World Health Organization

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Background Paper:

Programmatic Options for Implementation of Malaria RTS,S Vaccination Schedule for Young Children

1. Introduction:

The review of evidence for a recommendation on the use (or not) of RTS,S vaccine is the responsibility of the Joint Technical Expert Group (JTEG) on Malaria Vaccines which serves as the working group for WHO's Strategic Advisory Group (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC). Given that the European Medicines Agency (EMA) on 24 July 2015[1] issued a positive regulatory assessment, JTEG's recommendations are now planned for review and final decision at a joint MPAC/SAGE meeting on 21 October 2015.

As part of the deliberations on the use of any new vaccine, the programmatic implications and operational feasibility of the proposed vaccination schedule are important issues to be considered.

Accordingly, as an input to the JTEG and SAGE/MPAC review processes, this background paper has been developed to provide an overview of the programmatic considerations and operational feasibility of the proposed schedule for RTS,S vaccination of young children.

This background paper has been prepared internally by WHO IVB and AFRO staff, with inputs from PATH Vaccine & Delivery, Malaria Vaccine Initiative staff, and confidentially reviewed by three members[2] of WHO's Immunization Practices Advisory Committee (IPAC) in order not to raise external expectations and avoid confusion among countries or partners that RTS,S was being recommended for use in advance of the SAGE/MPAC discussions. It is envisaged that IF a positive recommendation on the use of RTS,S is forthcoming, then a broader consultative process with country programmes will be undertaken to design and plan for the introduction of RTS,S vaccine. Until that time, this paper serves to provide some preliminary thoughts based on the knowledge and experience of immunization programme experts.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002376.jsp&mid=WC0b01ac058004d5c1

[2] Chris Morgan, Chair IPAC, Dr. Adelaide Shearley and Robert Steinglass, IPAC Members.

2. RTS,S Vaccine Characteristics, Use and Schedule

Product Characteristics: RTS,S Vaccine

- Duration of protection: Wanes with no substantial protection after approximately 18 months
- Vaccine Efficacy: 39% (95% CI 34.3, 43.3) against clinical malaria after 4 doses given to children 5-17 months of age
- Herd effect: None or minimal
- Formulation: Lyophilized (freeze dried powder)
- Preservative: No preservative
- Vaccination schedule: 4 doses (starting from 5 months of age, 3 dose primary series with a minimum interval between doses of 4 weeks, followed by a later fourth dose 15-18 months after the last dose)
- Storage temperature: 2-8˚C
- Effect of freezing: Freeze sensitive; Must not be frozen
- VVM type: To be confirmed (but will have VVM)
- How vials and diluents are packaged: Vaccine and diluent vials clipped together
- Packed volume per dose: 9.7 cc

At its September 2014 meeting, JTEG reviewed data from the phase 3 trials[3] of RTS,S/AS01 with results up to 12 months following administration of a fourth dose.

Following a review of the available data, three possible scenarios for a recommendation have been identified: (i) a recommendation not to use RTS,S vaccine; (ii) a recommendation for limited use of RTS,S vaccine in selected countries to answer some key remaining questions about risk and benefit; or (iii) broad recommendation for use at national level.

In the event that there is a recommendation for use, it is likely that RTS,S vaccine would be recommended for either sub-national or national use in medium to high malaria transmission settings in Africa, where long lasting insecticide treated nets (LLINs), rapid diagnostic tests (RDTs) and Artemisinin-based Combination Therapy (ACT), and seasonal malaria chemoprevention (SMC) in highly seasonal areas, have already been scaled up.

With regards to the schedule, JTEG has proposed the following:

- Target age group of 5-17 month old children.
- A three dose primary series with a minimum interval between doses of four weeks, followed by a later fourth dose.
- The primary doses should be initiated as close as possible to age five months and completed by nine months of age.
- Co-administration has been evaluated with measles and DTP-containing vaccines and is considered acceptable.
- A fourth dose is critical and should be administered 15-18 months following the last dose of the primary series.[4]

[3] RTS,S/AS01 Phase 3 trial in 15,460 infants and children in 2 age groups: infants aged 6-12 weeks and children aged 5-17 months. Both groups received 3 monthly doses followed by a fourth dose after 18 months.

3. Programmatic questions to be considered

Given the above guidance, there are a number of programmatic questions that need to be considered.

Apart from the RTS,S vaccine trials which were conducted under controlled and well-resourced conditions, there is no "real life experience" with delivering a vaccine with a schedule like that proposed for RTS,S. Drawing upon collective experience and practical knowledge, this paper outlines programmatic options and considerations in response to the following questions:

1. **Geographic focus:** What are the specific operational requirements for use of the RTS,S vaccine at sub-national, rather than national, level (i.e. the target population is in specific districts selected on the basis of malaria endemicity and coverage of malaria interventions)?

2. **Delivery strategy:** What are the programmatic options for delivering 3-doses of RTS,S vaccine between 5-9 months? What are the pros and cons of facility-based vs campaign strategies?

3. **Adding new vaccination contacts:** Operationally, what will be required to introduce two new immunization visits/contacts between 5-9 months of age? Will these be acceptable to health workers and caregivers/communities? What benefits/drawbacks could these new visits/contacts have? What will be needed to ensure high coverage of all three doses?

4. **Fourth dose:** What is the best programmatic approach to assure that all children receive a fourth dose 15-18 months after the last dose (i.e. between ages of 24-27 months of age if last dose given at 9 months with measles vaccination)? What strategies/incentives would facilitate implementation and uptake of the fourth dose? What special measures/actions should be taken if fourth coverage is low?

