The Malaria Vaccine Pilot Evaluation

An evaluation of the cluster-randomised pilot implementation of RTS,S/AS01 through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa: a post-authorization observational study

M A S T E R P R O T O C O L

PASS information

Title	An evaluation of the cluster-randomised pilot implementation of RTS,S/AS01 through routine health systems in moderate to high malaria transmission settings in Sub-Saharan Africa: A Post-Authorization Observational Study
Protocol version identifier	RTSS_MVIP_v9 22 April 2020
Date of last version of protocol	19 October 2018
EU PAS register number	Study not registered
Active substance	RTS,S antigen and AS01E Adjuvant
Medicinal product	Mosquirix™
Product reference	EMEA/H/W/002300
Procedure number	Not applicable
Study sponsor	World Health Organization
Joint PASS	No
Research question and objectives	Primary impact objectives The primary objectives of the impact evaluation are to estimate the effect of the routine delivery of RTS,S/AS01 on.: • all-cause mortality (excluding accidents); • the incidence of hospital admission with severe malaria; overall and each country. Primary safety objectives The primary objectives with regard to safety are to estimate the effect of RTS,S/AS01 introduction on: the incidence of hospital admission with: • meningitis • cerebral malaria (data pooled across the three countries). and on all-cause mortality in boys and girls, to determine whether there is any evidence that RTS,S/AS01 increases mortality in girls, overall and in each country

	Primary feasibility objectives The primary objectives with regard to feasibility are to estimate: • the proportion of children aged 12-23 months who received three doses of RTS,S/AS01 by 12 months of age (in each country) • the proportion of children aged 27-38 months who received their fourth dose of RTS,S/AS01 by 27 months of age (in each country)
Country(-ies) of study	Three moderate to high malaria endemicity countries of sub-Saharan Africa: Ghana, Kenya and Malawi
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Revisions	**Date:** April 22, 2020 **Revisions made by:** David Schellenberg Mary J Hamel Paul Milligan

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2 List of abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
ARC	National AEFI Review Committee
ATP	According to Protocol
AVPU	Alert, Voice, Pain, Unresponsive
BCG	Bacillus Calmette–Guérin
BCS	Blantyre Coma Scale
BH	Birth History
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
CORP	Community Own Resource Person
CRF	Case Report Form
CRO	Clinical Research Organization
CSF	Cerebro-Spinal Fluid
DHS	Demographic and Health Survey
DIFP	District Immunization Focal Person
DSMB	Data and Safety Monitoring Board
DSS	Demographic Surveillance System
DTP	Diphtheria, Tetanus, Pertussis
DTP3	Third Dose of DTP vaccine
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPI	Expanded Programme on Immunization
g/dL	Grams per deciliter
GACVS	Global Advisory Committee on Vaccine Safety
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GIS	Geographic Information System
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
Hb	Hemoglobin
Hct	Hematocrit
HepB	Hepatitis B
Hib	Haemophilus influenzae type b
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HRP2	Histidine-Rich Protein 2
HSB	Health-Seeking Behaviour
ICD-10	International Classification of Disease 10th revision
ICF	Informed Consent Form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICTRP	International Clinical Trials Registry Platform
ID	Identification, Identifier
IEC	Independent Ethics Committee
IHME	Institute for Health Metrics and Evaluation
IMR	Infant Mortality Rate
IRB	Institutional Review Board
IRS	Indoor Residual Spraying
ITN	Insecticide-Treated Net
JTEG	Joint Technical Expert Group
K	Intra-Class Correlation Coefficient
LAR	Legally Acceptable Representative
LLIN	Long-Lasting Insecticidal Net
LP	Lumbar Puncture
M	Month
MCV1	First Dose of Measles-Containing Vaccine
MCV2	Second Dose of Measles-Containing Vaccine
MenA	Meningococcal group A vaccine
MICS	Multi-Indicator Cluster Survey
MIS	Malaria Indicator Survey
MoH	Ministry of Health
MPAC	Malaria Policy Advisory Committee
MVIP	Malaria Vaccine Implementation Programme
MVPE	Malaria Vaccine Pilot Evaluation
NRA	National Regulatory Agency
OPV	Oral Poliovirus Vaccine
PAG	Programme Advisory Group
PCR	Polymerase Chain Reaction
PCV	Pack-Cell Volume
PI	Principal Investigator
PIE	Post-Introduction Evaluation
pIMD	Potential Immune-Mediated Disease
PIP	Pilot Implementation Programme
PSU	Primary sampling units
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
RDT	Rapid Diagnostic Test
RMP	Risk Management Plan
RR	Risk Ratio
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on immunization
SAP	Statistical Analysis Plan
SE	Study End
SOP	Standard Operating Procedures
SPM	Study Procedures Manual

SSA	Sub-Saharan Africa
TOR	Terms of Reference
UN	United Nations
UNFPA	United Nations Population Fund
VA	Verbal Autopsy
VE	Vaccine Efficacy
VR	Village Reporters
WHO	World Health Organization

3 Responsible parties

WHO takes overall responsibility for the conduct of this study. The main responsible parties for this protocol are as follows:

Dr Mary Hamel, Senior Technical Officer (WHO/HQ/FWC/IVB/IVR) and Dr David Schellenberg, Scientific Adviser (WHO/HQ/HTM/GMP) are the designated contact people at WHO HQ, Geneva, for the study.

Coordinating investigators for each country will be listed in country-specific protocols.

A list of all investigators, including contact details, will be kept in a stand-alone document (Annex 3).

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4 Abstract

Title	An evaluation of the cluster-randomised pilot implementation of RTS,S/AS01 through routine health systems in moderate to high malaria transmission settings in Africa
Version and Date of the protocol	V 9.0-22 April 2020
Main Authors	David Schellenberg, Mary Hamel and Paul Milligan
Rationale and background	RTS,S/AS01 has been developed as a vaccine to prevent disease caused by *Plasmodium falciparum*. A phase 3 trial in 15,459 infants and young children in 7 sub-Saharan African countries showed that in the 12 months following completion of the first three doses, the incidence of clinical malaria was reduced by 51% (95% confidence interval (CI) 47%, 55%) and the incidence of severe malaria was reduced by 44.5% (95% CI 24%,60%) in children aged 5-17 months at the time of dose 1[1]. Estimated efficacy decreased over time: in successive 6 month periods, the efficacy of 3 doses against clinical malaria declined from 68% in the first 6-month interval to 39% in the second, and 28% in the third interval, resulting in an overall efficacy estimates of 46% (95% CI 42, 50) against clinical malaria and 38% (95% CI 18, 53) against severe malaria by 18 months after dose 3. A fourth dose, given 18 months after dose 3, increased efficacy against clinical malaria over the whole of the 4-year study period (a median of 48 months follow-up) from 26% (95% CI 21, 31) to 39% (95% CI 34,43) and from -2 (95% CI -31,20) to 31.5% (95% CI 9,48) against severe malaria. Vaccine efficacy over the whole study period in those who received 4 doses of RTS,S/AS01 was also confirmed against malaria hospitalization (37%, ATP, 95%CI 27-48.5), all-cause hospitalization (15%, ATP, 95%CI 6-25) and severe anaemia (62%, ATP, 95%CI 26.5-81). Vaccine efficacy for all time periods and endpoints was substantially lower in children aged 6-12 weeks at the time of dose 1 than in the 5-17 month olds and thus further evaluation in the young infants was not recommended by WHO. This protocol therefore focusses on the evaluation of RTS,S/AS01 when administered to children age 5 months and above. The benefits of RTS,S/AS01 were demonstrated in the presence of

[1] The efficacy estimates presented here are from according to protocol analyses of multiple episodes, considered the most relevant analytical approach to inform understanding of the potential public health impact of the intervention.

high ITN coverage and where the identification and treatment of clinical and severe malaria episodes was optimized. The enhanced access to good quality curative services likely limited disease progression and precluded the measurement of vaccine impact on mortality. However, modelling suggests 1 life may be saved per 200 children vaccinated with 4 doses of RTS,S/AS01 outside trial settings in moderate to high transmission settings.

No fatal adverse events were assessed as causally related to RTS,S/AS01 vaccination. The overall incidence of SAEs (both all SAEs and non-malaria SAEs) in the phase 3 study was lower in children receiving RTS, S/AS01 than in children in the comparison arm. Among children receiving the vaccine at 5-17 months of age, febrile convulsions were an identified risk in RTS,S/AS01 recipients in the 7 days following vaccination. In the same age group, meningitis was identified as a potential risk, with more cases of meningitis in RTS,S/AS01 recipients, compared to the control group (relative risk (RR) 8.0 (95% Confidence Interval (CI) 1.1-60.3)). Unplanned, exploratory analyses in children in the 5-17 month age category revealed more cerebral malaria cases in the RTS,S/AS01 group and, for both age categories, more deaths from all causes combined in vaccinated girls compared to the control group.

The European Medicines Agency provided a positive scientific opinion on the benefit/risk balance of RTS,S/AS01 in mid-2015, accepting a proposed Risk Management Plan which included a Phase 4 study to investigate the observed safety signals. In late 2015, WHO's expert vaccination and malaria advisory committees recommended pilot implementation studies to assess (1) the programmatic feasibility of delivering RTS,S/AS01 with three to four new immunization contacts, including the fourth dose in the second year of life; (2) the vaccine's impact on mortality and (3) the vaccine's safety in the context of a routine immunization programme. [1]

This Master Protocol describes the evaluation of the first-time use of the RTS,S/AS01 vaccine, implemented in a pilot programme by Ministries of Health using an expanded schedule of their routine EPI contacts, building on the national immunization programmes which routinely deliver vaccines to young children living in SSA countries. Delivery of RTS,S/AS01 will be the responsibility of the MOH and implementation is expected to continue beyond the period of the evaluation, assuming the benefit-risk assessment remains favourable. Using routine systems for vaccine introduction will facilitate ongoing vaccine delivery and expansion country-wide should WHO provide a positive policy recommendation. Efforts to assure vaccine access beyond the period of the pilot implementation

started in late 2017.

The RTS,S/AS01 Malaria Vaccine Implementation Programme (MVIP) comprises pilot implementation of the vaccine, with support for optimisation of the implementation, GSK's Phase 4 studies and the WHO-led RTS,S/AS01 Malaria Vaccine Pilot Evaluation (MVPE) described in this protocol. These evaluations will provide data to bridge the knowledge gaps currently inhibiting wider scale use of RTS,S/AS01. The programme has been designed to complement the GSK-sponsored Phase 4 study. Data from the pilots will inform policy-making at global and national levels, allowing decisions to be made about larger-scale adoption of RTS,S/AS01.

Study Design

This will be an evaluation of the pilot implementation of RTS,S/AS01 by Ministries of Health in three countries in sub-Saharan Africa. The first dose will be administered as soon as possible after children reach age 5 months, followed by doses two and three at approximately one month intervals, and a fourth dose 15-18 months after dose three.

The pilot implementation will use a cluster-randomized design, with some areas Districts, Sub-counties or Clusters, referred herein as "clusters") introducing RTS,S/AS01 at the beginning of the programme and other clusters, initially without RTS,S/AS01, acting as comparison areas. The division of areas into implementation or comparison areas will be randomized in order to generate the strongest possible evidence on the impact and safety of the vaccine.

Identical monitoring systems will be established in both implementation and comparison areas to record impact and safety outcomes~~. Follow-up of children aged up to 39 months will enable key outcomes to be evaluated up to 1 year following the fourth dose of RTS,S/AS01 in the majority of vaccinated children. (see also 'Population', below).~~ in children 1-59 months of age.

This master protocol assumes that ~~a total of~~ approximately 60 ~~clusters~~ areas will be identified per country, evenly split between implementation and comparison areas, with each cluster contributing approximately 4,000 children per year to the evaluation of RTS,S/AS01. All areas will contribute to the evaluation of the impact on mortality through surveillance at the village level where Village Reporters (VR) will document deaths. A sub-set of clusters, with access to care in up to 24 sentinel hospitals across the programme (up to 8 per country), approximately equally split between implementation and comparison areas, will contribute to the hospital-based surveillance of safety and cause-specific impact assessments. Feasibility will be evaluated by estimating vaccine coverage and other relevant data in a representative sample of

households in each cluster, by using the routine administrative data from vaccinating facilities across the whole pilot programme, and - where feasible - by using data from clinic-based vaccination registries.

Population

Children are eligible for the malaria vaccine starting at 5 months of age, with the 4th vaccination dose provided around 2 years of age, however surveillance will include all between the ages of 1 and 59 months living in the areas designated for RTS,S/AS01 malaria vaccine implementation, and comparison areas. The household surveys to asses feasibility of reaching children with 4 vaccine doses will be carried out through community based household vaccine coverage surveys in children 5-48 months old.

Evaluation of the pilot implementation will run for a total of about 46 months in each country.

Variables

The primary objectives of the impact evaluation are to estimate the effect of the routine delivery of RTS,S/AS01 on all-cause mortality and on the incidence of hospital admission with severe malaria, overall and in each country.

Secondary objectives include assessment of the effect of RTS,S/AS01 on all-cause hospital admissions, on admissions for specific causes, and on the incidence of non-malaria hospital admissions.

The primary objectives of the safety evaluation are to estimate the effect of routine delivery of RTS,S/AS01 on a) the incidence of hospital admission with meningitis and b) the incidence of hospital admission with cerebral malaria, pooled across the three countries, and c) on all-cause mortality in boys and girls and to determine whether there is any evidence that RTS,S/AS01 increases mortality in girls, overall and in each country; and pooled across three countries

The safety evaluation will also use spontaneous reporting to detect adverse events following immunization (AEFI) with RTS,S/AS01.

The primary objective of the feasibility evaluation will be to estimate the coverage of RTS,S/AS01 in the implementation areas, defined as the proportion of children aged 12-23 months who had received 3 doses of RTS,S/AS01 by 12 months of age, and the proportion of children aged 27-38 months who had received their fourth dose of RTS,S/AS01 by 27 months of age.

Secondary feasibility objectives are to measure, in implementation and comparison areas, the timely administration of RTS,S/AS01 vaccination; the coverage of other recommended EPI vaccines; the coverage and utilization of ITN/LLIN and IRS; and the patterns of

health-seeking behaviour for febrile children. In addition, there will be study of the effect of strategies to achieve optimal coverage of the fourth dose; whether the introduction of additional contacts between 5-9 months of age influences drop-out rates for routine vaccinations and changes the number of fully vaccinated children; and whether the introduction of RTS,S/AS01 is associated with growth (measured by MUAC) or increased coverage of other key childhood interventions, including anti-helminth administration (deworming) and Vitamin A supplementation.

Data Sources

The impact evaluation will capture data at the community level through resident Village Reporters (VR) specially trained to document and report deaths in the target age group. Trained VR supervisors will conduct Verbal Autopsies, using WHO-recommended methods. This will allow assessment of impact on all-cause mortality excluding deaths due to accidents and injuries, and will provide the opportunity to capture vaccination status and to confirm age at death. Sentinel hospital admission data will be used to measure the impact of RTS,S/AS01 introduction on incidence of admission with severe malaria.

In addition to strengthened routine pharmacovigilance, involving training of health care workers and sensitisation of communities, safety data will be captured in up to 24 sentinel hospitals by means of systematic, prospective, monitoring of all paediatric admissions, paying particular attention to meningitis and cerebral malaria.

The feasibility of routine RTS,S/AS01 deployment will be evaluated primarily through the assessment of vaccine coverage in two standardised household surveys conducted across the pilot implementation areas. These data will be complemented by routine ("administrative") health facility data and, to the extent possible, by facility-based electronic vaccination registries.

Study Size

The implementation of the RTS,S/AS01 vaccine will use the EPI, building on routine systems. The evaluation period is the time needed to monitor a sufficient number of children for vaccine safety, impact and feasibility. The evaluation of mortality drives the overall scale of the Malaria Vaccine Pilot Evaluation. In order to detect in each country a 10% decrease in all-cause mortality in vaccine-eligible children, and assuming a minimum mortality risk of 25 per 1000 in the target age group, a total of 60 areas each contributing approximately 4,000 children per year to the evaluation, and evenly split between implementation and comparison areas, will be required. Country-specific protocols will include updated sample size estimates, based on cluster size and local mortality estimates, and

are expected to require a range of 46-60 areas per country. Each year this will generate a total of approximately 120,000 children in the implementation areas and 120,000 children in the comparison areas in each country.

Hospital-based safety surveillance will be nested within parts of the MVPE area and include up to 8 hospitals per country, serving up to 24 areas across the Programme. This is designed to enable detection, with 90% power, of a 2.6-fold increase in the risk of meningitis and an 1.7-fold increase in the risk of cerebral malaria in children living in areas where RTS,S/AS01 is introduced. In addition, all health care facilities in the study areas will be supported to identify and report AEFI and VRs will identify non-hospitalized deaths. All AEFI and deaths will have their relationship with immunisation status evaluated.

A representative sample of 100 households per cluster (up to 6,000 households per country) will be surveyed to estimate the coverage of vaccinations in both implementation and comparison areas with a precision of +/- 2% in each of the three countries**.**

Data Analysis

Impact on survival will be evaluated by comparing the rate of death among children living in implementation areas with the rate of death among children living in comparison areas, with analysis by gender. as a subgroup analysis, as described in section 9.4.

The incidence rates of hospitalised probable meningitis and of cerebral malaria in vaccine-eligible age groups will be compared between implementation and comparison.

The proportion of children who received RTS,S/AS01 doses 1, 2 and 3 (children aged 12-23 months) and dose 4 (children aged 27-38 months) will be estimated from household surveys, using documented evidence (using vaccination cards) and maternal recall.

Milestones

The milestones will be adapted based on the timing of vaccine introduction in the intended study sites in the target SSA countries.

5 Amendments and updates

Number	Date	Amendment or update	Reason

7.2	09 Feb 2018	Amendment	Changes proposed by advisory committees on review
8.1	19 Oct 2018	Ammendment	Changes proposed by advisory committees on review
9.0	22 Apr 2020	Ammendment	Changes to include statistical analysis plan

6 Milestones

All timings are tentative and dependent on the timing of implementation of RTS,S/AS01 by Ministries of Health, following confirmation of adequate surveillance systems in each country. Please also refer to figure 2 in section 7.6.5.

