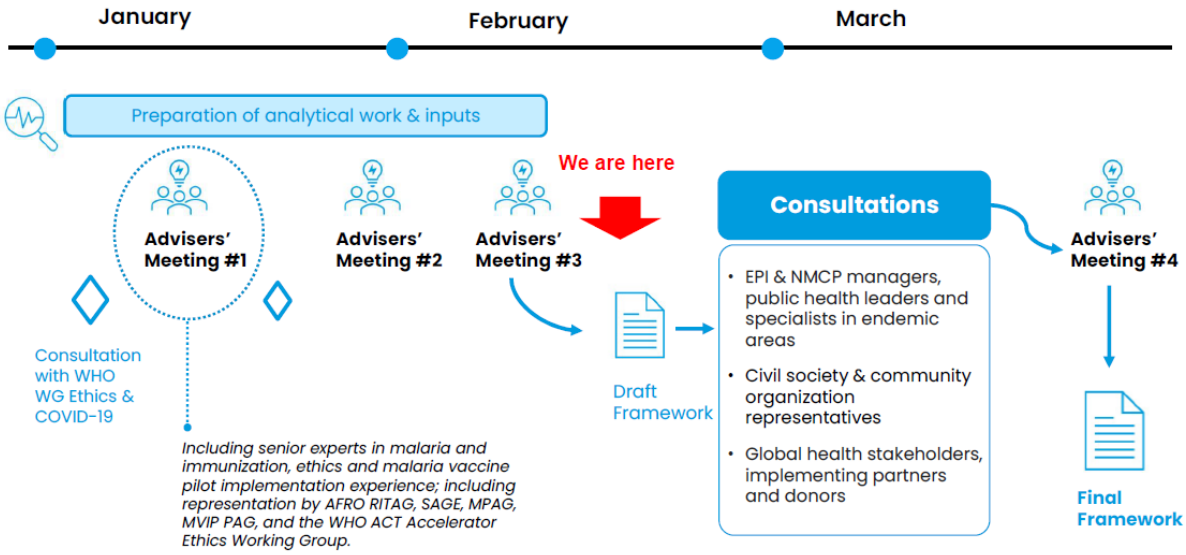
Allocation Framework to guide where limited supply should go

Supply[1]

- 1 vaccine, single manufacturer
- Supply limited, ramping up with target to reach 15 million doses/yr
- RTS,S product transfer to Bharat Biotech started, expected to be completed by 2029, the latest
- Capacity expansion requires attention and likely ext. support
- Candidate R21/Matrix-M in Ph3

1/ WHO Malaria Vaccine Global Market Study, available: https://www.who.int/publications/m/item/who-malaria-vaccine-global-market-study-september-2021

Process for the development of the Malaria Vaccine Allocation Framework



VIII. QUESTIONS & ANSWERS

A. Topic: Vaccine & SMC

Looking at the outcome of the comparative study of the SMC Vs RTS,S it appears clearly that RTS,S is superior to SMC. Could this be related to the uptake of antimalaria SMC in children which takes place at home contrary to the vaccination?

All the SMC drugs were given under direct observation. All the 3 days treatment of SMC issuance were given under the surveillance of the study team. It's directly given, so when we talk of coverage it is about the actual number of children who have received the SMC intervention.

RTS,S/SMC coverage: why don't we have a hundred percent coverage or some figure close to that?

In practice, it is very difficult to have a 100% coverage of 5,000 children because there is always a reason why we cannot. As you can see, the vaccination coverage is quite high. And those who did not receive would be those who are out the location at the time of vaccination. And it would be very difficult to get all the people stay in place for the whole period of vaccination. In addition to travels, the other reason why children do not receive SMC is when they had been recently treated with ACT (within 2 or 3 previous weeks). Apart from these 2 reasons, there are very few cases where vaccination is declined.

As supplies of vaccine are limited where best will the vaccine be deployed with SMC or among children not eligible for SMC?

This is such an important question - where will the severely limited supply go initially and while supply is increased. WHO is coordinating the development of a Framework for limited vaccine supply through a transparent and participatory process that is built on ethical principles. An expert advisory group, with strong representation from the African continent has been convened to draft the Framework.

SMC protection lasts over a period of 28days; How long does the protection of the vaccine last?

It remained high up for 6 months toward the end of the transmission season. It was difficult to assess accurately after end of season given there were little malaria.

There are countries where the SMC does not cover all areas according to WHO criteria.
How do you plan to include non-SMC areas if a combination of SMC and RTS vaccine is advocated?

For areas where SMC is implemented, both interventions should be combined to maximize impact. For areas where SMC is not being implemented, we can target the periods of maximum malaria transmission.