5. **Demand generation:** What information, education and communication (IEC) strategies will be needed for the RTS,S vaccine? Will special efforts be needed given its non-traditional schedule and specific safety signals to monitor, as well as its partial efficacy and limited duration of protection?

6. **Vaccine Management & Logistics:** How will RTS,S be handled in the cold chain? Are there any special requirements? Is the available presentation optimal? What is expected in terms of wastage?

7. **Integration:** What are the opportunities for integration with the RTS,S vaccination schedule, with other vaccines, with broader malaria control, and with other maternal and child health services?

[4] There are currently no data available to inform whether one or more additional booster doses are needed to maintain vaccine efficacy and prevent rebound of severe disease. This will need to be evaluated, both for safety and efficacy, and recommendations updated as the data become available.

#1. Geographic focus: What are the specific operational requirements for use of the RTS,S vaccine at sub-national, rather than national, level (i.e. the target population is in specific districts selected on the basis of malaria endemicity and coverage of malaria interventions)?

Most childhood vaccines are introduced nation-wide, although in some countries the process of introduction has been planned in a phased manner (e.g. region by region). The basic rationale for nation-wide use of the current infant vaccines is that: (i) epidemiologically there is no localized "at risk" group (i.e. the entire population needs protection) as most of the infant vaccines are against communicable and infectious diseases; (ii) logistics and distribution of supplies is standardized hence easier to manage.

For RTS,S vaccination the conditions are different: (i) populations in "medium to high malaria transmission zones" stand to benefit the most from RTS,S vaccination which is of low efficacy and limited duration of protection; (ii) other more cost effective malaria control interventions (e.g. LLINs, RDTs, ACTs, SMC) are available and could be optimized first; (iii) RTS,S vaccine is expected to be less cost-effective in lower transmission settings; and (iv) supply of RTS,S vaccine may be limited initially. For these reasons, RTS,S vaccine will most probably be deployed at a sub-national level.

There is extensive experience of implementing preventive sub-national vaccination campaigns – for example, polio, Meningitis A, Japanese Encephalitis, and tetanus toxoid, as well as responding to targeted outbreaks for measles and yellow fever. Accordingly, if a campaign mode is chosen as a delivery strategy for RTS,S vaccination, then the logistics and distribution of supplies should draw on these previous practices and guidance. The need to conduct three rounds in close succession, followed by a 4th round sometime later, will intensify the level of effort and financing required and must be considered carefully when planning and allocating resources.

Sub-national delivery via a facility-based strategy is possible (See Table 1) but would require the following issues to be considered and addressed:

- Specialized training for health workers/vaccinators in the targeted areas (and provision for training of any new staff who may be rotated into the area).

- Customized (or adaptation of) Child Health Vaccination Cards, recording sheets (including supply forms), ledgers and registers in the targeted areas.

- Tailored information, education and communication materials for the sub-national targeted population.

- Other communication efforts nation-wide to explain why RTS,S vaccine is only being offered in certain areas, and to counter misinformation and harmful rumours that RTS,S vaccination is an "experimental" research trial.

- Dedicated system for monitoring RTS,S vaccine stock supply and distribution in the targeted areas.

- Co-ordination or integration with other disease control (especially malaria) efforts.

Table 1: Summary of Pros & Cons of Sub-national vs National Introduction of RTS,S Vaccine

Geographical Focus	Pros	Cons
Sub-national	• Lower overall cost and more cost-effective • May require little or no expansion to the cold chain capacity • Opportunity to learn more about programmatic requirements	• Requires tailored training, communications, recording forms/systems, and supply management • Could be negatively perceived as "experimental" research trial • Children older than 9 months who move into the area would not be protected
National	• Standardized roll-out of training, communications, revision of recording forms/systems, and vaccine management supply chain	• Potential for inadequate vaccine supply • Higher overall costs • Not cost-effective to target entire population • May require expansion of cold chain capacity • Could undermine utilization of other malaria control interventions

If a threshold coverage for other malaria control interventions was to be a condition that had to be met prior to RTS,S vaccine introduction the National Malaria Programme would be responsible for providing the coverage data and/or implementing a survey in the sub-national areas targeted for RTS,S vaccine introduction. If not all the targeted sub-national areas met the threshold criteria for the other interventions, it would be advisable and more efficient (repeated small scale vaccine introduction would be difficult and time-consuming to plan and manage) not to introduce RTS,S vaccination anywhere in the country until all targeted areas had achieved and sustained the minimum requirements.

#2. Delivery strategy: What are the programmatic options for delivering 3-doses of RTS,S vaccine between 5-9 months? What are the pros and cons of facility-based vs campaign strategies?

There are two main delivery strategies for any vaccine: (i) Facility-based delivery[5] whereby caregivers bring their children to the health facility or outreach post for vaccination; and (ii) campaign delivery which typically is a mass event, held periodically, where vaccination teams are deployed nationally or sub-nationally in an effort to vaccinate a large number of children within a short space of time.

RTS,S vaccine could be delivered via either of these delivery strategies although adjustments would need to be made to both. A summary of the pros and cons is provided in Table 2.

For facility-based delivery, two new vaccination visits between 5-8 months would need to be established to accommodate the RTS,S schedule of providing 3 doses by 9 months of age (it is proposed that the third dose would be given at the 9 month contact along with measles vaccination). The implications of creating two additional contacts in the routine vaccination schedule are discussed in detail in #3 below.