Milestone	**Planned date**
Country-specific protocol submitted to Independent Ethics Committee & Regulatory Authority in country 1	*Q3. 2018*
Country-specific protocol submitted to Independent Ethics Committee & Regulatory Authority in country 3	*Q3. 2018*
Start of dose 1 in country 1 = Start of evaluation data capture	*Q2. 2019*
Dose 4 provided to last of children who were first vaccinated in year 1 in country 1	*Q1. 2023*
Start of dose 1 in country 3	*Q3. 2019*
Dose 4 provided to last of children who were first vaccinated in year 1 in country 3	*Q4. 2023*
Surveillance complete in country 1	*Q1. 2023*
Surveillance complete in country 3 = End of evaluation data capture	*Q4. 2023*
Final report of study results	*Q4. 2023*

Milestones in *italics* are dependent on the timing of implementation of RTS,S/AS01 by Ministries of Health and will drive the timing of the beginning and end of evaluation data capture.

7 Rationale and background

In 2015, WHO estimated that 214 million malaria episodes caused 438,000 deaths, the vast majority in young children in sub-Saharan Africa (SSA). Current control tools are only partially effective, and all are based on insecticides or drugs, both of which are increasingly threatened by resistance. Available tools are unable to control malaria everywhere, even with good coverage, and there is an urgent need for new interventions[2]

7.1 Efficacy of RTS,S/AS01

RTS,S/AS01, the world's first malaria vaccine, was evaluated in a phase 3 trial in 15,459 infants (6-12 weeks old at the time of dose 1) and young children (5-17 months old at the time of dose 1) in 7 sub-Saharan African countries[3–6]. Three doses of RTS,S/AS01 generated protection against clinical malaria which, though moderate compared with the efficacy achieved by vaccines against common viral diseases, is substantial in the context of malaria where there is a very high burden of disease and available interventions cannot offer high levels of protection (table 1). In the 12 months following completion of the primary vaccination course in children aged 5-17 months at the time of dose 1, the incidence of clinical malaria was reduced by 51% and the incidence of severe malaria was reduced by 44.5%. Protection appeared to wane over time: by 18 months after the primary vaccination course, efficacy was 46% against clinical malaria and 38% against severe malaria. Efficacy against clinical malaria of 3 doses alone declined in the successive 6-months periods from 68% in the first 6-month interval to 39% and 28% in the successive 6-month intervals. A fourth dose, given 18 months after dose 3, increased efficacy to 39% against clinical and 31.5% against severe malaria over the whole of the study (a median of 48 months follow-up) whereas, among the children randomised to receive only three doses of RTS,S/AS01, efficacy against clinical malaria fell to 26% and against severe malaria to -2.2%. The 4th dose of RTS,S/AS01 therefore appears to be needed to maintain efficacy against severe malaria.

Over the whole (median 4-year) follow-up of children in the phase 3 trial, vaccine efficacy was also confirmed against malaria hospitalization (37%, ATP, 95%CI 27-48.5), all-cause hospitalization (15%, ATP, 95%CI 6-25) and severe anaemia (62%, ATP, 95%CI 26.5-81). These benefits were demonstrated in the presence of high ITN coverage and where the identification and treatment of clinical and severe malaria episodes, as well as other medical care, was optimized. The enhanced access to good quality curative services likely limited disease progression and precluded the measurement of vaccine impact on mortality. However, modelling suggests a substantial potential survival impact of RTS,S/AS01 outside trial settings (1 life saved per 200 fully vaccinated children in moderate to high transmission settings)[7].

Vaccine efficacy was substantially lower in those whose first vaccine dose was at 6-12 weeks of age than in the 5-17 month olds and thus further evaluation in the younger age group of infants is not recommended by WHO.

Table 1: Summary of RTS,S/AS01 vaccine efficacy (95% Confidence Interval) in the 5-17 month age category for all episodes of clinical malaria and severe malaria from Month 2.5 to selected time points (primary case definitions, ATP population). Source: WHO JTEG

Clinical Malaria	RTS,S Group				Control Group				VE
	N	n	T	n/T	N	n	T	n/T	(95%CI)
M2.5-M14	4553	2558	4035.9	0.63	2327	2489	2024.6	1.23	51.3% (47.5, 54.9)
M2.5-M20	4557	4257	6186.0	0.69	2328	3639	3100.4	1.17	45.7% (41.7, 49.5)
M2.5-SE 3-dose schedule	2306	6597	7335.8	0.9	2336	8352	7352.4	1.14	26.2% (20.8, 31.2)
M2.5-SE 4-dose schedule	2276	5691	7247.4	0.79					39.0% (34.3, 43.3)
Severe Malaria	**RTS,S Group**				**Control Group**				**VE**
	N	**n**	**T**	**n/T**	**N**	**n**	**T**	**n/T**	**(95%CI)**
M2.5-M14	4582	87	4358.3	0.020	2336	80	2219.3	0.036	44.5% (23.8, 59.6)
M2.5-M20	4582	129	6379.0	0.020	2336	105	3243.5	0.032	37.7% (18.0, 52.6)
M2.5-SE 3-dose schedule	2306	159	7600.5	0.021	2336	157	7664.8	0.020	-2.2% (-31.3, 20.4)
M2.5-SE 4-dose schedule	2276	101	7459.6	0.014					31.5% (9.3, 48.3)

N = number of subjects included in each group
n = number of episodes included in each group
T = person years at risk
n/T = Incidence = person year rate in each group
SE = Study end (variable follow up period for each participant with a median of 48 months)
VE (%) = Vaccine efficacy (Negative binomial random-effects model)

7.2 Safety of RTS,S/AS01

The safety of RTS,S/AS01 in the phase 3 trial was evaluated by comparing the rates of events, detected through both active and passive surveillance, in children receiving 4 doses of RTS,S/AS01 and the rates in children receiving 3 doses of RTS,S/AS01 followed by meningococcal C conjugate vaccine at the time of the 4th dose, with the rates in children in the control group who received three doses of rabies vaccine followed by meningococcal C conjugate vaccine at the time of dose 4.

No fatal adverse events were causally related to RTS,S/AS01 vaccination. An increase in the risk of self-limiting febrile seizures, as seen previously with several other vaccines, was not associated with any long-lasting sequelae. Among children in the older age group, an increase in the number of cases of meningitis and of cerebral malaria was found in the group receiving the malaria vaccine compared to the control group. The significance of these findings in relation to RTS,S/AS01 vaccination is unclear. An excess of meningitis and cerebral malaria was not seen in infants first vaccinated aged 6–12 weeks.[6]

7.2.1 SAEs in the phase 3 trial

Up to 20 months after dose 1, at least one SAE was reported in 18.6% (95% CI 17.6, 19.6) of RTS,S/AS01 recipients compared with 22.7% (95% CI: 21.1, 24.3) of the control children. SAEs related to vaccination were reported in 0.2% of RTS,S/AS01 and 0.0% of the rabies vaccine recipients. Over the entire study period (i.e. including follow up after dose 4 of RTS,S/AS01) at least one SAE was documented in 24.2% of the children vaccinated with four doses of RTS,S/AS01,

25.3% of the children vaccinated with three doses of RTS,S/AS01, and 28.4% of the children in the control arm. The equivalent figures for non-malaria SAEs (22.6%, 23.7% and 26.4%, respectively) followed a similar pattern.

An SAE related to vaccination was reported in 8 children receiving a 4th dose of RTS,S/AS01 (1 injection site cellulitis, 1 convulsion and 6 febrile convulsions); in 4 children vaccinated with three doses of RTS,S/AS01 and one dose of meningococcal C conjugate vaccine (1 injection site reaction, 1 epilepsy, 1 febrile convulsion and 1 pyrexia); and in one child in the control group (febrile convulsion). Six cases of potential immune-mediated disease (pIMD) were reported: 3 cases among children vaccinated with four doses of RTS,S/AS01, 1 case among children receiving three doses of RTS,S/AS01, and 2 cases among children in the control group.

7.2.2 Febrile convulsions

The rate of generalised convulsive seizures with fever within 7 days of primary vaccination in RTS,S/AS01 recipients was 1.04 cases/1000 doses compared with 0.57 cases/1000 doses of control vaccine. The incidence of febrile convulsions within 7 days of administration of the fourth dose of RTS,S/AS01 was 2.5 cases/1000 doses, compared with 1.2 case/1000 doses in children vaccinated with 3 doses of RTS,S/AS01 but receiving meningococcal C conjugate vaccine at the time of the 4th dose, and 0.4 cases/1000 doses in the control group. Febrile convulsions within 7 days of vaccination are therefore considered an identified risk in RTS,S/AS01 recipients, for which the cause is unknown.

7.2.3 Meningitis

More meningitis cases were documented in children aged 5-17 months who received RTS,S/AS01 than among children in the control group. Table 2 summarises meningitis cases during the 20 month period following Dose 1.

Table 2: Meningitis cases in children aged 5-17 months at dose 1 in the phase 3 trial

Analysis available	**Follow up (post dose 3)**	**Number of cases in RTS,S/AS01 *group*** *(Number of RTS,S/AS01 study participants)*	**Number of cases in control *group*** (*Number of control study participants*)	**RR**	**95% CI**
June 2014	18 months	16 *(5949)*	1 *(2974)*	8.0	1.1-60.3

The 16 cases comprised a mixture of aetiologies (4 meningococcal, 1 viral, 1 pneumococcal, 1 *Haemophilus influenza,* 9 unknown).

Five meningitis cases occurred in children between study month 20 and study end, including 2 cases in a child who received a fourth dose of RTS,S/AS01, compared with 3 cases in the same time period among children randomised to receive three doses of RTS,S/AS01. There were no further cases in the control group.

Hence 22 meningitis cases occurred in the 5-17 month age category throughout the complete study period (median 48 months follow-up from dose 1): 11 in children who received 4 doses of RTS,S/AS01, 10 in children who received 3 doses of RTS,S/AS01, and 1 in children in the control arm. Almost two thirds of cases were reported from just two of the 11 phase 3 trial sites (9 cases in Lilongwe, Malawi, and 5 in Kombewa, Kenya). There was no clear temporal clustering of cases,

with 12 cases (11/5949 in RTS,S/AS01 recipients and 1/2174 in children in the control arm) occurring in the 14 months following dose 1.

Among infants aged 6-12 weeks when first receiving RTS,S/AS01, 9 meningitis cases occurred in the RTS,S/AS01 groups and 3 in the control group in the 20 month period following Dose 1 (RR = 1.5 [95% CI: 0.4, 5.5]). The number of meningitis cases per group was similar by the end of the study (5 in children receiving 4 doses of RTS,S/AS01, 7 in children receiving 3 doses, and 6 in the control group).

Despite the lack of a consistent aetiology, the absence of a temporal relationship with vaccination, the suggestion of clustering of cases in some sites and the lack of a plausible mechanism by which RTS,S/AS01 could lead to meningitis, the documented imbalance of meningitis cases warrants follow-up in the context of a pilot implementation study, as well as the Phase 4 study. Together these studies will provide evidence to help establish or exclude a causal association between meningitis and RTS,S/AS01 and further characterise and evaluate this safety signal.

7.2.4 Cerebral malaria

Exploratory analyses of the phase 3 trial data compared the distribution of severe malaria, as identified by a computer algorithm, in the study groups. An imbalance was observed amongst cerebral malaria cases (parasitaemia >5000 and Blantyre Coma Score <3) in the 5-17 month category: in the 20 months after Dose 1, 16 cerebral malaria cases occurred in the RTS,S/AS01 group (5948 children), while 5 such cases occurred in the control group (2974 children). In addition, cerebral malaria and anaemia (parasitaemia >5000, Blantyre Coma Score <3 and haemoglobin <5 g/dL) was observed for 6 subjects in the RTS,S/AS01 group and 1 subject in the control vaccine group.

Nine cerebral malaria cases (with or without anaemia) occurred among the 2719 children who received a 4th dose of RTS,S/AS01, 12 cases among the 2681 children vaccinated with RTS,S/AS01 followed by meningococcal C vaccine, and 4 among the 2702 children in the control arm.

There were 12 deaths among the cerebral malaria cases: 10 in the RTS,S/AS01 groups and 2 in the control group.

The potential association between cerebral malaria and RTS,S/AS01 warrants further follow-up and evaluation in the context of the pilot implementation.

7.2.5 Mortality and gender

In girls, but not in boys, there was a higher mortality rate among those vaccinated with RTS,S/AS01 (with or without booster) than among controls, in both age categories . The all-cause mortality ratio, comparing vaccinated to controls, was 1.91 (95% CI: 1.30, 2.79) in girls and 0.84 (95% CI: 0.61, 1.17) in boys. However, this finding was *post-hoc*, and hence difficult to interpret, mortality rates were low in the trial, and particularly so in girls randomized to receive the comparator vaccine, and the absolute differences in the numbers of deaths by gender were small (35 of the 1467 girls and 26 of the 1509 boys randomised to receive 4 doses of RTS,S/AS01; 32 of the 1500 girls and 19 of the 1472 boys in the 3 dose group; and 17 of the 1503 girls and 29 of the 1471 boys in the control group). Nevertheless, further follow-up of gender-specific mortality in children receiving RTS,S/AS01 is warranted.

7.2.6 Summary of Safety

The overall incidence of SAEs – both all SAEs and non-malaria SAEs - in the phase 3 study was lower in children receiving RTS,S/AS01 than in children in the comparison arm. Febrile convulsions were an identified risk in RTS,S/AS01 recipients in the 7 days following vaccination, but the incidence rates equilibrated between the groups by 30 days post vaccination. Meningitis was identified as a potential risk. The imbalances observed for cerebral malaria and gender-specific mortality following post-hoc analyses of the phase 3 study data are also considered safety signals requiring further evaluation.

7.3 International regulatory and policy review

The vaccine received a positive scientific opinion from the EMA, reflecting the quality of the vaccine and favourable risk/benefit balance from a regulatory perspective[8]. In October 2015, the WHO advisory committees SAGE and MPAC recommended pilot implementation studies[9] to assess, in the context of routine immunization programmes:

- Programmatic feasibility of delivering RTS,S/AS01 with three to four new immunization contacts, including the fourth dose in the second year of life
- Vaccine impact on all-cause mortality, including gender-specific mortality
- Vaccine safety with specific attention to meningitis and cerebral malaria.

The Malaria Vaccine Implementation Programme [10] will enable the first-time use of the vaccine in real-life settings and thereby bridge the knowledge gaps currently inhibiting wider scale use of a tool with considerable potential public health impact. Data from the pilots will inform policy-making at global and national levels, allowing decisions to be made about larger-scale adoption, providing learnings on where and how to use the vaccine to optimize its impact and cost effectiveness in complementing other malaria interventions. The experience gained during the pilot implementations may also benefit future malaria vaccines facing similar questions (e.g. feasibility of a new dosing schedule, use alongside other malaria interventions).

7.4 Alignment of the Malaria Vaccine Pilot Evaluation and the Phase 4 evaluation

The Malaria Vaccine Implementation Programme has two main components: (1) vaccine implementation by the MoH, (2) evaluation of vaccine implementation including the WHO-led RTS,S/AS01 Malaria Vaccine Pilot Evaluation and the GSK-led Baseline and Phase 4 studies.

As part of the Risk Management Plan agreed between GSK, the vaccine manufacturer, and the EMA, a set of Baseline and Phase 4 studies will evaluate vaccine safety in children receiving RTS,S/AS01 and estimate the vaccine's impact and effectiveness. Cohort event monitoring will involve active surveillance (home visits and continuous monitoring of outpatient visits and hospitalisations) of approximately 65,000 children across the three countries of the RTS,S/AS01 Malaria Vaccine Implementation Programme (20,000 unvaccinated prior to the Malaria Vaccine Implementation Programme, 22,500 vaccinated during the Pilot Implementation of the malaria vaccine, and 22,500 unvaccinated from the control areas of the Malaria Vaccine Implementation Programme). The Phase 4 study surveillance will be based in one or two hospitals per country in RTS,S/AS01 implementing areas (vaccinated clusters), with an equal number of hospitals from comparison areas (unvaccinated clusters) generating comparable data.

A high degree of coordination between the GSK-led studies and the WHO MVPE will ensure their complementarity. The two sets of evaluations will take place in different areas. However, resources developed for the GSK-led studies will assist the MVPE (see section 10.6, 'Capacity building') and enhance the comparability of the safety data generated by each evaluation programme. As far as possible, the approach to the collection and processing of samples, and data analysis, will be harmonised through the use of the same reference laboratory (section 10.5.2) and case definitions (10.4). At the global level, safety reports from the GSK and WHO-led studies will be reviewed on a 6--monthly basis for ongoing safety monitoring by the Data Safety Monitoring Board of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation.

7.5 Selection of countries for the pilot programme

WHO launched a public call for expressions of interest in the MVIP from the MOHs in sub-Saharan Africa in December 2015. Ten countries, all classified as low or lower-middle income countries per World Bank definition, submitted written expressions. A country selection process from January to April 2016 included the following criteria:

- Confirmation of engagement and interest from MOHs including discussions about the purpose of the pilots and cluster randomized vaccine introduction.
- Functional immunization and malaria control programmes as evidenced by DTP3 and MCV1 coverage, and LLIN usage (using the most recent survey-based estimates).
- High all-cause mortality in the planned regions of the pilots, with high malaria transmission indicating that a large proportion of childhood deaths are due to malaria in such settings.
- Existence of at least one highly capable sentinel hospital per region to facilitate the collection of high quality data on meningitis and cerebral malaria.
- National pharmacovigilance readiness.

In addition, prior participation in the RTS,S/AS01 Phase 3 trial was considered favourably.

Subnational settings in Kenya, Ghana and Malawi were identified based on these criteria, each with a track record of strengthening malaria and immunization programmes, as well as experience introducing new vaccines, and links with immunization and malaria research infrastructures for the evaluation components.