In Senegal, SMC is administered to children aged 3 to 120 months. But this target is divided into 3 slices: from 3 to 11 months, from 12 to 59 months and from 60 to 120 months.
In which age group is the RTS,S vaccine more effective?

The vaccine efficacy was higher in children first vaccinated 5-17 months of age than those vaccinated from 6 weeks of age, with coadministration of other childhood vaccines. there was no difference in VE between children 5-11 mo of age and 12-18 months of age at first vaccination.

It seems that despite SMC many children are still suffering from malaria infection and severe malaria. Is that occurring mainly in the non-high transmission season, and would the vaccine then protect during that period in areas where SMC is deployed?

Severe malaria was drastically reduced 70%, in RTSS+SMC group.

B. Topic: Vaccine efficacy

Is there any risk on the efficacy of the vaccine regarding the genetic diversity of the circulation of the parasite?

This is an issue being currently addressed. Samples have been collected but not yet analyzed. A study has been published and is available on the phase 3 trial. It was conducted between 2009 and 2011 in 11 different sites in 7 seven countries. There was an analysis done to check on the matching pattern between the vaccine and the parasites living in the community. The study indicated that if there was a full match, the vaccine efficacy was increased by 30%. But on the flip side, very few samples had a complete match. In Western Kenya for example, less than 1% of the parasite had this match. The positive side of it is that there would be less pressure for selection. However, it has been recommended that this be monitored over time with other vaccines.

You used the word 'substantial" reduction in malaria deaths and cases after R,TSS, but no statistical numbers were presented. Is that because they are not yet available?

In the pilots, after 24 months for vaccine introduction, with approximately 62% coverage of RTS,S over that 24 month period (a period when vaccine uptake was scaling up) hospitalizations for severe malaria were reduced by ~ 30% (pooled across countries). All cause child mortality was reduced by 9%.

Did you assess the impact of the vaccination on genetic diversity of P.falciparum?

This was done with data from the phase 3 trial. We did not do this as part of the pilot introductions.

Do we have specific figures (proportions) of reductions in hospitalization or those with severe malaria by country - to demonstrate impact?

In the pilots, after 24 months for vaccine introduction, with approximately 62% coverage of RTS,S over that 24 month period (a period when vaccine uptake was scaling up) hospitalizations for severe malaria were reduced by 30% (pooled across countries).

Is there information on how long the vaccine protects? Does this differ in different geographical settings?

Efficacy wanes, but overall, there is measurable efficacy until ~3.5 years after vaccination with the 4-dose schedule. This is sufficient to provide protection during the highest risk period, (most severe malaria and deaths occur prior to 3 years of age, before the child develops acquired immunity). An extended follow up study showed that the benefit gained during those first 4 years was not lost for 7 years follow-up (with vaccine efficacy remaining positive).

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When does the vaccine start waning off in a fully vaccinated child with RTS,S?

In the phase 3 trial efficacy against clinical malaria was 67% for the first 6 months, dropping to 39% in the next 6 months, explaining the high impact observed with seasonal vaccination.
see:
https://www.who.int/immunization/sage/meetings/2015/october/1_Final_malaria_vaccine_background_paper_v2015_09_30.pdf

At which stage can we say that a child is fully vaccinated?

Benefit is from the time of the 3rd dose, and the 4th dose prolongs protection

Is there a vaccination coverage threshold that could produce herd immunity for a specific geographical area?

No, there will not be herd immunity with this vaccine. Because the focus is on young children, who are only a small part of those harboring malaria parasites, the vaccine is not expected to reduce transmission.

RTS,S is not meant to produce herd immunity. It is meant to reduce disease burden by decreasing morbidity and mortality. That's why vaccinees are asked to continue using other means of prevention.

Does the missing 4th dose significantly reduce the efficacy or time protection of the vaccine?

This is an important question - from extended follow up of the phase 3 trial, children benefit from 3 or 4 doses of the vaccine. Modeling suggests that the 4th dose increases vaccine efficacy minimally (by 10%). The pilots (and a case control study led by Dr. KP Asante, will help to understand the added benefit of the 4th dose.

What is the estimated efficacy level of this vaccine according to the manufacturer to be like the reference efficacy?

Vaccine efficacy in the phase 3 trial at 12 months follow up was ~50% against clinical and severe malaria. At 4 years follow up, following a 4th dose provided at 18 months after the 3rd dose, VE was 40% against clinical and 32% against severe malaria.

When does vaccine efficacy start waning off in a fully vaccinated child with RTS, S?

About 75% efficacy in the six months followed the vaccination and about 31 % in the in the next 6-12months.

Which of variants of P.falciparum the vaccine could be eliminate?

The vaccine is currently seen to reduce childhood illness and death, rather than an elimination tool. The vaccine will only be provided to young children, a small proportion of the population that harbors parasites.