[5] Facility-based delivery includes planned outreach where a mobile team from the facility travels to more remote communities within their catchment area and provides vaccination services on a regular basis (e.g. once per week or month).

For campaigns, it would be necessary to plan for three rounds of mass vaccination with a minimum of 1 month between rounds. There is ample experience with polio implementing multiple rounds (usually 2) with OPV vaccine, although RTS,S is an injectable vaccine and the logistics and human resources requirements are more complicated. Very large scale childhood vaccination campaigns with injectable vaccines have been successfully conducted in Africa for measles, yellow fever, and meningitis vaccination, although because only one-dose is required these have been limited to one round (this strategy could be applicable for delivery of the fourth dose to ensure high coverage). There is experience with PIRI[6] (Periodic Intensification of Routine Immunization) in Africa and elsewhere (e.g. India) where 3 rounds of campaigns at monthly intervals have been implemented to deliver the routine vaccination schedule of 3 doses of DTP/Penta, pneumococcal conjugate (PCV), etc.

Table 2: Summary of Pros & Cons of Facility-based vs Campaign Delivery of RTS,S Vaccine

Delivery Strategy	Pros	Cons
Facility-based	• Makes use of existing system and resources • Vaccination available throughout the year (continuous) • Additional visits used to catch up missed or delayed vaccinations • Opportunity to combine with other child health visits • Easier record keeping • Possibly better verification of age of child or date of birth (facility records)	• Need to add at least two new contacts to immunization schedule • Coverage may be lower • Possible or perceived increase in workload of health workers • May have higher wastage, strain cold chain, and impose other logistic challenges
Campaign	• Likely to achieve higher coverage (reach the hard to reach) • Could initially be used to catch-up all children 5-17 months with RTS,S • Could be used to boost coverage of other antigens (Penta/PCV/Rota/ MCV) if integrated • More visibility, and may be useful at first introduction of RTS,S to a programme • May suit targeting specific season or location • Countries may already be committed to campaign delivery modes	• More costly, especially noting the need for three rounds at one month intervals • Disruption to routine services • Vaccination for other age groups may be demanded and more difficult to control • Vaccination only available during campaign (time limited) – may result in some children not completing the schedule if they miss a round • Record keeping more challenging (e.g. give out vaccination cards, transcribe tally sheets back into facility register) • Potential difficulties verifying the age of the child and vaccination history; little time to share information with parents.

[6] Periodic Intensification of Routine Immunization: Lessons Learned and Implications for Action. http://www.who.int/immunization/programmes_systems/policies_strategies/piri_020909.pdf

#3. Adding new vaccination contacts: Operationally, what will be required to introduce two new immunization visits/contacts between 5-9 months of age? Will these be acceptable to health workers and caregivers/communities? What benefits/drawbacks could these new visits/contacts have? What will be needed to ensure high coverage of all three doses?

The proposed primary series for RTS,S vaccination is a schedule of three doses from the age of 5 months, with a minimum interval of 4 weeks between doses, to be completed by 9 months of age.

In Africa, the commonly used vaccination schedule is: 6, 10 and 14 weeks (for Penta, Polio, PCV and Rota vaccines) with measles/yellow fever vaccine at 9 months. The introduction of RTS,S vaccine would therefore require the addition of two new visits or contacts between 5-8 months; the nine-month measles/yellow fever contact could be used for the third dose of RTS,S.

With campaign delivery there would be no need add additional immunization contacts to the national EPI schedule (although the intended target group would need to be effectively communicated to caregivers because it is a narrow age-range and not typical). Providing for a one-month interval between doses, the target group would be all children 5-7 months for the 1st round, 6-8 months for the 2nd round, and 7-9 months for the 3rd round[7].

Communicating the need for the sequence of three vaccinations across rolling age groups is likely to be challenging. This problem can be addressed in several ways:

- Caregivers can be instructed to bring vaccination cards or birth certificates to the campaign (but note this is not the practice for most campaigns which are supplemental and do not record doses);

- Recording each dose of RTS,S vaccine given on the child's vaccination card (this means that cards will need to be provided to caregivers that do not have/bring them) and instructing the caregiver to bring the child back for the subsequent dose at the next campaign one month later. Visual reminders about the date of the next campaign round (either hand-out flyers or stickers on the cards) can also be used.

Verification of the exact age and date of birth of the child (particularly in the absence of any records or birth certificate/registration) may also be challenging, with some options including:

- When documentation is unavailable, mother's recall and verification of the age of the child can be aided by linking the target age to an event, national holiday, or seasons.

- Many programmes have campaign experience with determining age when administering vitamin A supplementation to infants aged 6 months and above; and

It is anticipated that the vaccination of infants between the ages of 5-8 months will be acceptable to healthcare workers or caregivers. Many infants come late for their vaccinations so there is experience and acceptance to vaccinate this age group. In measles outbreak response vaccination,

[7] Alternatively, if a decision was taken to do "catch-up" vaccination for the entire target of 9-17 month olds which JTEG has specified as the group at greatest risk/benefit, then the campaign would target those 5-15 months in the 1st round, 6-16 months in the 2nd round, and 7-17 month in the 3rd round. Vaccinating a wider-age range would have obvious cost implications and the impact of such a strategy would be questionable given that herd immunity is not relevant.

infants from the age of 6 months are targeted. Polio campaigns vaccinate all children under the age of 5 years, although this is an oral vaccine.