7.6 Overview of RTS,S/AS01 delivery and evaluation

7.6.1 Approach to delivery of RTS,S/AS01

This protocol describes the evaluation of the routine delivery of RTS,S/AS01 by Ministries of Health using an expanded schedule of their routine EPI contacts, building on the national immunization programmes which routinely deliver vaccines to young children living in SSA countries. Delivery of RTS,S/AS01 will be the responsibility of the MOH, guided by good participatory practices and will include the development, testing and implementation of training materials and strategies for relevant staff; adaptation of relevant delivery and surveillance systems (e.g. involving child vaccination health cards, recording sheets, supply forms, ledgers and registers); and updates of

cold chain assessments for pilot implementation areas. A draft Practical Operating Guide for the Malaria Vaccine Implementation Programme is included in Annex 4.

Given the importance of receiving all 4 doses to maximise benefit from the vaccine, the MoH will be encouraged to develop its routine services to identify and track children to maximise the coverage of the 4-dose regimen. Should routine data show inadequate coverage of RTS,S/AS01 there is provision within the programme budget to explore supplementary activities to boost coverage. The emphasis will be on approaches which are potentially sustainable by routine immunisation services.

If a decision is taken to terminate the RTS,S/AS01 vaccination programme in a country, specific efforts will be made to maximise the completeness of the vaccine regimen in children who have received one or more doses, assuming the reason for termination is not a vaccine safety concern.

As part of the implementation process, pharmacovigilance systems will be evaluated and assistance provided, as necessary, to strengthen routine vaccine pharmacovigilance. The routine vaccine safety surveillance systems will be supported to generate information to support decision-making about vaccine use and to maintain the public's trust by providing data to counter fear and misinformation. The activities will be guided by the Global Vaccine Action Plan [11] and progress with system strengthening monitored using the standard indicator – the AEFI reporting rate per 100,000 surviving infants per year – which is expected to be at least 10 cases per 100,000 surviving infants per year. Activities will include encouragement of AEFI reporting; strengthening of AEFI investigation, data analysis and causality assessment; and managing the communications response to vaccine safety events. As such, the RTS,S/AS01 MVIP is expected to help increase health workers' awareness of safety issues, improve the sensitivity of adverse event case detection, allow identification and correction of any problems and enhance the interpretation of pre- and post-vaccine introduction safety data.

7.6.2 Evaluation Design

The evaluation will be conducted in the context of the early, limited deployment of the RTS,S/AS01 vaccine by routine health systems. Vaccine implementation is expected to continue beyond the evaluation period and with the progressive roll out beyond the pilot areas if there are no significant safety signals or concerns about the feasibility of deploying the vaccine. It will take until about month 30 of the programme for children receiving dose 1 in the first year to receive their fourth dose. Routine vaccinations with RTS,S/AS01 are therefore expected to continue at least until month 30 of the programme.

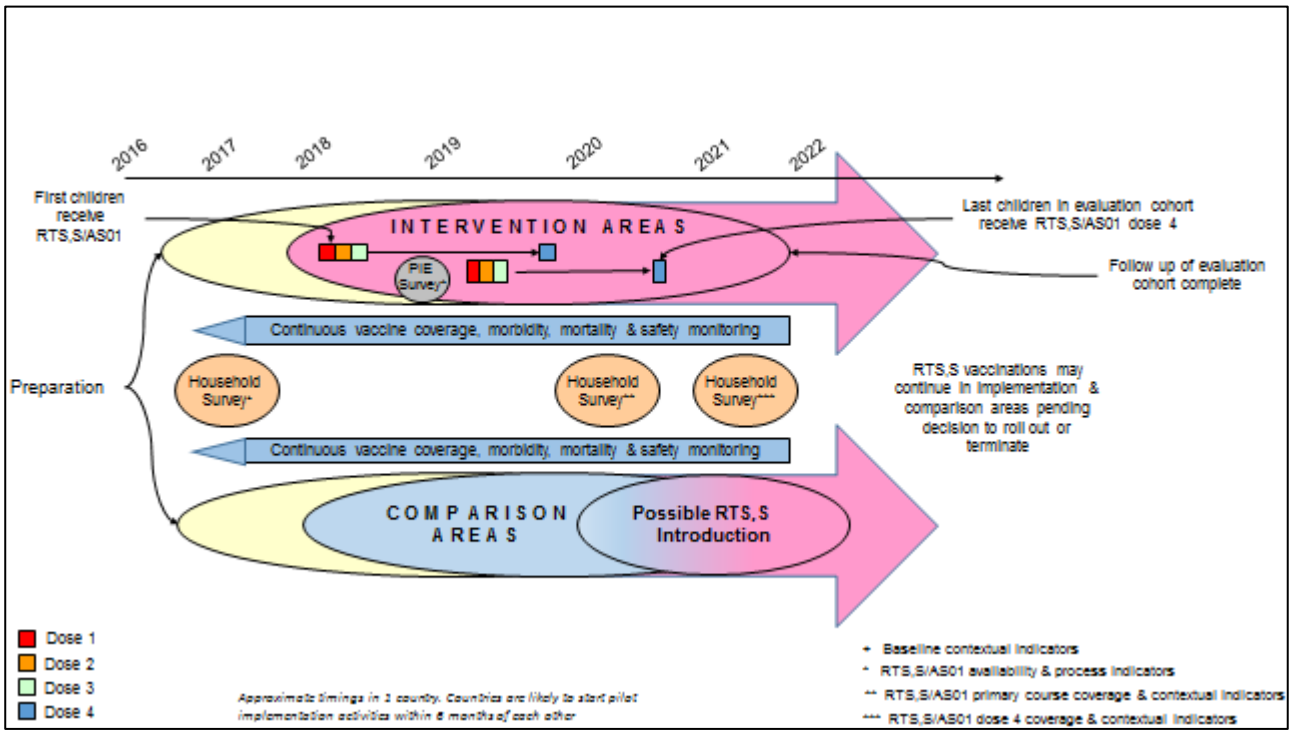
The pilot implementation will use a cluster-randomized design, with some areas (Districts, Sub-counties, Clusters, referred to herein as "clusters") introducing RTS,S/AS01 at the beginning of the programme and other clusters, without RTS,S/AS01, acting as comparison areas. Randomization is a fair way to choose implementation areas during the initial period of implementation in which delivery of the new vaccine, which involves visits outside the existing EPI schedule, is being piloted. The division of areas into implementation or comparison areas will be randomized, by the respective country's EPI team, to enable the MVPE pilot implementation programme to generate the strongest possible evidence on the impact and safety of the vaccine by limiting potential biases and providing a contemporaneous comparison group that allows for strong statistical inferences to be made. The approach to sensitisation of communities and in-country stakeholders at all levels will be described in country-specific protocols. In general, communities will be informed about the randomised introduction of the RTS,S vaccine through the EPI programme and

the corresponding social mobilization plan. This will include information on the potential risks and benefits of the vaccine, including the moderate level of protection it provides so that the use of other preventive measures is sustained by the communities. Through the same means, communities will learn whether they are living in an area that has been randomised to receive the vaccine, or not, at the beginning of the programme, and provided with updates as the programme progresses (see also section 14).

Areas will be allocated to intervention or comparator, taking into account the capacity of hospitals and health facilities within the areas (three levels, described in section 10.2.2), malaria transmission (as reflected by the *P falciparum* prevalence in children aged 2-10 years modelled to the cluster level[12], divided into tertiles), geographic location (such as county/region) and population size (divided in tertiles), using a constrained randomization procedure to ensure that the vaccination and comparison areas are balanced for these characteristics, which could be associated with the incidence of the outcome measures[13].

Figure 1 illustrates the overall design with details presented in the following sections.

Figure 1: Overview of the WHO-led RTS,S/AS01 Malaria Vaccine Pilot Evaluation



7.6.3 Study dates

- Surveillance systems to be developed/consolidated during 2018 - early 2019 in all countries.
- Baseline household surveys planned to be conducted by March 2019.
- Vaccinations planned to start February-May 2019 (e.g. Country 1, Q1 2019; Country 2, Q2 2019; Country 3, Q2 2019).

- Dose 1 planned to be complete February-May 2020, for children contributing to the evaluation of feasibility, depending on timing of start of vaccinations and period required to vaccinate target number of children.

- Dose 3 planned to be complete by June – September 2020.

- Dose 4 planned to be complete by August 2021 – November 2021, dependent also on timeliness of doses 1 – 3 and dose 4.

- Surveillance planned to be continued August 2022 – November 2022.

Please also refer to figure 2 in section 7.6.5. Detailed timelines, including dependencies between activities, will be elaborated in country-specific protocols.

7.6.4 Vaccination Schedule

RTS,S/AS01 will be given as a four dose schedule with the first dose administered as soon after 5 months of age as possible, followed by doses two and three at approximately one month intervals, and a fourth dose 15-18 months after dose three. The evaluation will continue for sufficiently long to ensure that children who receive RTS,S during the first year of the programme will have received the fourth dose at least 12 months before the pilot evaluations are completed. Children will be eligible for vaccination according to the manufacturer's instructions, as approved by the national regulator.

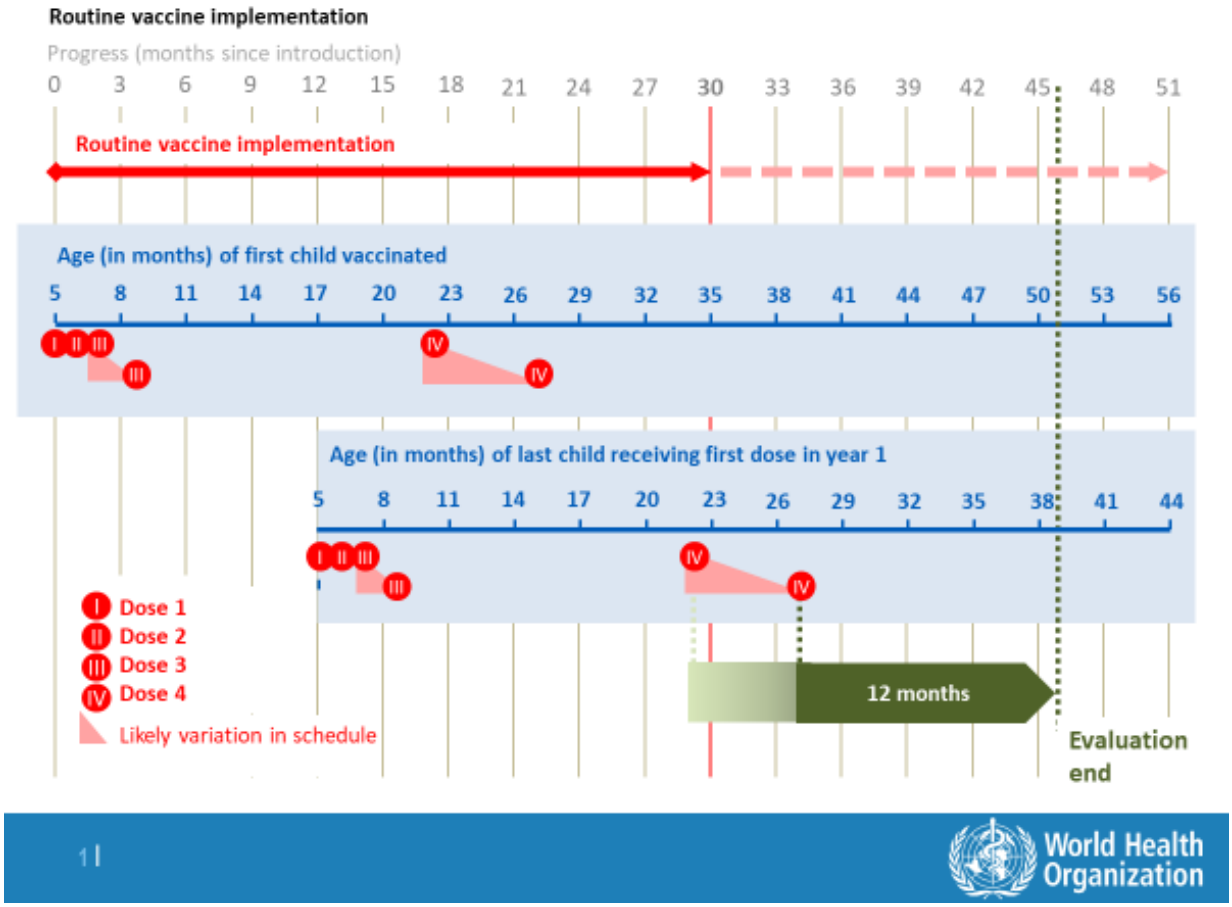
RTS,S/AS01 can be co-administered, as demonstrated in Phase 2 and 3 trials, with other vaccines in the national immunization programme (hepatitis B, diphtheria, tetanus, pertussis, polio, measles, yellow fever).[14,15] Depending on the delivery schedule adopted by the national EPI programmes, it is possible that the first dose of RTS,S/AS01 will be administered with the 3rd dose of DTP and dose 2 or, more likely, dose 3, delivered at 9 months of age, could be co-administered alongside existing vaccines, e.g. measles and yellow fever vaccinations. The specific schedules, and the potential for introduction of other new vaccines (e.g. Men A in Ghana in late 2016) into the routine schedule, will be described in country-specific protocols.

Age-eligible children will be identified by health workers at health facilities and outreach clinics, in the course of routine child health and vaccination programmes in the pilot areas, and invited for doses of RTS,S/AS01, as they are for other vaccinations.

7.6.5 Evaluation of RTS,S/AS01

Identical monitoring systems will be established in both implementation and comparison areas to record impact and safety outcomes. Figure 2 presents an illustrative overview of study timings which will be updated, if necessary, in country-specific protocols. Surveillance will be maintained in children aged 1-59 months throughout the pilot. This will allow assessment of the effects of vaccine introduction in the age groups of children eligible to receive RTS,S/AS01, while the data for children too young or old to be eligible for the vaccine, provide information about background rates of outcomes in the same cluster (see the statistical analysis plan (SAP).

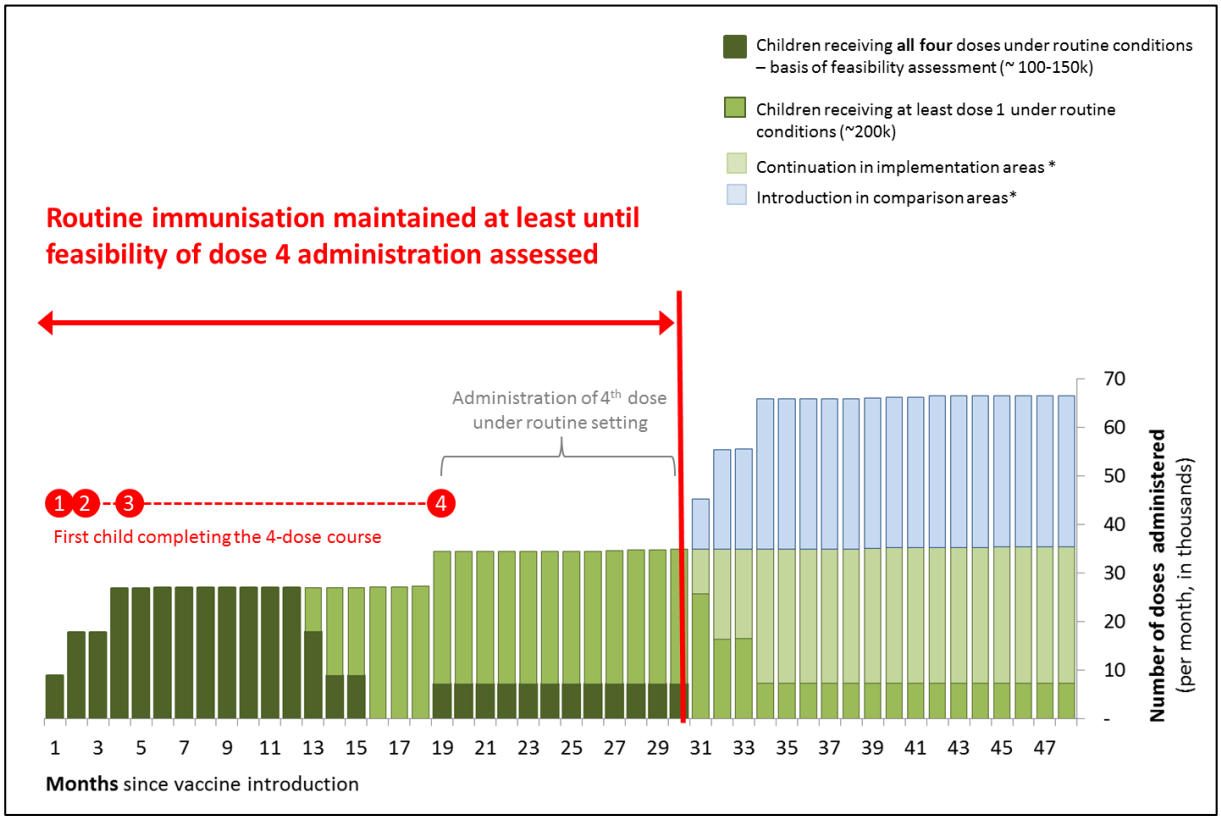
Figure 2: Illustrative overview of study timings.



This protocol describes the evaluation of a pilot implementation programme which has been designed on the basis of up to 60 areas per country, evenly split between implementation and comparison areas, with each cluster contributing approximately 4,000 study children per year. Country-specific protocols will present the number (expected to range from 46-60) and size of areas in the respective country. All areas will contribute to the evaluation of the impact on mortality. Mortality surveillance will be undertaken at the village level by Village Reporters (VR) documenting deaths in the area in which they live. A sub-set of clusters, with access to care in up to 8 sentinel hospitals per country (a maximum of 24 across the programme), equally split between implementation and comparison areas, will provide hospital-based surveillance data for safety and cause-specific impact assessments. Feasibility will be evaluated by generating vaccine coverage and other relevant data in a representative sample of households in each cluster, by using the routine administrative data from vaccinating facilities across the whole pilot programme, and, where feasible, by using data from clinic-based vaccination registries. Pooled analyses of safety and impact data will be conducted to the extent possible.