What type of epidemiological facies do you think this vaccine is suitable for (seasonal transmission or area of continuous transmission)?

The WHO recommendation specifies for areas of moderate to high transmission, however the combination with SPC shows a clear added value in areas of seasonal transmission.

C. Topic: Vaccine safety

Are there conditions that will predispose to AEs on receipt of the vaccines?

No evidence of predisposing conditions that would lead to AEs. The vaccine can be associated with febrile seizures in the first few days after vaccination - this is not unique to this vaccine.

Has the RTSS vaccine or other potential vaccine being used in other at risk groups such as pregnant women and immuno suppressed patients

The vaccine was shown to be safe and immunogenic in HIV infected and exposed children or malnourished children. It has not been studied in pregnant women.

D. Topic: Pilot implementation of RTS,s vaccine

What is the price of a whole vaccination cycle, product wise?

Manufacturers have publicly committed to only add 5% to their manufacturing costs, and it should soon be made public since UNICEF has put out the tender for the vaccine.

How did our colleagues manage the training of HCW?

Kenya. Their roles are pretty in line with our mandate in the MCP, i.e. we are the ones monitoring the data on malaria, the incidence, the measured outcome of the impact of the vaccine on the population, the issue of behavior, of social change communication. Malaria vaccine was a central part of our messaging, with the issue of ensuring commodities, availability of other malaria interventions like diagnosis, treatment, etc.

The EPI, division of immunization and vaccines, oversaw infrastructure, capacity-building, ensuring services and direct communication is availed to mothers and caregivers of these children.

Though tasks were split, we work together through a malaria vaccine implementation sub-committee. And the collaboration goes all the way from the national level to the county, sub-county and facility levels as well. Involvement of health promotion units was also concerned with the messaging part.

Malawi. CHW in Malawi work with employees of the preventive health section in the MOH. They are the ones implementing activities at the local level. Immunization activities are thus basically handled by the CHW in the communities, where they are called Health Surveillance Assistants. Their activities include implementation of routine vaccines' administration. Collaboration is easy since our health agencies and surveillance systems are based right in the community. So the CHW link the community to the health facility. Their presence is one of the major factor that helped improve the coverage of the vaccine.

Ghana. MCP's role consists in malaria prevention and case management, while EPI does the vaccination. Program's dichotomy is only at the national level. But at regional and districts' levels where the implementation occurs, f.ex. the health workers will do the vaccination, supervise the ITNs distribution and the other interventions. But at the national level, we are in charge of joint meetings, supervision and monitoring.

Was there any implementation of vision and strategy in this campaign? What was the exact strategy and how was it implemented? From the international database, VG base on reporting of adverse drug reaction and adverse event following immunization, there are very few cases reported on the international systems. Most of them are from Ghana, very few from Kenya and Malawi. What are the implemented actions in terms of pharmacovigilance regarding vaccines, and if there are any deployments of these vaccines in other countries, what is the action plan?

Ghana: The fact that we have improved pharmacovigilance, especially within the context of RTS,S explains why Ghana contributed most of the data. Out technical advisory committee is also very strong with its joint malaria vaccine adverse event monitoring committee that meets every 2 weeks and is championed by FDA. This works right from the community level through the district/region and then the national level.

Malawi: Pharmacovigilance is led by the Pharmacy and Medicine Regulatory Authority, and at the district level there are committees, and, thanks to the MVIP, all the health workers are trained in vaccines provision and reporting. There are still challenges but improvement for reporting especially is underway.

There has been significant investment in pharmacovigilance and despite challenges, there was improvement at national level. Pharmacists took the lead but made sure all segments of the field join. And they work together to improve this vigilance. Over time, we noticed some districts were good, but others still need training. So efforts are being done to sustain the gains made.

Did the Kenya program had to modify their HMIS tools and the DHIS reporting module to take care of the vaccine reporting? If yes, how is this handled given that this is not a country-wide intervention?

We did modification of tools. In the DHIS2 we added malaria vaccine modules in the specific sub counties. We printed stickers for the mother child booklets for the recording of the doses of

malaria vaccine given and the return dates. These are stuck within the booklets. we printed separate malaria vaccine tally sheets and summary tools. The AEFI reporting tool is similar for all antigens including malaria vaccine. The permanent register was modified to include malaria vaccine. All the modifications affected the implementing sub counties.

In Ghana and Kenya, who can vaccinate and can trained CHWs deliver the vaccine?

In Kenya the vaccine is offered in immunizing health facilities. The human resource policy is that nurses administer vaccines at the health facilities whereas community health volunteers assist in defaulter tracing, weighing babies, conducting health talks....