If the chosen delivery strategy is facility-based, then the addition of two new visits between 5-8 months will be required for the RTS,S schedule. The decision on the timing of these contacts should be made based on country-specific factors and opportunities. For example, many countries in Africa are implementing a contact at 6 months of age for vitamin A supplementation, which is also a critical time point for feeding advice on introduction of foods to supplement breast feeding. Others have the implemented the practice of monthly healthy mother and baby visits, and malaria vaccine introduction could provide additional stimulus to support this practice. Accordingly, flexibility should be allowed for countries to decide the timing of the additional RTS,S vaccination contacts that is optimal for their context. Those that do not have a 6-month contact for another purpose, may prefer to begin RTS,S vaccination at 5 months, giving a slightly longer window of opportunity to provide the subsequent two doses.

Given that there are no issues with co-administration[8], it is practical that all programmes use the measles/yellow fever contact at 9 months to administer the 3rd dose of RTS,S vaccine.

While the exact timing of the additional two new contacts may vary from programme to programme, every programme will need to consider the following operational aspects of adding new contacts:

- Training of health workers and vaccine management (cold chain capacity, waste disposal).
- Information, Education and Communication to caregivers and communities announcing and explaining the new contacts.
- Revision of child health/vaccination cards and all forms, tally sheets, coverage monitoring charts, ledgers, and registers to include RTS,S vaccine.

As the target group is small and facility-based vaccination is offered on a continuous basis throughout the year, it is not anticipated that the addition of two new contacts for RTS,S vaccination will add significantly to the workload of health workers, although *"time-in-motion"* studies could be undertaken if this was a concern[9]. There may be an initial perception from health workers that they are being asked to do more or feel that they will be further overburdened and this needs to be managed proactively through discussion, supportive supervision and seeking opportunity to integrate with other service delivery (see below).

Many health facilities, particularly in remote and hard to reach areas where RTS,S vaccine is most likely to be relevant, are not appropriately staffed due to human resource constraints and/or unfilled vacancies. Where workload is already a problem it needs to be addressed otherwise it could undermine the quality and success of the programme.

[8] Co-administration of RTS,S vaccine with Pentavalent (DTwP/Hep B/Hib), OPV and measles vaccines has been confirmed.

[9] "Time in motion" studies were conducted for the administration of iPTI with immunization contacts. See: Manzi, F., et al. Intermittent preventive treatment for malaria and anaemia control in Tanzanian infants; the development and implementation of a public health strategy. *Trans R Soc Trop Med Hyg.* 2009 Jan;103(1):79-86. (Abstract accessed June 17, 2015 http://www.ncbi.nlm.nih.gov/pubmed/18823639).

A strong benefit of adding two additional immunization contacts between 5-8 months of age is that it will provide the opportunity to administer any previously missed doses of other vaccines. Drop-out rates generally increase with age and it could be postulated that additional contacts may serve to increase retention and completion of the vaccination schedule. The interval between the last dose of DTP/penta3 at 14 weeks and the next visit at 9 months for measles vaccination is very long. Introducing new contacts in this intervening period, particularly for a vaccine against malaria which is expected to be in high demand, could actually prove to be very positive in terms of keeping vaccination present in the minds of caregivers. More frequent visits may actually serve to reduce drop-out rates (and possibly wastage rates for some antigens but this would need to be studied) and increase immunization coverage rates and the number children who are fully vaccinated.

It is worth noting that analyses of timeliness of vaccination show that a large proportion of children are delayed in coming for vaccination and receive their doses late, particularly DTP3 and measles[10]. While this is not something to encourage, it does demonstrate that delayed vaccinations are currently (in the absence of any new contacts) very often being given at the ages proposed for RTS,S vaccination.

The number of antigens in the infant vaccination schedule has increased dramatically in many developing countries over the last 10 years, and in fact the schedule in the early months has become somewhat crowded. It is now common for 3-4 vaccines to be administered at one visit, for example at 14 weeks Penta3, PCV, Rota plus OPV and IPV vaccines are recommended. While safe, there is sometimes concern and reluctance on the part of both health workers and caregivers to administer multiple injections at the same time to small infants. In this respect, the new contacts required for RTS,S vaccination can be viewed positively as they will serve to spread out the vaccination schedule and not subject young infants to yet another injection at a time when they are already receiving many others[11].

It could be assumed that the need for caregivers to bring their children for two extra vaccination visits will have personal opportunity costs (time, transport costs, etc) but these perhaps will be offset by a reduction in the time and money spent caring for infants who fall ill with malaria. The effective social mobilization and information, education and communication (IEC) efforts that will be required for high coverage of all three doses and to ensure that caregivers bring their children to the new vaccination contacts are discussed in detail in section #5 Demand Generation below.

[10] Clark, A and Sanderson, A. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet* 2009; 373: 1543–49.

[11] However, in countries that include Yellow Fever and Meningitis A vaccination at 9 months together with measles vaccine, the introduction of RTS,S vaccine could result in 4 injections at 9 months of age. This could be reduced by either offering RTS,S vaccine earlier at 8 months of age, or moving MenA vaccination later (WHO recommended age for vaccination is between 9-18 months).