Areas will be defined according to the size of the birth cohort, aiming for an annual birth cohort of 4,000 children. Feasibility will be evaluated in the context of routine ongoing RTS,S/AS01 vaccination. Figure 3 illustrates that a minimum of 30 months of routine vaccination will be required to provide sufficient observation time to assess the feasibility of providing the fourth dose to children receiving their first dose in the first year of the programme (dark green in figure 3). All children receiving any doses of RTS,S/AS01 in the 30 month window (light green in figure 3) will contribute to the evaluation of safety and impact.

Figure 3: Overview of children contributing to feasibility, safety and impact evaluations



* To be decided by authorities of pilot countries

7.6.6 MVIP and decision-making for vaccine roll out

The MVIP has been developed to support and evaluate the first phase of the RTS,S/AS01 malaria vaccine implementation. The positive scientific opinion of the European Medicine's Agency confirms the vaccine is considered safe for public health use from a stringent regulatory perspective. The MVIP is designed to assess the feasibility of introducing the four-dose vaccine, consolidate the vaccine's safety profile, and measure its impact. In so-doing the MVIP will set the scene for larger-scale implementation.

7.6.6.1 Informing a decision to roll out the vaccine more widely

The main safety signals identified in the Phase 3 trial, for which a causal relationship with the vaccine has not been established, were an 8-fold increase in the risk of meningitis, an approximate doubling in the risk of cerebral malaria and, in the context of very low overall mortality among trial participants, an imbalance by gender among those who died during the course of the trial, with more deaths among girls than boys vaccinated with RTS,S/AS01 (section 7.2). It is possible that new safety signals will be identified in the MVIP. Safety data will be evaluated by the safety monitoring systems described in the sections 10.15 and 13.2.

Specific criteria and thresholds for decision-making have not been established. During the early stages of the MVIP a framework for policy decision-making for RTS,S will be developed. This will describe how data collected through the programme will be used to inform the policy recommendations of WHO's Malaria Policy Advisory Committee (MPAC) and its Strategic Advisory Group of Experts (SAGE) on immunization.

The Joint Technical Expert Group (JTEG) was convened with representation from SAGE, MPAC and additional independent experts, to monitor the Phase 3 trial of RTS,S/AS01. JTEG recommended that WHO should monitor emerging findings from pilot implementation and, based on those findings, "it would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose"1. The JTEG recommendation did not state how data should be used, for example defining what should be considered "high coverage of the fourth dose" or whether demonstration of impact on mortality would be required for a policy recommendation.

The framework for policy decision-making is expected to enable SAGE and MPAC members to discuss and refine ideas on the relative contributions of the collected data (feasibility, safety, impact) to a future policy recommendation. The framework will provide clarity on the expected use of the data for the SAGE and MPAC recommendations, expected in 2020 and/or 2022, a period in which changes in SAGE and MPAC membership are likely. It is expected that Ministries of Health, funders, potential funders, and manufacturers will refer to the framework for planning purposes, reducing the likelihood of gaps in funding or vaccine availability should the vaccine be recommended for broader use.

It is not anticipated that the framework would articulate binding "go" or "no go" criteria. Rather two sets of data-driven criteria would be agreed: (i) a set of high-bar thresholds above which it is very likely the vaccine would be recommended for broader use (e.g. very high coverage of doses 1 – 4, safety concerns resolved), and (ii) a set of low-bar thresholds beneath which it is very unlikely the vaccine would be recommended (e.g. very low coverage of doses 1-4, confirmation of an 8-fold increase in meningitis in vaccine recipients). Should neither set of thresholds be met, a more nuanced discussion would be required to consider the public health utility of the vaccine (i.e. consideration of the benefit/risk profile).

The MVIP will use mathematical modelling to assist in identifying a rational basis for proposing vaccine coverage thresholds that predict significant impact on severe malaria or mortality.

7.6.6.2 Garnering commitments for vaccine supply

WHO, PATH and the vaccine manufacturer, GSK, have signed a legal agreement which includes a commitment by GSK to supply, without charge, sufficient quantities of the RTS,S vaccine to allow the sound implementation of the MVIP, up to a maximum of 10 million doses. These are expected to enable all three pilot countries to continue routine delivery of RTS,S in implementation areas and to implement the vaccine in comparator areas, if appropriate, until the end of 2022.

The collaboration agreement also includes access provisions to ensure the availability and affordability of the malaria vaccine beyond the pilots, should success of the programme be confirmed and WHO recommend its broader use. The agreement provides some assurances about the cost of the vaccine but it is recognised that the vaccine may not be readily affordable to many low income countries. To ameliorate this risk and to facilitate longer-term access, the MVIP will bring together partners from funding agencies which have an interest in supporting large-scale introduction and use of the vaccine beyond the pilots, should this be recommended by WHO. The

intention is to ensure continuity of supply and availability of the vaccine through the use of public funds.

The necessary national and international political commitment to ensure appropriate action based on the findings of the pilot implementation will be cultivated as the MVIP proceeds.

8 Research questions and objectives

8.1 Key questions on impact, safety and feasibility

(See SAP)

The following key questions will be evaluated in groups of children, eligible to receive RTS,S/AS01 vaccine, residing in the RTS,S/AS01 implementation and comparison areas.

Impact:

- Is there any reduction in all-cause mortality following the introduction of the \ routine delivery of RTS,S/AS01??
- By how much does the routine delivery of RTS,S/AS01 vaccine reduce the incidence of hospital admission with severe malaria?

Safety:

- Does the introduction of routine RTS,S/AS01 vaccination result in an increased rate of meningitis and/or cerebral malaria in communities where the vaccine is introduced?
- Does the introduction of RTS,S/AS01 have a different effect on all-cause mortality for boys and girls? Does RTS,S/AS01 increase mortality in girls?
- What is the frequency and profile of RTS,S/AS01 reported AEFI?

Feasibility:

- What coverage is achieved with RTS,S/AS01 (including the fourth dose in the second or third year of life) and how timely are the doses?
- What is the coverage and timeliness of recommended EPI vaccines (including MCV2) and does it change with RTS,S/AS01 introduction?
- What is the coverage and utilization of other recommended malaria prevention and control measures, including ITN and IRS, and does it change with RTS,S/AS01 introduction?
- Do treatment seeking behaviours for febrile children, use of malaria prevention measures, and EPI vaccination coverage change with the introduction of RTS,S/AS01?
- What strategies help to achieve optimal coverage of the fourth dose?
- Does the introduction of additional contacts between 5-9 months of age influence vaccine programme drop-out rates and the number of fully vaccinated children?
- Does the introduction of RTS,S/AS01 alter the coverage of other key childhood interventions, including Vitamin A supplementation?

The overall impact of RTS,S/AS01 will be evaluated in the MVPE. As with other vaccines, any risks identified need to be weighed against the benefits to understand the overall impact of the

vaccine. The overall assessment will consider both feasibility and impact outcomes. The evaluation of risks and benefits will be made by the Data Safety Monitoring Board and presented to WHO's Global Advisory Committee on Vaccine Safety (GACVS), SAGE and MPAC to develop the WHO policy recommendation on the large-scale deployment of the RTS,S/AS01 vaccine.

8.2 Objectives related to impact and community-based surveillance

[See also statistical analysis plan (SAP)]

8.2.1 Primary impact objectives

The primary objectives of the impact evaluation are:

- To estimate the effect of the routine delivery of RTS,S/AS01 on all-cause mortality (excluding accidents) [2]
- To estimate the effect of routine delivery of RTS,S/AS01 on the incidence of hospital admission with severe malaria (severe malaria anaemia or cerebral malaria)

in each country and overall.

8.2.2 Secondary impact objectives

The secondary objectives of the impact evaluation are to estimate the effect of routine delivery of RTS,S/AS01 on incidence hospital admission with cerebral malaria

- the incidence of hospital admission with severe malaria anaemia (patients admitted, who had severe malaria anaemia)
  - incidence of all-cause hospital admission
  - incidence of non-malaria hospital admission
  - incidence of cause-specific hospital admission
  - incidence of the requirement for or provision of blood transfusions
  - cause-specific mortality (from verbal autopsy or hospital diagnosis)
  - malaria-specific mortality in hospital
  - all-cause mortality, excluding deaths due to trauma or accidents
  - malaria-specific mortality in hospital in boys and in girls

in children eligible to receive the vaccine, in each country and overall.

8.3 Objectives related to safety and surveillance in sentinel hospitals

8.3.1 Primary safety objectives

- to estimate the effect of RTS,S introduction on the incidence of hospital admission with probable or confirmed meningitis (data pooled across the three countries)

[2] Please refer to section 7.6.5 for an explanation of the age ranges targeted for different endpoints

- to estimate the effect on the incidence of hospital admission with cerebral malaria (data pooled across the three countries)
- to estimate the effect of RTS,S introduction on all-cause mortality in boys and girls and to determine whether there is any evidence that RTS,S is increases mortality in girls, overall and in each country

8.3.2 Secondary safety objectives

Exploratory analyses will:

- Explore the association between RTS,S/AS01 and AESI, as agreed with each country's immunization program and regulatory authority, and with the Data Safety Monitoring Board (Annex 5).

8.4 Analysis populations

(See SAP)

- For each death and each hospital patient, cluster of membership will be determined from the location of normal residence. Within each implementation and comparator area, the following groups will be defined: children who are age-eligible for the vaccine and children who are not age-eligible for the vaccine, based on date of birth and age at the time of the RTS,S/AS01 introduction.
- All primary outcome measures will also be analysed, in an exploratory secondary analysis, in children who received DTP3.

8.5 Objectives related to feasibility

The primary quantitative outcome assessment of feasibility will be based on RTS,S/AS01 coverage estimated in repeated household surveys. Coverage of the first 3 doses and of the fourth dose will be estimated through household surveys in the middle and towards the end of the programme, respectively. These surveys, and a pre-implementation baseline household survey, will also generate estimates of the coverage of routine EPI vaccines, recommended malaria control measures, vitamin A and antihelminth treatment coverage, may include nutritional status by MUAC, and will document patterns of health-seeking behaviour for febrile children.

8.5.1 Primary feasibility objectives

For the second household survey:

- To estimate the proportion of children aged 12-23 months, who had received three doses of RTS,S/AS01 by 12 months of age (in each country).

For the third household survey:

- To estimate the proportion of children aged 27-38 months, who had received their fourth dose of RTS,S/AS01 by 27 months of age (in each country).

8.5.2 Secondary feasibility objectives

The first, second and third household surveys are designed:

- To estimate the coverage of recommended EPI vaccines in children from areas implementing RTS,S/AS01 and in children from areas not implementing RTS,S/AS01.

- To estimate the proportions of children receiving each individual dose (the first, second, third, fourth, as appropriate) for each recommended vaccine

- To estimate the coverage and utilization of ITN/LLIN, IRS and any other recommended malaria prevention and control measures, in children from areas implementing RTS,S/AS01 and in children from areas not implementing RTS,S/AS01.

- To document patterns of health-seeking behaviour for febrile children among children from areas implementing RTS,S/AS01 and in children from areas not implementing RTS,S/AS01.

- To assess if the introduction of additional contacts between 5-9 months of age alters drop-out rates for routine vaccinations and changes the number of fully vaccinated children.

- To assess whether the introduction of RTS,S/AS01 is associated with a change in the coverage of other key childhood interventions, including anti-helminth administration (deworming) and Vitamin A supplementation.

It will be important to investigate, as part of the second survey or preferably as a separate study before the second survey, the agreement between malaria vaccine status by caregiver recall, from the home-based record, and from immunization registers, in order to understand the validity of RTS,S/AS01 status from different sources.

Exploratory analyses will assess changes in malnutrition as measured by MUAC score (but not necessarily in all countries) following the introduction of RTS,S/AS01.

9 Research Methods for Impact Evaluation

9.1 Study design

The EPI programme will randomize areas (districts, sub-counties, clusters) to either implement or not implement the vaccine at the beginning of the pilot programme. The areas not initially introducing the vaccine will act as comparison areas. This randomized approach will enable a rigorous assessment of safety and impact in the pilot area. The evaluation design is described in more detail in section 7.6.5. The assessment of impact will draw on data from all clusters. The evaluation has been designed on the basis of each cluster contributing approximately 4,000 children to the evaluation per year, generating approximately 240,000 children per country per year, equally split between implementation and comparison areas. The geographic area covered will vary according to population density but is expected to include a total population (all ages) approaching 5 million people in each country.

9.2 Setting

9.2.1 Surveillance population and surveillance period

The population contributing to the impact evaluation surveillance systems will include vaccinated and unvaccinated children living in areas of moderate to intense malaria transmission and aged from 1 month to 59 months. The surveillance period will be 46 months, to provide 12 months of surveillance activities after children vaccinated during the first year of the programme receive their fourth vaccine dose, assuming that the first dose of RTS,S/AS01 is given as soon as possible after 5 months of age, that the third dose is given by 9 months of age, and the fourth dose is given by age 27 months. A 12 month surveillance period after dose 4 brings children to 39 months of age. Data will be collected in children aged up to 59 months to enable documentation of delayed critical events in children vaccinated at the beginning of the programme (figure 2, section 7.6.5). Collecting information on children reported to have died between the ages of 1 and 59 months should facilitate operational activities and minimise the risk of excluding relevant events due to inaccuracies in initial reporting of age in young children in such settings, and the data for those too young or old for RTS,S/AS01 provides important information about underlying rates of outcomes in the same cluster.

9.2.2 Community-based surveillance

The majority of deaths in many sub-Saharan countries occur in the community, rather than in hospitals or health facilities. The evaluation of the impact of RTS,S/AS01 on survival will therefore require the development and consolidation of community-based systems to document and report deaths. Experience from the INDEPTH network of demographic surveillance systems (DSS) has confirmed the feasibility of recruiting and training a cadre of village-based reporters (VRs). Their role is to identify and document deaths occurring in their village and any surrounding area assigned to the VR. Deaths may be identified either through (i) door-to-door visits of each household in the VR's assigned area, in which case there will be approximately 131 VRs per cluster, employed full time and each expected to visit around 150 households every 3 months, or (ii) by VRs being notified of any key events by a specially developed local network of informants, in which case there would be around 25 VRs per cluster, each VR capturing information from around 800 households. The MVPE will build on relevant existing and developing capacities and systems to generate key vital event data for the evaluation and do so with the aim of strengthening sustainably the local capacity for vital event monitoring.

9.2.3 Community sensitisation

Following approval of the protocol by the relevant ethical committees/IRBs, the country-based PIs will work with MoH staff involved in the implementation of the vaccination programme to sensitise and engage relevant local stakeholders (e.g. Regional and District Directors, Regional and District Medical Officers, etc) and communities (e.g. through village meetings – 'Durbars') and/or their representatives (e.g. Councillors). This will be done in a locally appropriate manner, guided by good participatory practices, and described in more detail in Annex 6 and fully in the country-specific protocols.

9.2.4 Identification and training of Village Reporters

Where possible, existing cadres of village-based workers will be supported, as locally appropriate and necessary, to act as VRs for the documentation of deaths in children in the target age group. The potential for this cadre also to support reporting of AEFI will also be assessed. Where such a cadre does not exist criteria for selection of VRs will be agreed locally. These criteria will likely include a specified level of education and being resident in the area in which they will be responsible for reporting deaths. Recruitment will proceed according to a locally agreed competitive selection process. A surplus of VRs will be identified and trained from each cluster to create surplus capacity in the event of trainees unable to complete the course, unwilling or unable to take on the role, illness, migration of the VR, etc.

The VR training programme will ensure an understanding of the:

- Importance of mortality monitoring in general.
- Need to understand the causes of death in order to prioritise action to intervene and to assess the impact of new measures to improve survival.
- Content and rationale for standard operating procedures, including locally appropriate ways to inquire about deaths.
- Use of local events calendars to help capture critical dates (especially dates of birth and death) accurately.

Vaccine safety principles and AEFI surveillance will also be included in settings where the identified cadre is considered able to contribute to the strengthening of routine pharmacovigilance.

Training will include small group work and evaluations, with the best trainees invited to participate in a piloting exercise. The VRs' performance in the piloting will be reviewed before a final selection of VRs and reserves is made. We will seek to build on any relevant training materials and approaches that have previously been developed (e.g. for Demographic Surveillance Systems) in the area.

9.2.5 Identification and training of supervisors for Village Reporters

In some settings VRs may be supervised by members of the District Health Team, District Council or other established cadre. Where no such capacity exists, VR technical supervisors will be identified from amongst the trainees (see 9.2.4) and may include staff known to the evaluation partners.

Each VR technical supervisor will cover one cluster and supervise the activities of the VRs in that cluster.

The VR Technical Supervisors will be trained in:

- Quality Assurance, including the conduct of repeat and accompanied interviews
- Verbal Autopsies (VA), using the WHO-recommended VA questionnaire and including the seeking of consent.
- Reporting AEFI, where AEFI identification is included in the activities.

In addition to the technical supervisor, a local supervisor will also be identified for each VR. The local supervisor will be a Community Own Resource Person (CORP) such as a village chief, local Councillor, headman etc., who will tend to hear about any deaths in the area and help to ensure that the VR has documented them.

Each VR will meet approximately monthly with both his or her technical and local supervisors. Such a hybrid approach to supervision has been shown to be useful.[16]

Where a death has been documented, a locally appropriate period of time will elapse before the technical supervisor seeks consent from the parent/carer to conduct the verbal autopsy.

The senior technical member of the evaluation team will occasionally join the hybrid supervision meetings, and conduct partial repeat and accompanied VR Supervisors interviews. Care will be taken to interact sensitively with bereaved families and to keep the frequency of interactions to the minimum required to assure the quality of data.

9.2.6 Identification of deaths

Following appropriate local sensitisation (see section 9.2.3) the assistance of leaders and CORPS will be sought to notify the VR about any death in a child under 5 years of age. A wider age group than that for vaccine during the pilot period is included in surveillance. This minimises the risk of missing an event due to errors in the dates, and the data for children too young or too old to receive RTS,S/AS01 provide important information about background rate of mortality in the same cluster.

When the VR is notified s/he should visit the family as soon as possible to confirm the event and complete the 'Fact of Death' notification.