Dr Jessica rose the issue of complacency leading to gradual dropout of RTS,S doses, especially the 4th. This dose is an issue we need to think about. If this situation occurred in your setting, please share how you handled it. Maybe as Pr Dicko showed, combining the 4th dose to SMC could be a good approach. Ghana, Kenya and Malawi, how do you intend to address this complacency?

Ghana: The findings on the issue of failed 4th dose in Ghana revealed it resulted from rumors. We suffered from anti-vaccines campaigns from the onset, but with time we overcame their effects. We believe that whatever action is taken should start with D1.

But we also think that another problem of with the 4th dose is because it's going beyond the 2nd year of life. We have a lot of experience with 1st and 2nd year of life interventions, and for the other routine the last doses are given at 18 months, e.g. MR 2nd dose and meningitis type A.

We have been working hard with PATH and WHO to catch up the missed dose with home visits. But if science would allow, we would give the RTS,S 4th dose alongside the other vaccines, thus avoiding to bring back again the children in their 3rd year of life, which is very difficult.

What are the most probable facts behind the high drop off rates in Ghana for the fourth dose ?

Low coverage is common to vaccine doses given during the second year of life. MOHs in the 3 countries have been working to improve uptake through a variety of ways including periodic intensification of routine immunization activities (PIRIs). Community engagement also continues.

Is it possible to give first 3 vaccine doses at EPI and the 4th dose through community campaigns?

It is a good idea, but it has not been implemented in trials and the pilot conducted in areas of moderate to high transmission. The WHO recommendation provides for some flexibility in the administration of the vaccine. There is also a learning agenda in it. So, when new methods of delivery are tested by countries and found to have better results, they should be documented and shared.

4th dose appeared to be necessary in the phase3 trial but there was uncertainty around this finding, the need for the 4th dose is being assessed as part of the ongoing pilots. (Give primary doses through EPI and 4th via campaigns?)

Yes, there would be some advantages to that strategy, including that it would allow the option of adding additional (5th, 6th) doses, as they are doing in the extension of the trial described by Alassane.

Would co-delivery of RTSS with IPTi (through the EPI platform) be encouraged? We of course could not expect complete overlap in dosing but perhaps the 3rd IPTi and RTSS vaccine could be given during the same visit? Is this feasible?

This is feasible and may be an important way to increase protection from malaria.

If the EPI platform is to be used to deliver RTSS is there a minimum national coverage (DPT % coverage) that would suggest this platform is sensible for a country to deliver RTSS through?

The expert advisory group for the Allocation Framework of limited vaccine supply considered this very thoughtfully. They pointed out that unlike measles vaccine, where we aim for high

coverage for herd immunity, the malaria vaccine provides individual protection - if a child receives at least 3 doses, the child will benefit. Dr. Mgaywa will speak about the allocation framework, but it is likely that in the highest need areas (where parasite prevalence is highest, child mortality is very high, and health systems are poor), higher impact might be achieved by reaching 50% of children with 3 doses, than achieved by reaching 80% of children in an area of lower need. Therefore they have not recommended a minimum DPT3 coverage before malaria vaccine introduction.

Are RTSS vaccine targets similar to EPI targets?

Yes

E. Topic: Storage

What exactly are the cold chain and delivery needs eg storage between 2 and 8 degrees. Does the vaccine vial need reconstitution, if so how long does it last when reconstituted Is there a vaccine vial monitor on the vial to ensure viability if taken on outreach to remote communities? What is the cost per dose delivered?

The malaria vaccine is stored in the EPI refrigerators within temperatures of +2 and +8 degrees. Its reconstituted and discarded after 6 hours. It has a VVM and temperatures are monitored in the health facility twice to maintain viability. Healthcare workers use vaccine carriers during outreaches. Waste management is similar like for other vaccines. Waste is transported to a central place for incineration.

F. Topic: Cost & procurement

Have cost-effectiveness studies of RTSS implementation been conducted? If yes, what is the cost per child for full coverage of all doses--including procurement of vaccine and syringes, training, community engagement, supervision and M&E?

Yes, modelling studies reported at SAGE meeting in Oct, see Annex 8 in: https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Oct2021.pdf

You can also access the document (Full Evidence Report on the RTS,S/AS01 Malaria Vaccine, reviewed by SAGE and MPAG in October 2021) here: http://terrance.who.int/mediacentre/data/malaria/documents/mpag-october2021-session5-rtss-malaria-vaccine.pdf?sfvrsn=9507a63b_10

When will the vaccine be introduced in other countries?

Gavi is developing the malaria programme now, and applications are expected to be out in some months. The first new countries to introduce will probably be in late 2023.

IX. Additional references:

Malaria vaccine guidelines online MAGICapp platform.
MVIP Bulletin (Join the MVIP Distribution List)
i. Issue 1.Dec.2020
ii. Issue 2.April.2021
iii.Issue 3.September.2021
iv.Issue 4. November 2021