Table 3: Summary of Pros and Cons of Introducing Two Additional Immunization Contracts for RTS,S Vaccination Between 5-8 Months of Age

	Pros	Cons
Introducing Two Additional Contacts	• Opportunity to provide missed doses of other vaccines • Reduces burden of multiple injections at existing contacts • Helps to spread out the vaccination schedule to more regular intervals (no long gap between 14 week and 9 month visits) • May increase vaccination coverage and completion of schedule (fully immunized child) • May support other efforts to increase well-baby preventive health visits in the first year of life • Other vaccines administered at older ages (beyond 1st year of life) could also benefit	• Potential increase in workload of healthcare workers (but anticipate that this would be manageable if human resources constraints were not an issue) • May add complexity to outreach service planning if target populations increase in size • Need to communicate requirement for additional visits (as discussed below) • Possible time and financial opportunity costs for caregivers (as discussed under Demand Generation below)

#4. Fourth dose: What is the best programmatic approach to assure that all children receive a fourth dose 15-18 months after the last dose (i.e. between ages of 24-27 months of age if last dose given at 9 months with measles vaccination)? What strategies/incentives would facilitate implementation and uptake of the fourth dose? What special measures/actions should be taken if fourth coverage is low?

While there are several WHO recommendations for vaccination in the 2nd year of life[12], only the recommendation for a DTP booster between the ages of 1-6 years overlaps with the target age for the RTS,S vaccine fourth dose at 24-27 months old. Typically, in Africa, countries schedule the DTP booster either at 15-18 months with the 2nd dose of measles vaccine, or at 6 years of age at school entry. Irrespective of the schedule, implementation of the DTP booster dose remains very weak and coverage data is not presently collected by WHO. There is interest to strengthen the performance of vaccination in children beyond the first year of life but work on this is just beginning. This could potentially be an area for synergy with RTS,S vaccination.

Provision of the fourth dose may also benefit from consideration of options for integration with other disease control or maternal and child health services, as discussed below. Many countries in Africa do have regular 6 monthly vitamin A supplementation for all children 6-59 months of age. Provision of the booster dose of RTS,S vaccine at 24 months could be combined with the visit for vitamin A supplementation where such programmes are being implemented.

There is limited experience of using incentives for immunization. In some countries, Long-lasting Insecticide-treated Nets (LLINs) have been given when a child completes their full vaccination schedule, elsewhere conditional cash transfers[13] (CCTs) have proven successful. However, such strategies require further study before they can be recommended routinely.

[12] MCV2 15-18 months; Meningitis A 9-18 months; alternative 2 dose PCV schedule with booster 9-15 months; alternative 2-3 dose Hib schedule with booster 6 months after last dose.

[13] Lagarde M, Haines A, Palmer N. The impact of conditional cash transfers on health outcomes and use of health services in low and middle income countries. Cochrane Database of Systematic Reviews 2009; Issue 4. Art. No.:

Given the target age group, the delivery of the RTS,S fourth dose at 24-27 months of age will require special efforts, especially social mobilization and IEC. If uptake and coverage of the fourth dose is poor, it may be necessary to deliver this dose via a special campaign strategy to ensure compliance. This would have operational cost implications.

#5. Demand generation: What information, education and communication (IEC) strategies will be needed for the RTS,S vaccine? Will special efforts be needed given its non-traditional schedule and specific safety signals to monitor, as well as its partial efficacy and limited duration of protection?

The introduction of RTS,S vaccine will require a very well prepared IEC strategy and materials, and will need to actively engage local opinion leaders for success.

There are a number of information needs that are novel and specific to RTS,S, including:

- partial protection and need to link to other malaria control interventions
- subnational and/or seasonal deployment (if adopted)
- new age group for vaccination
- importance of primary schedule and fourth dose
- risk-benefit, safety and AEFI arrangements; and
- rationale for campaign approach (if adopted).

It will be critical to communicate the non-traditional age group vaccination schedule, reinforcing any links to other preventive services proposed from age five months onwards. It will also be important to explain that the vaccine is less effective and for a relatively shorter duration compared to other vaccines. IEC will need to continually reinforce the need to continue the use of other malaria control interventions (LLINs, SMC, etc).

Immunization programmes and partners have previous communications experience with other vaccines that do not protect against all causes of a particular illness, such as for the introduction of pneumococcal conjugate vaccine and Rotavirus vaccine against pneumonia and diarrhoea, which also require other control interventions[14]. There are also established resources for communication strategies for the introduction of new vaccines, including those developed by UNICEF, that could be applied to RTS,S.

As discussed previously, if RTS,S vaccination is deployed at a sub-national level it will also be necessary to have IEC efforts address this, particularly given the potential for misunderstanding/rumours that RTS,S vaccine introduction is an experimental research trial.

Given the safety signals for RTS,S vaccine, it will be very important (as it is for all new vaccine introductions) to have communication plans and systems in place for handling any adverse events following vaccination. WHO has a wealth of materials, trainings and guidance available to support countries.[15]

CD008137; DOI: 10.1002/14651858.CD008137. and Cueto, S. Conditional cash-transfer programmes in developing countries. *The Lancet* 2009;374:1952-1953.

[14] WHO. (2013) Ending preventable child deaths from pneumonia and diarrhoea by 2025. The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/

[15] Vaccine Safety Basics: WHO On-line e-Learning Course in Vaccine Safety (http://vaccine-safety-training.org/home.html) and Vaccine Safety Events: Managing the Communication Response (www.euro.who.int/data/assets/pdf_file/0007/187171/Vaccine-Safety-Events-managing-the-communications-response-final.pdf)

#6. Vaccine Management & Logistics: How will RTS,S be handled in the cold chain? Are there any special requirements? Is the available presentation optimal? What is expected in terms of wastage?