In the event of a death in a child 1 – 59 months of age, the technical supervisor will be notified by the VR e.g. by phone/SMS. After a locally acceptable period of time, the technical supervisor will visit the bereaved family and complete a VA, to generate the 'Cause of death' classification, for children confirmed to have died while aged 1-59 months.

VAs will be carried out on all deaths in the age range 1-59 months, either using the full VA questionnaire, or alternatively (depending on local capacity) using a minimal set of questions that include age at death, sex, vaccine status, location of normal residence, and whether the death was due to illness or accident/ trauma.

9.2.7 Expected numbers of events

Sample size planning used a mortality risk of 25.2 per 1000 children (based on rates for children aged 6 – 36 months from 2015 World Bank data – see section 9.5), which translates to 10 deaths per 1,000 per year in the target age group. A cluster with an annual birth cohort of 4,000 can thus expect 40 deaths per year, and hence the field supervisor(s) responsible for a cluster can expect to

complete 3 or 4 Verbal Autopsies (VA) per month. The Country evaluation co-ordinator will oversee field activities and ensure the flow of data documenting the cause of death across all clusters: a study with 60 areas is expected to document approximately 2,400 deaths in the target age range per year, equivalent to 200 per month.

9.2.8 Case definitions

Refer to section 10.4.

9.3 Variables

The following variables, at a minimum, will be recorded for each identified death: date of birth, date of death, age at death, gender, place of normal residence, longitude and latitude of the place of normal residence, place of death if different, whether cause of death was illness, or due to accident or trauma , and dates of each dose of each vaccination (BCG, OPV, DTP (or DTP/HepB/Hib, as appropriate), measles and RTS,S/AS01), when available. The vaccination history will be captured from the child's health card wherever possible. A photograph of the health card may be taken and stored with the child's CRF to facilitate validation of vaccinations received and dates. Where no health card is available the information will be solicited from the caregiver via maternal recall (no dates) and documented as such. When vaccination information is collected through maternal recall, the caregiver/mother be asked about each vaccine (per country-specific EPI guidelines) and the number of doses, with detailed prompts characterizing the vaccines to enhance the quality of the recall (e.g., describing oral polio vaccine as bitter drops; etc.). In a subset of cases, parents may be asked additional questions to validate maternal recall. A validation study should be conducted in each country to understand the reliability of malaria vaccination status from different sources for children who have died, by comparing vaccination status from the home-based record, and from caregiver recall, with records at the immunization clinic. The distance to the nearest health facility, and distance from the nearest hospital will be calculated. Verbal autopsy will be performed for all children aged 1 – 59 months at the time of death. Verbal autopsy will follow the recommended WHO protocol using the 2016 WHO verbal autopsy instruments[17] but including data on vaccination history (record-based and/or recall). Cause of death will be assigned using the WHO-recommended approach, currently the analytical software InterVA[18]. Other methods (such as IHME's tariff method using the SmartVA application)[19] can also be run on WHO VA 2016. Annex 7 presents the list of causes of death according to the VA procedure. Consent for the VA will be documented; if consent for the VA is not provided, the basic details of the death will be reported but cause of death and other details will not be available. If no information is available about the death that enables the VA classification, the cause of death will be classified as "CAUSE OF DEATH UNKNOWN".

The effect of RTS,S/AS01 introduction on all-cause mortality excluding accidents (the primary outcome) will be estimated by comparing the number of deaths in vaccine-eligible age groups in intervention and comparator areas, adjusted for differences in the incidence of mortality in non-eligible age groups in the same clusters. Effects will be measured using incidence rate ratios and rate differences. Denominators (person time at risk), required for estimating rate differences, will be estimated using estimates from the most recent national census.

Secondary outcomes will be analysed in the same way.

Alternative methods of estimating denominators may also be investigated using one of the following models:

- MODEL A: A list of children aged 1-59 months maintained by VRs for their respective areas, or

- MODEL B: A population estimate modelled using all available data either to (i) allocate populations within census units to a finer spatial level [20,21] or (ii) use a combination of very high resolution satellite imagery and small area focussed micro-census surveys to estimate population size and distribution.

- Model C: Any alternative approach able to generate robust estimates of the denominator population, as agreed between the in-country evaluation partners and WHO.

In the first modelling approach, census estimates from the most recent national census will be distributed on the basis of typical per-land cover class population densities, which have been estimated for African countries for which very fine resolution population data are available, following approaches described elsewhere[21]. The typical population densities are then applied as weightings to redistribute census counts according to the land cover and to map human population distributions at a finer spatial resolution using asymetric modelling techniques[22]. This modelling method distinguishes urban and rural populations in the redistribution of populations. The population distribution datasets will be projected to the relevant year using United Nations (UN) national rural and urban growth rates and made to match the total national population estimates provided by the UN Population Division.

In the second modelling approach, 'bottom-up' geospatial population enumeration is undertaken in the absence of national population census data. Recently acquired very high resolution satellite imagery (50cm or finer spatial resolution) will be processed to map individual buildings and small settlements across the pilot implementation area, as well as to provide information on neighbourhood housing densities and urban/rural metrics. Small area focussed micro-census surveys will be undertaken across the areas of interest to obtain data on how the satellite-derived metrics translate into population numbers and age/sex compositions. This will enable construction of statistical models to predict population numbers and compositions into unsampled locations across the study areas, and to include measures of uncertainty in the predictions. This approach has been applied in (i) Northern Nigeria, as part of polio vaccination planning and coverage work[23] and (ii) Afghanistan, in collaboration with the government's statistics office and UNFPA. High predictive accuracies have been demonstrated in both instances.[24]

These approaches will allow estimation of the number of children in the target age-range in each cluster, together with uncertainty parameters around the estimates, and generate estimates of the community mortality impact of RTS,S/AS01 deployment.

The data from the VAs (Annex 8) will be captured electronically and processed using InterVA and/or equivalent software to generate cause of death classifications according to the International Classification of Disease (ICD) version 10 or 11.

9.4 Data sources

The analysis will include all deaths in the target age group, recorded by VRs. Cause-specific mortality analyses will draw on the results of VAs performed by VR supervisors and processed by InterVA or other WHO-recommended VA-coding process.

The denominators will be estimated using one of the approaches described in section 9.3 for the whole of the pilot implementation area in each country. Time at risk will be based on the estimated denominator and may be adjusted for seasonal variation in births.

The number of children receiving vaccines will be obtained from the MoH`s vaccination registries.

9.5 Study size

Planning was based on the assumption that 4,000 children would be born per cluster per year, with 30 months of vaccination and a total surveillance period of 46 months, each cluster contributing 23,750 person years at risk (pyar) if all children survive. If 1% of children die in their first month of life, and 0.08% die every month after the first month, infant mortality would be 18.7 per 1000, mortality (based on estimates of rates for the 5 to 36 months age group) would be 22.2 per 1000, and the average time at risk per cluster would be 23,134 years.

Table 3 shows how this generic approach compares with the expected mortality between 6 and 36 months of age, based on infant and child mortality data in 2015 from the World Bank[26,27]. The expected mortality between 6 and 36 months of age was estimated as follows: mortality between age 6 to 11 months was assumed to be 50% higher than the mortality during age 1 year, and between age 1 and 4 years the mortality decreases with age as follows: 35% in year 1, 27% in year 2, 20% in year 3 and 18% in year 4. It is assumed that mortality rates in areas with high malaria endemicity are 50% higher than the estimates from the World Bank data.

Table 3: Infant and under five mortality estimates 2015 from World Bank Data, and expected mortality 6m to 36m in high endemic areas in selected countries.

Country	Infant Mortality (per 1000)	Under Five Mortality (per 1000)	Mortality 6m to 36m In high malaria endemic areas (per 1000)
Ghana	43	62	25.2
Kenya	36	49	17.2
Malawi	43	64	27.8

The mortality rate can be estimated from mortality risk as $-\log_e(1\text{-risk})/\text{time}$, where risk is the probability of dying during the time of follow-up, assuming an exponential distribution. A mortality risk of 25 per 1,000 equates to a rate, over 2.5 years, of 10.12712 per 1,000 pyar. A mortality risk of 21 per 1,000 equates to a rate, over 2.5 years, of 8.489455 per 1,000 pyar.

Based on a minimum mortality rate of 8.5 per 1000 pyar, 23 areas each in the evaluation and comparator areas, each with an annual birth cohort of approximately 4,000 subjects, would have 80% power to detect, at the 5% significance level, a decrease of at least 10% in overall mortality in each country. This compares with the modelled estimate of an 18% (range 6-29%) reduction in malaria-specific mortality in children under 5 years, assuming 72% coverage of a 4 dose regimen delivered at 6, 7.5, 9 and 27 months of age[7]. The sample size was obtained after applying the formula from Hayes and Bennett[25] with an intra-class correlation of (k) 0.1. The design effect is

3.01. The total number of areas per country is expected to range from 46-60 and will be presented as part of country-specific sample size calculations in country-specific protocols.

Figure 4 presents a sensitivity analysis showing how the coefficient of variation influences the required number of clusters.

Figure 4: Sensitivity analysis illustrating effect of changing mortality rate and inter-cluster coefficient of variation on number of areas required to detect a 10% reduction in mortality

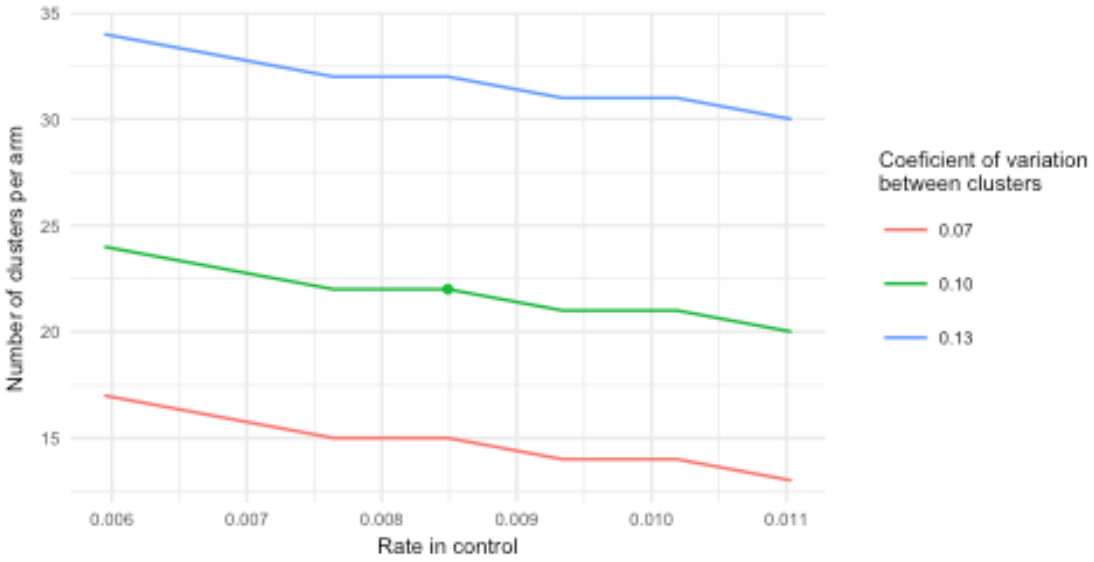


Table 4 shows the reduction in mortality that can be detected at a 5% significance level if the number of areas and the population remain constant but the parameters of baseline mortality and intra-class correlation (k) change.

Table 4: Sensitivity analysis of the sample size. Decrease in mortality that can be detected at the 5% significance level with a power of 80% by baseline mortality and coefficient of variation of the mortality between areas assuming 30 areas with an annual birth cohort of 4,000

Mortality risk per 1000 in non-implementing clusters	Coefficient of variation (K)	Detectable decrease in mortality
25	0.10	10.0%
25	0.15	12.6%
25	0.20	15.5%
25	0.30	21.3%
20	0.10	10.6%
15	0.10	11.5%
10	0.10	13.2%
5	0.10	17.3%

Based on simulations, a trial with these characteristics is estimated to have approximately 80% power to detect an interaction between gender and treatment of 1.15 (i.e an increased risk of mortality in girls of 1.035). This compares favourably with the 1.9-fold increase in risk among girls receiving RTS,S/AS01 in the phase 3 trial Mal-055.

The assumptions in the sample size calculations will be checked against empirical data once the programme is underway, in accordance with an analytical plan to be developed in the early phase of the programme.

9.6 Data management

Deaths will be identified by the network of VR as described above. VRs will capture information using a paper CRF. Annex 9 shows a sample of the VR CRF.

Technical VR supervisors will capture data using a tablet computer or similar mobile computing device and synchronise with the national MVPE data system. The VAs will also be captured electronically using mobile devices (e-CRF). Annex 8 shows a sample of the VA form. Annex 10 presents the CRF to compile the data needed for the evaluation of impact. Details of the system, including the steps to ensure adequate anonymisation and security of data, will be agreed with the research partners and detailed in country-specific protocols. Information from the different countries will be harmonized and compiled monthly. Information from the MoH`s vaccination registries will also be obtained, harmonized and compiled at least once every month. Annex 11 shows a sample of the vaccination registry recording data at the individual level.

9.7 Data analysis

Detailed statistical analysis plans will be developed during the course of the programme and reviewed by the Programme Advisory Group and, if necessary, external statistical experts, before

analyses are performed. The overall approach will be to compare mortality rates in implementation and non-implementation areas ,in terms of the incidence rate ratio and rate difference in vaccine-eligible age groups. Secondary analyses will explore limiting analysis of mortality rates to children reported to have received DTP3 to exclude children who are not brought for routine vaccinations and therefore would be unlikely to come for RTS,S . Comparisons will be made for all-cause mortality and for deaths where VAs enable the exclusion of deaths due to accidents. Pooled analyses of impact data from across the MVIP countries will be conducted in addition to analyses within each country. The limited extent of baseline mortality data is not expected to be sufficiently robust to inform these analyses.

9.8 Quality control

An independent Clinical Research Organization (CRO) will be contracted by WHO to assure the quality and integrity of the data collected. The CRO will review a set proportion of source documents, including informed consent forms. In addition, quality assurance procedures will be implemented by the evaluation partners to ensure that the data are generated appropriately and captured accurately in the databases. Checks will include partial repeat interviews and accompanied interviews. Partial repeat interviews, done by supervisors (both of VRs and of VR supervisors) on a randomly selected proportion of consenting interviewees, will seek to verify that the original interview took place, and to double-check the responses to key questions in those interviews. Accompanied interviews involve supervisors witnessing standard interviews to ensure the approach of the interviewer is appropriate and that responses to questions are elicited in a sensitive, acceptable and comparable way across the programme. Performance data will be reviewed monthly within each country and quarterly across the programme. Those areas identified as outliers, either because of increased or decreased reporting rates, will be prioritised for followed-up. Where a vaccine record or maternal recall do not provide information on the vaccine status, the potential to seek information from the clinic registers for deaths, in vaccine-eligible age groups in RTSS clusters will be considered where feasible. Monitoring of data quality and completeness is described in the SAP.

9.9 Limitation of the research methods

The absence of routine vital event registration systems complicates the evaluation of impact on survival. Especially in the most remote areas, it is possible that children who die will not be notified to either the authorities or the village-based reporting system.

The following steps will be taken to assure the quality and completeness of data captured by the VRs:

(i) Repeat and accompanied interviews by VR supervisors. Repeat interviews involve re-visiting households to confirm the intended visit took place and check the response to key questions, especially those which would trigger further actions or which are vital for the evaluation. Accompanied interviews are intended to ensure appropriate conduct from social, ethical and technical perspectives.

(ii) Performance data review. The frequency of key variables (e.g. number of households visited, number of deaths reported, etc.) will be reviewed monthly, VRs with outlying values identified and in-depth discussions held to identify the need for any corrective actions. If feasible, VRs will report weekly or monthly, regardless of whether deaths

occurred in the reporting period (zero-reporting), as an indicator of active engagement by all reporting units.

(iii) Data triangulation. There may be potential to compare data from VRs with data from other settings, including cross-referencing hospital-based deaths from the surveillance hospitals. For example, people attending routine vaccination clinics could be asked about the location, timing and approximate age of any deaths in their residential area, or data from any separate vital events registration system could be interrogated. Any deaths identified should feature in the VR reports and any data apparently missing from the evaluation database should prompt follow-up.

The strength of these approaches is not so much the direct detection of missed deaths, but the incentivisation of VRs, who will be made aware of the QA procedures, to make serious efforts to identify all deaths in their assigned areas. Estimates of mortality rates will be compared with estimates from DHS surveys and from DSS data.

The analysis approach used for estimating rate ratios does not involve population denominators. However, for rate differences, estimates of population at risk are required. The same absence of vital registration systems that affect the detection of deaths affect the definition of the children at risk. The values obtained from census data and from the models will be compared in selected areas with the estimated population at risk obtained from the number of households covered by the VR.

It is possible that children living in comparison areas will be brought for vaccination in areas allocated to RTS,S. Such "contamination" of comparison areas could potentially lead to an under-estimate the impact of the vaccine on all-cause mortality detected at the community level. The level of contamination will be reduced by selecting areas which are as geographically large as possible, making it more difficult for people to seek vaccinations outside their own cluster. It is inevitable that some degree of contamination will occur. Sensitivity analyses will be conducted to explore the potential effect on the estimates of impact, for example by comparing effect estimates using all the data with estimates obtained after excluding from analysis events occurring within given distance from cluster boundaries.

10 Research Methods for Safety Evaluation

10.1 Study design and timing

The safety of RTS,S/AS01 will be monitored through a strengthened routine pharmacovigilance system operating across the whole of the MVIP area, and by a specific surveillance system established in sentinel hospitals covering part of the MVPE area.

Across all three countries, a series of up to 24 sentinel hospitals will be identified across the MVPE, serving and/or comparison areas . The catchment area of each hospital is expected to have an annual birth cohort of, and provide services for, approximately 4,000 children in each cluster in its catchment areas. Hence a total of at least 48,000 children in implementation areas and at least another 48,000 children in comparison areas will contribute to the hospital-based evaluation of safety across the programme. The data from these hospitals will complement that generated by the hospitals involved in GSK's Phase 4 study (up to 6 in areas implementing and 6 in areas not implementing RTS,S/AS01, serving an area with a total annual birth cohort of approximately 24,000 children).

The safety evaluation will be based on outcomes recorded in age groups of children eligible to receive RTS,S/AS01. There will be 12 months of surveillance after the children vaccinated during the first year of vaccine introduction have received dose 4, assuming that the first dose of RTS,S/AS01 is given by around 5 months of age, the third dose is delivered by age 9 months and the fourth dose is given by age 27 months. A 12 month surveillance period after dose 4 brings children to 39 months of age (figure 2, section 7.6.5). However, admitted children aged 1 to 59 will be included in the evaluation, for practical simplicity, to enable documentation of critical events in children who are vaccinated near the beginning of the programme, and because events in children too young or old to receive RTS,S/AS01 provide useful information about underlying rates in the same cluster.

10.2 Setting

10.2.1 Selection of Sentinel Hospitals

Sentinel hospitals in the pilot study will be selected according to the following criteria:

- Either:
    - Catchment area comprising areas which will all implement RTS,S/AS01 or will all act as comparator areas for the pilot study, OR
    - Sentinel hospitals serving catchment areas some of which implement RTS,S/AS01 and others which act as comparator areas for the pilot study, OR
    - Availability of a Vaccine Registry which can be linked to inpatient data.
- A catchment area which includes approximately 4,000 infants from the MVPE area.
- A functional system of case note recording for patients on the paediatric ward.
- A track record of regular reporting of routine data (inpatient and vaccination clinic data) to the district health team.

- Demonstrable experience of LPs on children with signs of neurological illness.

Hospitals without prior experience of enhanced meningitis and cerebral malaria surveillance will be supported to improve these capacities such that they are fully operational before RTS,S/AS01 vaccinations begin.

10.2.2 Characteristics of Sentinel Hospitals

Sentinel hospitals will include different types of admitting facilities (table 5), offering a range of levels of investigation and care to different numbers of children. The number of each type of hospital will be balanced in implementing and comparison areas such that a similar number of children are admitted in each area to each type of facility. In addition to the signs and investigations included in the table, some hospitals may have the capacity to detect additional signs of value in the diagnosis of severe malaria (ophthalmoscopy on children with suspected cerebral malaria); significant bleeding (recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena); capillary refill; systolic blood pressure; pulse oximetry; acidosis (base deficit, plasma bicarbonate, venous plasma lactate); creatinine or blood urea; bilirubin; chest X-ray).

Hospitalisation will be defined as spending at least one night at a sentinel health facility or admitted and dying within the first 24 hours of admission.

Table 5: Characteristics of sentinel hospital

Hospital Level	Level 1	Level 2	Level 3
Patient notes system available	X	X	X
LPs performed	X	X	X
Electricity supply	X	X	X
-20°C storage facility	X	X	X
Recording of Clinical History			
Fever	X	X	X
Multiple convulsions	X	X	X
Altered consciousness	X	X	X
Recording of Clinical Signs			
Respiratory rate	X	X	X
Chest indrawing	X	X	X
Deep breathing	X	X	X
Neck stiffness	X	X	X
Bulging fontanelle in children under one year of age	X	X	X
Prostration	X	X	X
BCS / GCS	X	X	X
Ophthalmoscopy			X
Recording of Investigations			
Temperature (axillary/rectal)	X	X	X
Malaria RDT	X	X	X
Malaria microscopy for parasite count & species		X	X
Blood glucose (dip-stick or lab-based)	X	X	X
Hb / Hct	X	X	X
LP and visual macroscopic examination	X	X	X
CSF protein		X	X
CSF glucose		X	X
Antigen detection tests		X	X
Microscopy for cells & organisms		X	X
Culture – blood			X
Culture – CSF			X
Molecular and/or serological tests			(X)

10.2.3 Enhanced Hospitalisation Surveillance

Hospital-based surveillance will systematically document all admissions to the paediatric ward in order to capture information on the safety profile of RTS,S/AS01. This will be characterised by measuring the extent to which programmatic delivery of RTS,S/AS01 is associated with changes in the hospital-based incidence rates of meningitis, cerebral malaria, febrile convulsions, other illnesses, all-cause and malaria-specific mortality. Data will be collected from sentinel hospitals both in implementation and comparison areas.

Some pilot implementation countries may have a limited number of hospitals (1-3) with considerable experience in meningitis surveillance, or diagnosing meningitis or cerebral malaria in a research setting. These "highly capable" hospitals will be balanced between implementation and comparison areas by the restricted randomisation procedure (section 7.6.2). Such hospitals will require minimal support to begin capturing data on meningitis or cerebral malaria cases, and will be able to evaluate and document patient findings using a wider range of diagnostics than would be available in most hospitals (e.g. blood and CSF cultures). If introduction of RTS,S/AS01 is staggered for operational reasons, RTS,S/AS01 will first be introduced into the areas with highly capable sentinel hospitals to enable any clinically significant safety signals to be assessed early and with a greater range of diagnostic tools than will be available in other sentinel hospitals.

Training, including in routine pharmacovigilance (see section 13), inpatient management algorithms to assess case definitions in a standardised way, and shipping of CSF to reference laboratories will be established in all sentinel hospitals prior to the start of the pilots.

Relevant demographic, vaccination and clinical data will be captured in a CRF on all children under 5 years of age admitted to the paediatric wards of sentinel hospitals in the RTS,S/AS01 implementation and comparison areas. As far as possible, the routine Health Management Information System will be supported to capture standard information and additional modules added, as necessary, to capture the specific data required for the RTS,S/AS01 evaluation. Consolidated, quality assured, inpatient surveillance systems will be supported by Evaluation Partners in each country. Although hospitals are likely to vary in the level of expertise available, and their experience in surveillance for meningitis and cerebral malaria, minimum standards will be assured to enable the systematic, standardised clinical and laboratory assessment and management of all admissions.

10.2.4 Detection of Adverse Events Following Immunization (AEFIs)

Although routine pharmacovigilance is not conducted as part of the research protocol, the routine pharmacovigilance system will be strengthened through a standardised set of activities to support staff at all health facilities located within the MVIP areas (section 7.6). This pharmacovigilance strengthening will be the responsibility of the health care system, as will routine reporting on AEFI and AESI (see also section 13.2) with support from WHO. The strengthened pharmacovigilance system is designed to capture any spontaneously reported vaccine-related adverse events, including febrile convulsions and rare and unexpected AEFI, which might be experienced by some children following RTS,S/AS01 vaccination.

Adverse Events of Special Interest (AESI) may be captured through country-specific protocols, as agreed with national authorities, as a complement to the detailed information generated by GSK's Phase 4 study.

10.3 Study procedures

Data from all children admitted to hospital should be captured in a routine health Management Information System (HMIS). This will typically include minimal demographic and clinical information such as name, age, gender, area of residence, diagnosis, treatment and outcome (dead, alive, referred). Some hospitals may have an electronic system but the majority are expected to be paper-based. The content and functioning of the HMIS will be reviewed before study start and arrangements made to augment data collection, as necessary, for children in the target age range (i.e. from 1 month - 4 years inclusive). Informed consent will be sought for capture of any data not routinely collected and according to local requirements.

Demographic information, RTS,S/AS01 and other vaccination status, key clinical signs - including criteria for lumbar puncture - details of samples collected and the result of malaria and CSF testing will be captured in a CRF, as appropriate. An algorithm for investigations will be developed that is consistent with national guidelines, with agreed criteria in each country for sample collection. Relevant clinical staff will be provided with refresher training on the relevant national routine care guidelines to facilitate patient management according to the national guidelines. The MoH in each country will retain responsibility for assuring the availability of the treatments it recommends in its national guidelines. At the same time, the staff will also be trained in the pilot programme's investigation algorithm (which is aligned with the WHO and national guidelines of the three pilot countries) to ensure that children are assessed in a standard way, with blood and CSF samples collected as necessary to enable assessment of study endpoints against standardised case definitions. The MVIP will work with the MoH and evaluation partners to assure, as far as possible, the availability of the supplies needed for essential investigations and treatment.

Children will be managed according to national guidelines and the final clinical diagnosis and outcome will be recorded at the end of admission. All relevant clinical and laboratory data will be compiled in an electronic CRF to enable case ascertainment for the analysis of the evaluation's endpoints.

The enhanced hospital-based surveillance will be in place prior to the introduction of RTS,S/AS01, generating data for Programme Advisory Group review to confirm the integrity of the surveillance and allowing an assessment of the comparability of facilities in implementing and comparison areas in terms of completeness and quality of the data. Data from the enhanced HMIS will be monitored until the end of the evaluation, approximately 50 months after the start of vaccination (see section 9.2.1), using automated data routines to evaluate completeness and internal consistency of records.

Children with any sequelae following a diagnosis of meningitis or cerebral malaria will be invited to re-attend hospital for follow-up appointments after hospital discharge. These will be scheduled at intervals considered appropriate by the attending clinician.

If, at any time, the attending clinician suspects the admission is related to RTS,S/AS01 the procedures to report an AEFI should be followed (see section 13) and the Evaluation Partner's Clinical Surveillance Coordinator notified by phone or SMS text message. The fact that an event was reported as an AEFI will be captured in the CRF.

10.3.1 Data capture in sentinel hospitals

Children will be admitted to hospital according to local procedures. At the time of admission the standard HMIS data will be documented according to standard practice. All children aged 1 to 59 months will have a brief purpose-made questionnaire completed by the attending clinical staff in order to capture the demographic, vaccination and clinical information necessary to trigger specific investigations and eventually enable a final diagnosis to be made. Completeness of the hospital surveillance will be checked during the daily ward rounds, at which time every admission in the target age group should have had a hospital surveillance screening form completed, and at period visits by the clinical surveillance co-ordinator of the in-country evaluation partners. Completeness of data capture in the enhanced HMIS will be assessed through triangulation with hospital admission registers. Hospital staff will be encouraged to contact the clinical surveillance co-ordinator by phone in case of any concern or uncertainty regarding the assessment of patients contributing to the evaluation.

10.3.2 Informed consent for the collection of surveillance data

Where considered necessary by local IRBs, written, or witnessed and thumb-printed, informed consent will be obtained from each child's carer before data are included in the evaluation dataset. The intention is to capture data that should in any case be documented as part of clinical care. Consent will be sought for any data capture, diagnostic procedure or test required by the study which would not otherwise be needed to satisfy the relevant national paediatric inpatient protocol. Country-specific protocols will address this point in detail and provide country-specific information. The seeking of consent and capture of any study-specific data should not impede the assessment or management of the child. Data may be captured retrospectively once the Informed Consent Form (ICF) is signed/ thumbprinted. No study-specific procedures, including any follow-up visits specially-scheduled for the purposes of the evaluation, will be performed before the ICF is signed/ thumbprinted.

10.3.3 Data to be captured

The following data will be collected into a CRF (paper or electronic, annex 12) from all children aged 1-59 months admitted to hospital:

- From the standard, routine HMIS: age, date of admission, gender, normal place of residence (village or urban address), current place of residence if this is different, diagnosis, treatment and outcome of admission. Records will include identifiers of the sentinel hospital and the patient's hospital number.

Children from the programme area will have the following additional information collected:

- Date of birth (if not included in the routine HMIS), active participation in any clinical trial.

- Use of malaria control measures (ITN, IRS, anti-malaria drugs), other health care seeking for the current illness or drug use in the previous 14 days. This will include whether evidence of prescription was available or if drug use was reported, and capture information on antibiotic and anti-malarial use (which may affect detection of bacteria and/or *P falciparum*), and medication for chronic conditions (e.g. HIV).

- Vaccination history – types and dates of vaccinations received through the routine EPI. This will be captured from the child's health card wherever possible. A photograph of the health card may be taken and stored with the child's CRF to facilitate validation of vaccinations and dates. This will include dates of vaccination with OPV, BCG, DTP (or DTP/HepB/Hib, as appropriate), measles and RTS,S/AS01. Where no health card is available the information will be solicited from the caregiver through verbal recall (no dates) and documented as such. When vaccination information is collected through maternal recall, the caregiver/mother will be asked about each vaccine (per country-specific EPI guidelines) and the number of doses, with detailed prompts characterizing the vaccines to enhance the quality of the recall (e.g., describing oral polio vaccine as bitter drops; etc.). In a subset of cases, parents may be asked additional questions to validate maternal recall . Where a vaccine record or maternal recall do not provide information on the vaccine status, the potential to seek information from the clinic registers for meningitis and cerebral malaria cases in vaccine-eligible age groups in RTSS clusters will be considered where feasible.

- Any known pre-existing medical conditions e.g. HIV infection, congenital disease (including haemoglobinopathies).

- History of fever, difficulty breathing, convulsions, altered consciousness.

- Findings from physical examination including body temperature, respiratory rate, presence of chest indrawing, deep breathing, the components of the Blantyre Coma Score, neck stiffness, bulging fontanelle.

- Whether a blood sample was collected and, if so, the tests requested, results available during the admission and sample identification number for tests requested off the paediatric ward. All children will be expected to have a malaria test (RDT and microscopy) and a haemoglobin/PCV.

In addition, children under 2 years of age with a BCS <3, or assessed as P or U on AVPU[3] score, or aged 2 years and over and with a Glasgow Coma Score <11, will have the following data captured:

- Blood glucose result

- Whether a CSF sample was collected and, if so, the sample identification number and results available during admission.

At the time of discharge a final main and any secondary diagnoses will be recorded by the attending clinician, taking into account the clinical assessments, available test results, evolution of the illness and response to treatment, and the final outcome (alive, dead, referred, absconded).

All data will be recorded in a record form (CRF) and entered into the programme's database.

[3] AVPU: Alert, responding to Voice, responding to Pain, Unresponsive

10.3.4 Sample collection

Details of suspected meningitis or cerebral malaria cases – including medication history, findings on clinical examination and results of diagnostic testing - will be recorded in the CRF. Part of the CSF sample, collected according to routine practice, will be stored for further testing at the reference laboratory. Standard Operating Procedures will be implemented to govern sample storage and the transfer of samples to the central laboratory.

Local analyses of blood & CSF samples will be undertaken on site to the extent possible (table 5) and samples stored for additional processing in a reference laboratory. In some cases, anti-CS or anti-Hep B antibodies may be measured as supportive evidence of prior RTS,S/AS01 vaccination. Details of which examinations will be performed in which hospitals will be confirmed only once the hospitals have been selected but are expected to fall into the categories in table 5. At a minimum, CSF examination will include visual inspection before freezing and shipment to reference laboratories. Some hospitals may, in addition, perform microscopy, glucose and protein measurement, and run antigen detection tests, and a few will also culture CSF samples.

10.3.5 Record review

The clinical surveillance co-ordinator in each country will review clinical data as it accumulates to ensure its accuracy, completeness – including availability of sample information and local laboratory results - and internal consistency. Data monitoring at hospital, evaluation partner, country and programme levels will be supported by automated data review routines to enable targeted case review and follow-up action.

10.4 Case definitions

10.4.1 Meningitis

Meningitis was identified as a potential risk during the RTS,S/AS01 phase 3 study and particular efforts will be made to identify meningitis cases, defined in line with WHO's meningitis surveillance guidelines[28]. For all cases with a diagnosis of meningitis, and a sample of non-meningitis diagnoses, an independent expert review, blinded to vaccine status, may be conducted on the patient's record (this is dependent on the ability to conduct a record review beyond the CRF) before a final diagnosis is provided. This is required to manage, in a standardised way across the MVPE, the potential confusion between meningitis and other severe illnesses, such as cerebral malaria.

Table 6 summarises the meningitis case definitions. **"Suspected meningitis"** is a diagnosis based on clinical symptoms and/or signs defined as:

A child with one or more of the following present (with or without fever , neck stiffness, two or more seizures in the last 24 hours, bulging fontanelle, convulsions (partial, complex febrile or other atypical presentations), seizures if less than 6 months or greater than 6 years , altered consciousness, (Blantyre Coma Score less than 3 or, Glasgow Coma Score less than 11 or P or U on the AVPU scale [Alert Verbal Painful Unresponsiveness Scale]) or any other clinical symptoms indicative of meningitis or cerebral malaria by clinical judgement. Lumbar puncture will be encouraged in all such children, according to national diagnostic and treatment guidelines, for examination of cerebrospinal fluid (CSF).

Children will be considered to have "**probable meningitis"** if:

In a suspected case, the macroscopic aspect of the CSF is turbid, cloudy or purulent; or the CSF leukocyte count is >10 cells/mm3.

A child will be classified as a "**confirmed meningitis"** case if:

A suspected or probable case is laboratory confirmed by culturing or identifying (i.e. by polymerase chain reaction) bacterial, viral or other aetiology in the CSF.

Table 6: Meningitis case definitions for the MVPE

Clinical signs & laboratory results	In-country meningitis category	Results from Reference lab	Final meningitis category for analysis
[No neck stiffness AND (No altered consciousness OR alternative explanation for altered consciousness) AND No other meningeal sign*]	Not a meningitis case	Not needed for definition	Not a meningitis case
If one or more of the following is present (with or without fever): neck stiffness, two or more seizures in the last 24 hours or another meningeal sign including bulging fontanelle, or any seizures if less than 6 months, altered consciousness, (Blantyre Coma Score less than 3 or, Glasgow Coma Score less than 11 or P or U on the AVPU scale [Alert Verbal Painful Unresponsiveness Scale]) or any other clinical symptoms indicative of meningitis or cerebral malaria by clinical judgement	Suspected meningitis	Not needed for definition	Suspected meningitis
Any suspected case with macroscopically turbid, cloudy or purulent CSF; or with a CSF leukocyte count >10 cells/mm3.	Probable meningitis	No aetiological agent found or no sample available	Probable meningitis
Any suspected or probable case that is laboratory confirmed by culturing or identifying (i.e. by polymerase chain reaction) of bacterial, viral or other aetiology in the CSF .	Bacterial or viral meningitis	No aetiological agent found or no sample available	Probable meningitis
		Aetiological agent identified	Aetiology confirmed meningitis

10.4.2 Malaria

WHO's case definitions for malaria will be used. For all cases of severe malaria, including cerebral malaria, an independent expert review, blinded to vaccine status, may be conducted on the patient's record before a final diagnosis is provided (this is dependent on the ability to conduct a record review beyond the CRF). This is required to manage, in a standardised way across the MVPE, the difficulties of making some diagnoses, particularly cerebral malaria, which are difficult to standardize *a priori*.