RTS,S vaccine presentation is a 2-dose vial of lyophilized (freeze-dried powder) RTS,S antigen clipped to a 2-dose vial of liquid AS01 adjuvant suspension to be used for reconstitution (Figure 2). The "clip" presentation, which keeps the vaccine together with the correct reconstitution vial, is already used for another, prequalified, GSK vaccine, Tritanrix-HepB+Hib (pentavalent DTPw combination vaccine). This "bundled" presentation avoids the possibility of the wrong diluent being used and simplifies the inventory management processes at the country level.

Figure 2: RTS,S Vaccine

The vaccine requires storage at 2-8˚C. There is a VVM (VVM type yet to be confirmed) on the side of diluent ASO1 vial. In line with WHO's multi-dose vial policy (MDVP)[16], because there is no preservative, once reconstituted the RTS,S vaccine must be discarded after six hours, or at the end of the session, whichever comes first.

The pack is a 100-vial pack, which is the standard GSK pack for vaccines in 3 mL vials supplied through UNICEF.

Number of vials per carton	Number of doses per carton	Dimensions of carton (cm)	Cold chain volume (cc) per dose in carton	Doses (and cartons) per insulated shipping box[17]
2 x 50	100	17.8 x 14.7 x 3.7	9.7	2400 (24)

[16] WHO policy on the use of opened multi-dose vaccine vials (2014 Revision)
http://www.who.int/immunization/documents/general/WHO_IVB_14.07/en/
[17] GSK insulated shipping boxes are of dimension 34 x 25 x 43 cm.

The cold chain volume for RTS,S vaccine of 9.7 cc/dose is on the lower side of the current range (11.9 cc/dose) for this type of presentation (two dose vial of lyophilized vaccine[18]), but higher than that for an equivalent two dose liquid vial (6.9 cc/dose). As such, the cold chain storage requirement for RTS,S vaccine (4 doses), when compared to other new vaccines, is equivalent to the two-dose Rota vaccine i.e. approximately 35 cc/child. In countries where cold chain capacity is already limited/exceeded, the introduction of RTS,S vaccine may pose a logistics challenge. As with any new vaccine introduction, an assessment of the national (or sub-national) cold chain capacity to accommodate the new vaccine needs to be undertaken before RTS,S vaccine is introduced, and the necessary cold chain expansion plans (if needed) implemented. WHO has well-established standardized methods, tools, and guidance for cold chain assessments to assist countries.

The relatively higher impact on cold chain space requirements is balanced by less wastage than other presentations. The wastage with two dose vials is lower than that for five and ten dose vials. WHO Logistics Experts provided a preliminary "educated guess" estimate that the wastage rate of RTS,S vaccine will be around 10-15% in the field. This will need to be considered in micro-planning, especially for facility-based vaccination which includes outreach visits to small population groups.

#7. Integration: What are the opportunities for integration with the RTS,S vaccination schedule, with other vaccines, with broader malaria control, and with other maternal and child health services?

Opportunities for integration will vary by country, as the vaccination schedule, child health contacts and selection of interventions being implemented are different from country to country. Given the expanded age range of RTS,S vaccination, and its partial efficacy, opportunities for integration should be sought with:

- other vaccines;
- malaria control activities;
- other disease control activities;
- other well-child, preventive health visits in the early years of life (especially those linked to child nutrition and family planning.

Figure 3 provides a summary of the alignment of the RTS,S vaccination schedule with WHO recommendations for the timing of immunization and other maternal and child health interventions.

Integration with other vaccines

As discussed previously, the 3rd dose of RTS,S aligns with measles/rubella, Yellow Fever, and Meningitis A vaccination contacts, and also with alternative (but rarely used) schedules for PCV and *Haemophilus influenzae* type b (Hib) vaccines. The timing of the RTS,S fourth dose at 24-27 months of age aligns with the WHO recommendation for a DTP booster between the ages of 1-6 years, although most countries schedule their DTP booster either at 15-18 months of age (to align with the 2nd dose of measles vaccine) or 6 years of age at school entry.

Integration with malaria control activities

Continued implementation and high coverage of other malaria control interventions will be a priority, if not a prerequisite, with RTS,S vaccine introduction. Figure 4 summarizes the alignment of RTS,S vaccine with other malaria control interventions.

[18] Combo DTP-HepB liquid plus Hib lyophilized, both from GSK and SII; MCV (Msl, MR and MMR) from SII; Rubella from SII; Yellow Fever from Russia.

There is a well-established practice of linking the distribution of LLINs with immunization in Africa, using both fixed-site vaccination services and mass vaccination campaigns. Integrated LLIN and RTS,S vaccination would certainly be feasible.

In areas of the Sahel sub-region with highly seasonal malaria transmission, seasonal malaria chemoprevention (SMC) targets children 3-59 months to receive a 3-day course of SP-AQ with an interval of 1-month between courses for a maximum of 4 cycles per year[19]. While this schedule would align well with that for RTS,S vaccination, there are several issues including:

- Whether there is any negative interaction on the immune response to RTS,S vaccine when it is given concomitantly with SP and AS anti-malarial drugs.

- The likelihood that the recommended period of administration of SMC – during the months that children at most a risk of malaria – would not be optimal for RTS,S vaccination which ideally should be completed prior to the transmission season. However, giving RTS,S vaccination during the SMC period, presumably would offer future protection (i.e. the next transmission season) to those who were vaccinated. Hence, there could be complementarity of the interventions (SMC protection for the current season, given together with RTS,S vaccination for protection during future seasons).

- The need to identify and selectively vaccinate only those children who are 5 months of age (and track them for each round) rather than the entire target group for SMC which is children 3-59 months.

- The feasibility of providing the booster dose of RTS,S vaccination – 15 or 16 months later -- with the final round of the subsequent year's SMC intervention.