Uncomplicated malaria

- Plasmodium parasitaemia > 0 detected by malaria RDT (or microscopy in the absence of an RDT result)

AND

- Presence of fever (temperature ≥ 37.5° C), as recorded at the time of presentation

OR

- Occurring in a child with recent (24 hour) history of fever who is unwell and brought for treatment to a health care facility

AND

- Without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Severe malaria

- Plasmodium parasitaemia (> 0 detected/ µL) detected by RDT (or microscopy in the absence of an RDT result)

AND

- One or more of the following;

    - Impaired consciousness: a Glasgow coma score < 11 in children ≥ 2 years of age, a Blantyre coma score < 3 in children < 2 years of age, or child responding only to pain or unresponsive;
    - Multiple or atypical convulsions: more than two episodes within 24 h;
    - or prolonged at >15 minutes, or focal;
    - Respiratory distress (manifesting as chest indrawing or deep breathing);
    - Severe malarial anaemia: haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% ;

Cerebral malaria:

- Plasmodium parasitaemia with impaired consciousness (Glasgow coma score < 11 in children ≥ 2 years of age or Blantyre coma score < 3 in children < 2 years of age or assessed as P or U on AVPU score);

AND

- Clinician diagnosis of cerebral malaria

AND

- CSF findings not consistent with

- probable meningitis (LP must be done - if LP not done, cerebral malaria diagnosis is cannot be made)

10.4.3 Anaemia

All anaemia:

- haemoglobin <11g/dL.

Severe anaemia:

- haemoglobin <5g/dL (or a PCV<15%).

Malaria-associated anaemia

- haemoglobin ≤ 11g/dL (or a PCV ≤ 33%) in children < 12 years of age with a positive RDT (or bloodfilm)

Severe malaria-associated anaemia

- haemoglobin ≤ 5 g/dL (or a PCV ≤ 15%) in children < 12 years of age with a positive RDT (or blood film)

10.4.4 Admissions

All cause admission

- An individual requiring overnight stay in hospital/inpatient facility or individuals who are admitted and die before an overnight stay has been completed.

Malaria admission

- Admissions of an individual with confirmed malaria (including *P. falciparum* malaria).

Non-malaria hospital admission

- Admission of an individual with any condition except malaria. Primary diagnosis is not malaria, and malaria test, if performed, is negative.

10.4.5 Death

Deaths – all cause

- A fatality (of any cause).

Malaria associated mortality

- A fatality in an individual who has malaria (positive RDT or blood film if RDT not done)

Malaria attributed mortality

- A fatality for which malaria (including P. falciparum malaria) is listed as a contributing cause of death, based on the medical judgment/medical records for children who died at a sentinel hospital.

10.4.6 Febrile convulsions

Adapted from Brighton case definition for generalised seizures: generalised seizures that occur in a febrile children (6–60 months old) who does not have intracranial infection, metabolic disturbance or history of afebrile seizures[30].

10.4.7 Adverse Event Following Immunisation (AEFI)

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease[31].

10.4.8 Adverse Event of Special Interest (AESI)

Adverse events of special interest (AESI) are protocol-defined diseases corresponding to AEs that are potentially associated with RTS,S/AS01E, that have historically been associated with vaccines other than RTS,S/AS01E, or may hypothetically be associated with RTS,S/AS01E due to the fact that this vaccine has components which are new compared to current widely used vaccines. A list of AESI has been developed for evaluation in the Phase 4 study. The potential and value of including AESI in country-specific versions of this protocol will be determined on the basis of consultation with each country's immunization program and regulatory authority. AESI such as anaphylaxis, acute flaccid paralysis or purpura could be subjected to active surveillance in all health care facilities from the pilot areas.

10.4.9 Serious Adverse Event

An AEFI will be considered serious if it:

- Results in death.
- Is life-threatening.

NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the individual was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

- Requires in-patient hospitalisation or prolongation of existing hospitalisation.

In general, hospitalisation signifies that the individual has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the adverse event should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an SAE.

- Results in disability/incapacity,

NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the individual or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

10.5 Biological sample handling and analysis

10.5.1 Biological samples

All children admitted to sentinel hospitals are expected to have routine laboratory tests performed according to National or local guidelines, including, but not limited, to the following:

For all hospitalised children:

- Haemoglobin concentration, packed cell volume (PCV) or full blood count.

For suspected malaria cases:

- *P falciparum* infection using RDT or microscopy (RDT is preferred) .

For suspected meningitis cases:

- CSF examination according to routine practice (visual inspection; glucose, protein; microscopy, with culture & sensitivity if feasible)
- Blood glucose
- In addition, suspected meningitis cases will have a sample and at least 500 µL of CSF, when a CSF sample is taken as part of routine practice. These samples will be used for microbiological and molecular analyses at reference laboratories, if the guardian provides informed consent.

Country-specific protocols will describe existing local guidelines and any proposed changes for the purpose of the current evaluation.

Full details for obtaining, storing and shipment of biological samples will be provided in a study procedures manual (SPM) of Standard Operating Procedures, and adherence to them monitored. In brief, immediately after collection and processing, to the extent possible, in the sentinel hospital, the samples will be placed at -20°C until transfer to the evaluation partner's facilities and then on to the central reference laboratory.

Samples will not be labelled with information that directly identifies the child but with an identifier which will also be recorded in the child's hospital notes and the CRF. Collected samples will be used primarily to guide patient management and for protocol mandated analyses to enable classification for data analysis. In addition, samples may be used to perform research related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, the child's Legally Acceptable Representative (LAR) will be invited to give another specific consent to allow WHO or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Any sample testing beyond that to inform the clinical management of the admitted child will be done in line with the consent of the individuals' parent(s)/LAR(s).

Collected samples will be stored for a maximum of 5 years (counting from the end date of the MVPE), unless local rules, regulations or guidelines require different timeframes or different procedures. Any such extra requirements will be communicated formally to and discussed and agreed with WHO.

The country-specific protocols will specify the governance mechanisms for storage and use of samples.

10.5.2 Laboratory assays

Any biological sample evaluation will be limited to the scope of this study and only related to assessment of study endpoints; it could include, for example, serology or deoxyribonucleic acid polymerase chain reaction (PCR) for infectious diseases, or confirmatory tests for autoimmune diseases. The specific lab analysis on CSF samples is given in sections 10.9.1.1. and 10.9.1.2.

For all required biological sample evaluations, details of assay type, assay method, test kit/manufacturer and laboratory used, as applicable for the test conducted, will be recorded.

WHO will assure the supply of the consumables and reagents needed to perform first line routine testing for the cerebral malaria and meningitis according to national guidelines. In case second-line confirmatory testing is required (for instance PCR for meningitis), samples will be sent to a qualified referral second-line laboratory in the African region.

10.6 Capacity building

The pilot implementation study will draw on the materials, training and experience of the GSK-sponsored Phase 4 study, as well as previous experience in relevant undertakings, to strengthen the identification, investigation and management of the events of interest.

The Phase 4 study and WHO-led evaluation will involve different hospitals but there may be overlap in the research institutions involved in both. Investigators in the Phase 4 study will be encouraged to serve as a resource for colleagues within and beyond their institutions who are involved with the MVPE. Potential areas of support include:

Training:

Appropriate training packages and materials (e.g. medical Job Aid) developed for clinicians in the phase 4 study may be useful for the MVPE to facilitate diagnosis using decision-making algorithms.

Phase 4 investigators will be supported by online medical education training packages and a telemedicine system and, as such, may be well-placed to offer advice to personnel involved in the MVPE.

The pharmacovigilance strengthening plan may benefit from the training provided to health care and study staff participating in the phase 4 study.

Laboratory:

The laboratory-related systems developed by investigators for use in the Phase 4 study – such as sample-tracking and transfer - may also serve the needs of the MVPE. The pilot programme will benefit from the approaches to Quality Assessment, Quality Control and training for laboratory technicians resulting from the interactions with the reference laboratories contracted for the phase 4 and MVPE studies.

Alert system for time-sensitive events:

The MVIP will work to strengthen the routine pharmacovigilance system (see the Pharmacovigilance Strengthening Plan) and to use, to the extent possible, the routine system based on spontaneous reporting. The use of the national AEFI Review Committee to review and adjudicate endpoints will strengthen the national PV-related systems.

The national Coordinating Group will work with colleagues within the MoH to assure the supply of key commodities, such as malaria RDTs, LP kits and laboratory reagents, to enable the conduct of diagnostic procedures according to National guidelines.

The strengthening of capacities related to routine pharmacovigilance are described in section 13.

10.7 Variables

At sentinel hospitals the Case ID, Hospital ID, Date of admission, age at admission, gender, residence location, vaccination dates and doses, signs and symptoms at recruitment, samples of interest collected during admission and the code to identify the sample, and the final diagnosis (ICD 10 – or later - code) will be captured. Results from the external laboratory and the review of

the expert panel will allow the final classification of each hospital admission with the following key variables:

- Admission Date
- Age at admission
- Date of birth
- Date of death (when applicable)
- Gender
- Residence location (to permit calculation of distances e.g. to hospital)
- Cluster ID
- RTS,S/AS01 vaccination status (number and dates of doses received); health card or recall (no dates for recall)
- Other vaccination status (type of vaccine, number and dates of doses received); health card or recall (no dates for recall)
- Results of malaria microscopy and RDT at admission
- Severe Malaria
- Cerebral Malaria
- Anaemia
- Meningitis suspected
- Meningitis probable
- Meningitis etiologically confirmed at hospital level
- Meningitis etiological confirmed at reference laboratory level
- Etiology agent confirmed at hospital level
- Etiology agent confirmed at reference laboratory level
- (Other outcomes).

A Geographic Information System will be used to map the residence locations of inpatients in the sentinel hospitals and the population at risk in the catchment area will be obtained disaggregating the population count data to a finer spatial detail (see below).

10.8 Data sources

Information for this analysis will be obtained from the sentinel hospitals and the local and central laboratories. Information from the population at risk, based on the population of the hospital catchment area, will be obtained from the model described in 9.4.

10.9 Case ascertainment

An algorithm will be developed to categorise the meningitis and cerebral malaria status of all age-eligible admissions to sentinel hospitals, according to the case definitions presented in section 10.4 . The in-country evaluation partners will run the algorithm on the data for which they are responsible and assess the consistency of the algorithm-based diagnosis with the clinical diagnosis made in the light of the clinical history, signs on examination, results of investigations and response to treatment. If the case is classified as an AEFI, these data and classifications will be submitted to the National AEFI Review Committee (ARC) for review and validation. No assessment of causality will be made at the individual level for meningitis or cerebral malaria. Rather, conclusions about the likelihood that RTS,S/AS01 is responsible for a change in meningitis or cerebral malaria rates will be based on the analysis of data on exposure to the vaccine in the implementation and comparison areas.

The ARC will verify and classifiy all AEFI reported through the routine system before presentation to the cross-country Data Safety Monitoring Board (DSMB). During the DSMB meetings, the data will be presented from the three countries on the AEFI findings and on the MVPE safety analysis.

The DSMB will be provided the ARC assessments of the initially unclassified cases and have access to experts in meningitis and severe malaria diagnosis to inform their final decision on the classification, for analytical purposes, of individual cases. The experts may be provided with all available medical information on individual cases but will initially be agnostic to vaccine exposure.

Both the ARCs and DSMB will operate according to agreed terms of reference and adhere strictly to the protocol-defined case definitions. Each will make causality assessments for adverse events reported through routine pharmacovigilance; those of the DSMB will be considered definitive for the purposes of the analysis across the three countries of the MVIP.

10.9.1 Meningitis cases

Clinically-suspected meningitis cases will have a lumbar puncture performed according to the national treatment guidelines and the CSF examined with a view to identification of an aetiological agent. Where feasible, blood culture will also be performed to facilitate the classification of meningitis-like diseases (table 6).

10.9.1.1 CSF testing at the sentinel hospitals

The appearance of CSF will be documented (purulent, cloudy, gin clear, bloody) at the time of collection. In level 1 hospitals (table 5), samples will then be stored at -20^{o}C for transfer to the reference laboratory.

Level 2 hospitals will in addition perform microscopy and gram staining of CSF, documenting differential white blood cell counts, and measure protein and glucose in the CSF and blood glucose. Latex agglutination tests on CSF will identify *Neisseria meningitidis, Streptococcus*

pneumoniae and *Haemophilus influenza* type b. Cryptococcal infection will be diagnosed using Indian ink, for HIV-positive children and those with unknown HIV-status, if feasible.

Level 3 hospitals will in addition perform blood and CSF culture for *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenza* type b.

If necessary, WHO will assure the supply of reagents and consumables to ensure that diagnostic procedures can be conducted as intended.

10.9.1.2 CSF testing at the reference laboratory

All CSF samples from children aged 1 – 59months in sentinel hospitals will be transferred to a reference laboratory, regardless of the outcome of testing in the sentinel hospital. The same, WHO-appointed, Africa-based reference laboratory, either in The Gambia (WHO Collaborating Centre for New Vaccines Surveillance, Medical Research Council Unit, Fajara) or South Africa (Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, division of the National Health Laboratory Service, Johannesburg), will be used for all hospitals in the MVPE to maximize the comparability of the information generated. The reference laboratory will do molecular tests for bacterial, viral, protozoal and fungal causes of meningitis, provide Quality Assessment and Quality Control.

The MVPE will draw on the Job Aids and trainings developed for medical staff by the GSK-sponsored Phase 4 study in order to strengthen capacity and enhance comparability of the meningitis-related classifications generated by the two evaluations.

The clinicians in charge of the children's care will be responsible for initiating treatment according to standard practice and national guidelines. The treatment of individual patients should be based on the results of investigations available in the hospital to which the child is admitted and should not be delayed pending the results of investigations at the reference laboratory.

10.9.1.3 Surveillance function

The number of meningitis cases identified in sentinel hospitals will be monitored at regular intervals (at least quarterly) throughout the pilot programme. If the number of cases, either in vaccinated or unvaccinated children, is significantly above that seen in previous intervals, the relevant in-country authorities (to be specified in the country-specific protocols) will be informed and the need for additional investigation, for example using a case control study, agreed. The final decision for further investigation will take into account any additional surveillance data available in the countries.

10.9.2 Severe malaria cases, including cerebral malaria

Children admitted to sentinel hospitals with a measured fever or history of fever will be tested for malaria by RDT and/or (with RDT as a priority). Those with positive malaria tests will be managed according to national guidelines.

Any child hospitalised with an acute febrile illness and confirmed to have *P falciparum* infection will be considered a hospitalized malaria case.

Cerebral malaria will be defined as children with a positive malaria test result and impaired consciousness (Glasgow coma score <11 in children ≥ 2 years of age or a Blantyre coma score <3 in

children <2 years of age). If there is a history of seizure, the coma needs to persist for more than 30 minutes after the seizure. Other causes of coma (e.g. hypoglycaemia, bacterial meningitis) should be excluded.

10.10 Study size

Assuming a meningitis rate of 0.040% cases per year, a study with 12 areas each in the evaluation and comparator areas, and an annual birth cohort of 4,000 children in each of the evaluation and comparator areas, would have 80% power, across the three countries, to detect a 2.6-fold increase in risk. This sample size was obtained using the formula from Hayes and Bennet[25] with an intra-class correlation (K) of 0.4. This value of K means that the observed rate of meningitis may range from approximately 1/12,500 to 1/1,390 with a mean rate on of 1 /2500. In the Phase 3 trial there was 1 case from 2974 subjects (0.035%) in the control area and a relative risk of 8 to 10, depending on the follow-up.

The same sample size would provide 80% power to detect a 1.7-fold increase in the risk of cerebral malaria, assuming a baseline rate of 0.20% and an intra-class correlation (K) of 0.3. Cerebral malaria is expected to be more common than meningitis. In the Phase 3 trial, there were 6 cases from 2974 subjects (0.06%) in the control arm and a relative risk of about 2.

For the evaluation described in this protocol, approximately 360,000 children per year will be eligible for vaccination with RTS,S/AS01 in the three countries, with a subset of 48,000 per year within the population catchment areas of the sentinel hospitals (Sentinel Hospital level). Table 7 shows the empirical power to detect at least a given number of events according to the true risk and the population size and assuming 90% vaccine coverage. At the sentinel hospital level there would be more than 80% power to detect 1 or more occurrences of a rare event if the true risk is 1 per 10,000 subjects. There is more than 80% power to detect one or more occurrences of rare events in the whole MVIP if the risk is 1/100,000. The power to detect rare events of 1/1,000,000 is low even across the MVIP. The empirical power was estimated using Monte Carlo simulations of 100,000 trials with the given sample size and true probability level.

Table 7: Empirical power to detect rare events

Risk	Observed events				
	≥1	≥2	≥3	≥4	≥5
Sentinel Hospitals (Approximately 108,833 children vaccinated)					
1/10,000	100%	100%	100%	99%	98%
1/100,000	66%	29%	10%	2%	1%
1/1.000,000	10%	1%	0%	0%	0%
ALL MVPE areas (Approximately 816,000 children vaccinated)					
1/10,000	100%	100%	100%	100%	100%
1/100,000	100%	100%	99%	96%	91%
1/1,000,000	56%	20%	5%	1%	0%

10.11 Data management

Information from sentinel hospitals will be captured using electronic devices. Details of the system will be agreed with the research partners. A common database will be set up and information from the different countries harmonized and compiled monthly. Further information on the flow of safety data is given in section 13.2.

10.12 Data analysis

(see SAP)

Children will not be assigned individual identifiers at the time of vaccination and there will be no systematic linkage between records of children admitted to participating hospitals and records of children vaccinated with RTS,S/AS01 or any other vaccine. The effect of RTS,S/AS01 will therefore be assessed by comparing incidence in vaccine-eligible age groups, in populations where SMC was introduced and populations in comparator areas. Effects will be measured in terms of the incidence rate ratio (*the relative increase or decrease in incidence of the outcome due to introduction of RTS,S vaccine, in the age group of children eligible to receive the vaccine)* and the incidence rate difference (*the number of cases averted (or added) as a result of RTSS vaccine being introduced into an area, in the age groups of children eligible for the vaccine, expressed per 1000 child years or other suitable units)*.