There could be other possibilities to link education of new mothers about RTS,S vaccination to chemoprevention with intermittent treatment in pregnancy (IPTp). Under certain conditions in areas of Africa with high to moderate malaria transmission, WHO recommends for the use of intermittent preventive treatment for infants (SP-IPTi)[20] which is provided at 10 and 14 weeks and 9 months of age using vaccination contacts. However, this recommendation is not currently being implemented in any country.

Integration with other preventive services in the first two years after birth

Many countries in Africa are examining how additional 'well-child' preventive health visits in the first two years of life can improve child nutrition. Many countries have six-monthly vitamin A supplementation programmes for children 6-59 months. Visits at six months of age and later are a critical time point for counselling on the introduction of high quality, calorie-dense complementary foods. These could be used for the first dose of RTS,S vaccine at 6 months and also for the fourth dose at 24 months of age.

Some programmes are examining the integration of family planning services with immunization. These include family planning counselling contacts at or before 6 months after birth, as well as provision of injectable contraceptives which require attendance at regular intervals. Existing programs could be used for a first dose of RTS,S where they exist.

[19] WHO (2013). Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field guide.(http://www.who.int/malaria/publications/atoz/9789241504737/en/)

[20] WHO Policy recommendation on intermittent preventive treatment during infancy with sulphadoxine-pyrimethamine (IPTi-SP) for Plasmodium falciparum malaria control in Africa. March 2010. http://www.who.int/malaria/publications/atoz/policy_recommendation_IPTi_032010/en/

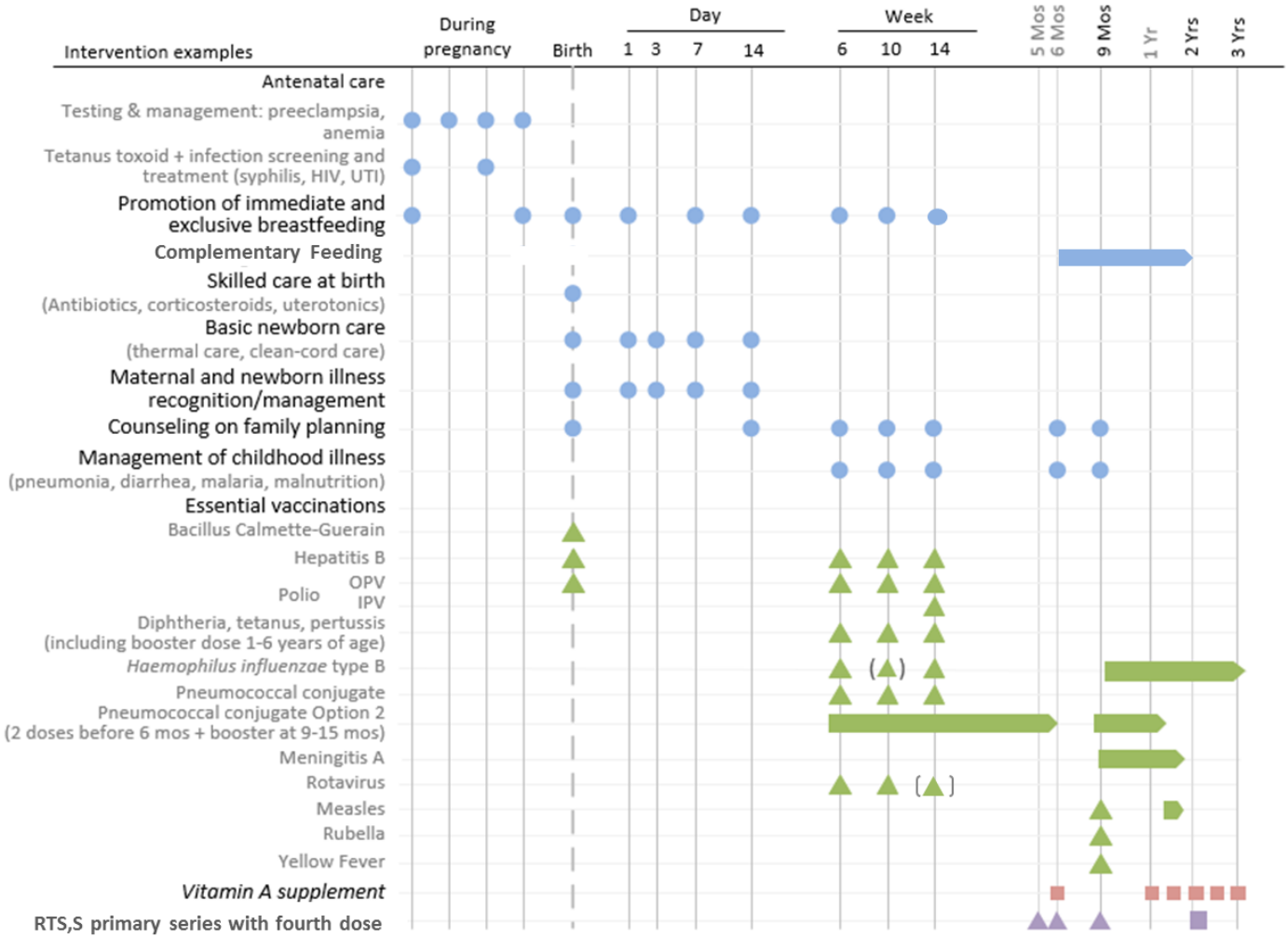
In countries without established preventive care programs integrated planning may enable RTS,S introduction to accompany the strengthening of such initiatives. For example, the creation of a new 6 month contact for RTS,S vaccination could be used for the promotion of continued breastfeeding, conselling on complementary foods, and family planning, or as a healthy mother and child contact for monitoring status of both.

General considerations with integrating health services

Any new plan to integrate health services should consider, both in planning and in monitoring, whether:

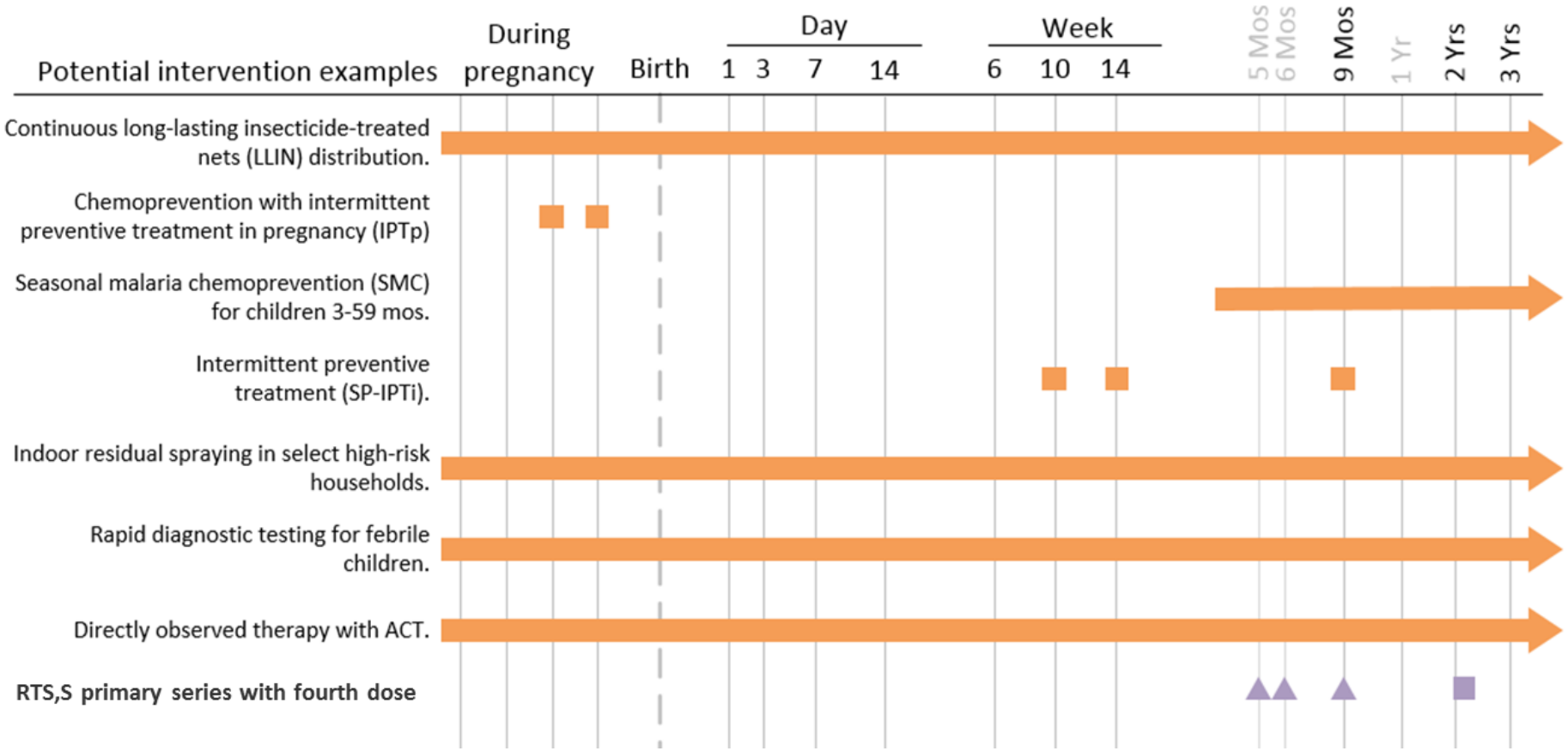
- integrated services adversely affect staff workload (for example unfeasibly extending time taken in patient contact) with impact on the quality of the service provided;
- combining the services is acceptable to families; and
- coverage of each service is being maintained.

Figure 3: Alignment of RTS,S Vaccination with WHO Recommendations for Immunization and Other Maternal & Child Health Interventions[21]



[21] PATH- Vaccine Access and Delivery/MVI

Figure 4: Alignment of RTS,S Vaccine with Other Malaria Interventions[22]



[22] PATH- Vaccine Access and Delivery/MVI

4. Conclusion

As this paper has summarized, there are many programmatic issues to be considered with the proposed infant schedule for RTS,S vaccination. The most challenging is likely to be the delivery of the fourth dose between 24-27 months of age, because apart from campaign strategies, in Africa this age group is not normally in contact with immunization services.

Nevertheless, if the use of RTS,S vaccine is at some point in time to be recommended by WHO, it is certain that with over four decades of experience implementing the Expanded Programme on Immunization (EPI) solutions could be found if the necessary financial resources were made available. The key strengths of immunization programmes are their ability to use innovative strategies to reach the hard to reach, and their capacity to monitor performance (coverage) in real time. This allows for a tradition of "learning by doing", and of adaptation and innovation from which the unique implementation schedule of RTS,S vaccination would benefit.