As a secondary analysis, rate ratios will also be estimated in children known to have received DTP3.

For mortality and severe malaria, effects will be estimated separately in each country, and averaged over the three countries. For meningitis and for cerebral malaria, the main analysis will be pooled across the three countries. Final analysis will be done after month 46 has been reached in all three countries. However, during the study incidence rates of the main outcomes will be monitored, and an analysis of the main safety outcomes and mortality, will be done when sufficient events have accrued for the analysis to have adequate power. Based on predicted rates of mortality and meningitis this is anticipated to be at about 24 months after start of vaccination.

As for other routinely administered vaccines, routine systems will record doses of RTS,S/AS01 on child-held health cards. Information on doses of RTS,S/AS01 received, and their timing, will be recorded for all admissions, along with the source of information (child health card, verbal report or other). When vaccination information is collected through verbal recall, the caregiver/mother will be asked about each vaccine (per country-specific EPI guidelines) and the number of doses, with detailed prompts characterizing the vaccines to enhance the quality of the recall (e.g., describing oral polio vaccine as bitter drops; etc.).

Hospital staff in the sentinel hospitals will also participate in the enhanced pharmacovigilance supported by the pilot implementation activities and report any suspected AEFI.

10.13 Quality control

Compliance with the treatment algorithm (number of cases presenting, completeness of clinical data, number requiring lumbar puncture, number with CSF result, number with samples received by reference laboratory) will be monitored monthly for each hospital and for each of the evaluation and comparator areas throughout the preparation and evaluation period.

Completeness of the hospital surveillance will be checked during the daily ward rounds, at which time every admission in the target age group should have had a hospital surveillance form completed, and at periodic visits by the clinical surveillance co-ordinator of the in-country evaluation partners.

10.14 Limitation of the research methods

Sentinel hospitals are likely to be a better-performing minority of the available hospitals and other health facilities, but they tend to serve a higher proportion of urban-dwelling, and possibly therefore less-poor, patients than are typical of the entire study population. Children presenting to hospitals are likely therefore to under-represent those with poor access to hospitals who may also be at greater risk of adverse outcomes. The hospital surveillance may therefore tend to under-estimate rates of severe disease. Rates also depend on distance from hospital and other factor affecting access to the hospitals, and the availability of alternative health facilities in the neighbourhood where patients can go. Estimates of rates and rate differences are therefore inevitably context-specific.

Even well-functioning routine health information systems face challenges with the completeness of routine data. Automated data monitoring routines will be developed to provide feedback to the evaluation team, at all levels, and to front-line health staff, so that deficiencies can be identified and remedial action taken as necessary.

The identification of vaccination status in admitted children will be a critical step. However, in the majority of sentinel hospitals it is likely that vaccination data will be available only on the child's health and vaccination card. These will have been modified in implementation areas to document doses of RTS,S/AS01 (section 7.6.1). Carers will be encouraged to carry the card to all contacts with the health services, per routine practice. Where the card is not available at the time of admission, carer's and their families will be encouraged to make the card available before the child's discharge. In the absence of the health card, immunization information will be collected via verbal recall.

Enumeration of the catchment population and the number of children who have been vaccinated is challenging given the scale of the MVIP, the absence of functional routine community-based data systems and availability of digitised catchment areas. The total populations will be estimated as described in section 9.3.

Contamination is a risk to any cluster-randomised approach. Provided the normal residence location of hospital patients can be mapped, sensitivity analysis can be used to this to understand the potential effects of contamination, by comparing results after excluding events located near the cluster boundaries.

10.15 Other aspects

The MVIP will encourage and support adherence to national treatment (and investigation) guidelines. It is accepted that these may vary across the countries. Nevertheless, in addition to country-specific analyses, the potential to pool data for analysis across the countries will be evaluated.

At country level, safety data will be accrued from the systematic reporting from the sentinel hospitals and spontaneous reports from the Adverse Events Following Immunisation (AEFI) system from both the MVIP and the GSK-led Phase 4 study. These data will initially be reviewed by the country MVIP co-ordination group whose composition will include representation from the National AEFI Review Committee (ARC), EPI, NMCP, NRA and the local research groups running the evaluation, with support from the country's WHO and PATH MVIP staff. Safety data from across the three pilot countries as well as data from the GSK-led Phase 4 study will be reviewed by the Data and Safety Monitoring Board (DSMB). The DSMB will monitor the data quality indicators on a quarterly basis, with statistical analyses presented as described in the SAP.

Safety concerns identified at country level will be reviewed by the DSMB and if confirmed will be escalated to the Programme Advisory Group (PAG). Country data reported to and reviewed by the DSMB will be available to the respective NRAs. The information will also be communicated to GSK so that identified safety signals can be evaluated in the context of all available safety information. GSK and WHO will communicate to the other party the result of their evaluations. The DSMB and PAG will agree a course of action to recommend to WHO's Programme Leadership Team and this will be communicated to the national co-ordinating groups, including the NRAs, and others as appropriate.

11 Research Methods for Feasibility Evaluation

11.1 Study design

The feasibility of delivering RTS,S/AS01 according to the recommended schedule will be evaluated through a combination of approaches. Malaria vaccine coverage will serve as the primary quantitative outcome measure for both programmatic feasibility and the community's acceptance of the vaccine and is described in this protocol.

Secondly, a programmatic assessment tool, such as WHO's Post Introduction Evaluation (PIE) tool, will examine the RTS,S/AS01 vaccination programme's operations with a view to improving the delivery of RTS,S/AS01. The PIE (or equivalent, WHO-recommended) tool will be adapted for the malaria vaccine pilot implementation and used 6 to 12 months after introduction of the vaccine in each country. This will evaluate performance in relation to pre-introduction planning, vaccine storage and wastage, logistics of administering the vaccine, and community receptiveness (amongst others).

Thirdly, a longitudinal, qualitative assessment, to be described in a separate protocol, will include exploration of any behaviour change, providing a contextual narrative and informing an understanding of the reasons that the quantitative estimates are what they are. The qualitative assessments will be implemented in all countries to provide insights as to whether and why behaviours, such as treatment seeking for febrile children, use of malaria prevention measures, EPI vaccination, etc., change with the introduction of RTS,S/AS01. The qualitative evaluation will complement the quantitative data gathered during representative household cluster surveys and will be described in a separate protocol.

Finally, these feasibility studies will be complemented by work, under a separate study protocol, to cost the set up and maintenance of vaccine delivery.

The primary assessment of feasibility will be based on repeated household surveys. Estimates of the coverage and timeliness of the first 3 doses and of the fourth dose of RTS,S/AS01 will be documented through two household surveys at the mid-line and end-line of the programme, respectively. These surveys, and a pre-implementation baseline household survey, will also generate estimates of the coverage of routine EPI vaccines, the coverage and utilization of recommended malaria control measures (e.g. ITN/LLIN, IRS), routine vitamin A and anti-helminth treatment, and document patterns of health-seeking behaviour for febrile children. Nutritional status through MUAC may also be measured. This will allow assessment of secondary objectives relating to the effect of RTS,S/AS01 introduction on the coverage of important preventive health interventions and care-seeking behaviour. The surveys may enable examination of the effect of strategies to optimise coverage of the fourth dose, and whether RTS,S/AS01 introduction influences drop-out rates for routine vaccinations (and therefore the number of fully vaccinated children). Data on the effect of strategies to boost coverage of the 4th dose will also be generated by the routine administrative systems (section 11.1.1).

11.1.1 Approaches to estimating the coverage of RTS,S/AS01

The coverage of RTS,S/AS01 will be estimated using three, complementary approaches:

(i) Routine, facility-based administrative coverage data, reported monthly.

(ii) A specially established or strengthened vaccination registry, potentially employing e-health and other forward-looking approaches, tailored to country needs, and with a focus on sustainability beyond the pilots. Any such innovations in vaccine registries will be balanced between implementation and comparison areas.

(iii) EPI cluster-sample household surveys, conducted thrice during the programme in order to provide representative community estimates of RTS,S/AS01 coverage (in the second and third surveys), along with coverage estimates for other EPI vaccines, for recommended malaria prevention and control measures, and for other childhood public health interventions of interest. Standard questions from the currently-recommended Malaria Indicator Surveys (MIS), Multiple Indicator Cluster Surveys (MICS) or Demographic and Health Surveys (DHS) will be used.

In this protocol we only briefly describe the routine administrative approach to estimating coverage, and the PIE surveys; these will be described in more detail in the country-specific RTS,S/AS01 Implementation Guidelines, to be developed by the MoH with support from WHO and partners. Separate protocols will be developed for work on vaccination registries and for the qualitative, behaviour change studies. This protocol focuses on the EPI cluster surveys.

The three approaches to estimate coverage each have pros and cons. Routine facility data should be reported from all vaccinating health facilities, but reporting may be incomplete. As this is a standard component of EPI monitoring, and therefore entirely managed by the MoH, it may be beyond the control of the evaluation partners engaged in the MVPE. Estimating the denominator may also be problematic: each facility estimates the coverage of each dose by dividing the number of doses delivered by an estimate of the proportion of the facility's catchment population eligible for that dose. Errors, especially in the estimation of the denominator, may lead to erroneous coverage estimates for individual facilities. For example, if children from outside the facility's official catchment area tend to receive their vaccinations at the health facility the coverage estimate may exceed 100%. At district level, movement of children between facilities and estimation of an individual facility's catchment population are less likely to result in biased coverage estimates as the number of children vaccinated with each dose of each antigen are compiled and the estimated population is that of the whole district.

Many countries have a facility-based vaccination register. Each child from the catchment population who is eligible for vaccination has a row in the register, capturing key demographic data and recording the dates of at least some of the vaccinations administered. These manual registers should enable coverage estimation of routine vaccinations and facilitate follow-up of children late for expected doses, but are cumbersome to use and frequently unreliable. Electronic vaccination registers have the potential to enhance the utility of this approach but are complicated and costly to establish.

Approach to estimating	**Pros**	**Cons**

coverage		
Routine 'administrative' data	- Should be available from every vaccination clinic - Regular reporting (monthly)	- Incomplete reporting - Technical problem of denominator estimation - Beyond the control of Evaluation partner
Electronic vaccination register	- Information captured on all children in a catchment area - Data easily retrieved and summarised	- Complicated and costly to establish - Likely to be available only in limited areas
Representative household surveys	- Accepted methodology to generate standard, internationally-accepted indicators	- Generates snapshot estimates of coverage at some point in the past - Captures data for only a sample of the population - Costly

Several well-established nationally-representative household surveys use standardised approaches to generate estimates of key health-related parameters, including vaccination coverage. These have the benefit of generating standardised indicators (e.g. the proportion of children aged 12-23 months who have been vaccinated against measles by the age of 12 months) which can be compared from one setting to another or in the same setting over time. The surveys are costly to conduct and provide only a snapshot of coverage at some time in the past. In the context of the MVPE, they will be less useful than administrative coverage estimates to determine the need for timely campaigns or other efforts to raise coverage e.g. of the fourth dose, though can provide a means to evaluate the effects of such efforts.

The pilot implementation will use a combination of approaches to document coverage and to identify, in a timely way, the need to intensify efforts to maximise coverage.

11.2 Setting

11.2.1 Timing of household surveys

A baseline household survey will be conducted in each country before or soon after the start of vaccinations, to provide data on the prevalence of malaria infection and coverage of EPI vaccines, in both intervention and comparator areas , before RTS,S/AS01 introduction. Follow-up surveys conducted approximately 18 and 30 months after the start of RTS,S/AS01 vaccination in intervention and comparator areas, will estimate the coverage of the standard EPI vaccines and, in intervention areas, the coverage of the primary series of RTS,S/AS01 (in the 18-month survey) and of the primary series and the fourth dose of RTS,S/AS01 (in the 30-month survey).

Guidance on the conduct of household surveys is available as follows:

DHS: http://dhsprogram.com/What-We-Do/Survey-Types/DHS.cfm
MIS: www.malariasurveys.org/toolkit.cfm
MICS: http://mics.unicef.org/

Each is used to generate nationally or sub-nationally representative estimates of key indicators and powered to generate estimates with precision at the first subnational administrative level (e.g. regions).

The choice of survey tool will be guided by any plans to conduct any of these surveys in the participating countries at the same time as the pilot implementation's household surveys. Where possible, the programme will work with the national survey designers to oversample the areas in which the MVPE is operating in order to optimise efficiency, avoid repeated interviews of some households and to contribute to an improved understanding of the national indicators. Where key data (e.g. on vaccinations or use of non-vaccine preventive interventions) are not included in a scheduled survey (see table 8) the relevant module(s) from the DHS survey will be incorporated.

It will be necessary to find out how well caregivers are able to recall whether their child has received the malaria vaccine and the number of doses. Surveys will rely on caregiver recall to establish vaccination history for children who do not have a card or home-based record. Sub-studies should be planned, nested within the midline survey or separately before the survey, to compare vaccination histories from recall, home-based record and the vaccination register in the clinic.

11.2.2 Survey population

Surveys will be carried out in a sample of households from implementation and comparison areas. Four groups of ~25 households (survey "clusters" or primary sampling units, PSUs) will be selected from each implementation and comparison cluster, such that each household in a PSU has an equal probability of being included in the sample. New samples of households will be drawn for each of the surveys. The same sampling methods as used in standardised national surveys (DHS, MIS, MICS) will be used to enhance comparability of the findings and interpretation of the external validity of the evaluation of the RTS,S/AS01 pilot implementation.

The surveys will include a representative sample of households. A typical approach would be a two-stage cluster design as described below, but this may be varied or adapted, provided a probability sampling approach is used.

In the first stage, enumeration areas (EAs) are selected with probability of selection proportional to the estimated population size of the EA. Shortly before the survey, a mapping team will visit the EA and identify all households in the EA. A household will be defined as a group of people who eat meals together and/or who acknowledge the same individual as head of their household. This list of households will serve as the sampling frame for that EA. Mapping teams may record whether any children <5 years of age live in each household, and the sampling frame could then draw only from those houses with the target population. In the second stage of the cluster design, a fixed number of households are systematically or randomly selected from the sampling frame ensuring that each household has an equal probability of selection. The selection of households will occur before the survey team visits the EA to ensure an unbiased sample. On the day of the survey, interviewers visit each of the selected households and questions the primary caretakers of all children under 5 years of age. All eligible children in a household should be included. If any primary caretakers of eligible children or the eligible children themselves are not present at the first visit, a revisit will be planned. To minimize the introduction of bias, no substitute household will be included if the owner is repeatedly absent or does not wish to participate to ensure the

representativeness of the selected sample. The supervisor will visit all households where people are reportedly absent, as a quality control measure. Prior to the day of the survey, included villages may be visited and an invitation letter left in each of the selected households. Both village and sub-village leaders will be briefed about the surveys.

All consenting primary caretakers/mothers of children aged 5-48 months will be interviewed and data collected on contextual factors (for example, exclusive breast feeding, use of insecticide-treated nets, socio-economic status, access to health facilities) as well as receipt of EPI vaccines and vitamin A. An interview will be conducted for each eligible child, thus some mothers may be asked interviewed more than once. The second household survey may be restricted to children aged 12-23 months, the target group for the assessment of coverage of RTS,S/AS01 doses 1-3, depending on the duration of implementation of dose 4 and any other local considerations.

11.3 Variables

The quantitative variables included in the analysis of feasibility will be taken from standard household survey questionnaires, summarised in table 8 and presented in annex 13. Data on vaccinations are not routinely collected in the MIS, and data on non-vaccine preventive interventions are only collected in the DHS. For these sections the DHS questions have been added to the MIS and MICS, as needed.

Table 8: Summary of relevant questions in standardised surveys

	DHS[4]	**MIS**[5]	**MICS 2017**[6]
Household Module			
Demographic data	Region & District Cluster number & Interview Date Household number Household members (to identify children in target age range and their carers) & educational status		
Wealth quintile (socio-economic) score	Q142 (floor type), Q143 (roof type), Q144 (wall type), 117, 119, 123 (household assets)	Q131 (floor), 132 (roof), 133 (walls), 108,110, 112-116 (household assets)	Questions HC4 (floor), HC5 (roof), HC6 (walls), HC7 to 19 (household assets)
Malaria control	Q125 & 126 (IRS) Q127-138 (ITNs)	Q117-118 (IRS), 119 to -130 (ITN)	IR1 IR2 (IRS) TN1 to TN16 (ITNs)
Maternal Module			
Mother's/carer's age & education	Q105, 107-111	Q102, 104-106, 108 Q111-112 (malaria messages)	WB1-7
Birth history questions (HHS2 & 3 only)	Q201-223	Q201-227	BH1-BH11
IPTp	Q423-425	Q301-306	MN16MN18

[4] See http://dhsprogram.com/publications/publication-dhsq7-dhs-questionnaires-and-manuals.cfm,

[5] See http://www.malariasurveys.org/toolkitfiles/02%20MIS%20Package_Household_Questionnaire.pdf,

[6] See www.malariasurveys.org/toolkit.cfm,

Child Health Module			
Vaccination dates	Q501-524A	*From DHS questionnaire*	IM1-IM28
Non-vaccine preventive interventions	Q605-607	*From DHS questionnaire*	
Health-seeking behaviour (HSB)	Q608, 610 to 614(diarrhoea) Q618 & Q619 (fever) Q526 (blood test for fever) Q620-621 (cough) : 624 625, 627, 628 HSB for fever &/or cough	Q404-405 (fever & blood test), 406 to 410 (HSB)	CA1, CA5, CA6 (diarrhoea) CA14, CA15, (fever) CA 16, 17 (cough), 20, 21 (HSB)
Treatment	Q 629 to 645	Q411-428	CA22, 23, 25 - 29B (malaria treatment)

A photograph of the health card may be taken and stored with the child's CRF to facilitate validation of vaccinations received and dates. Where no health card is available the information will be solicited from the caregiver (no dates) and documented as such. When vaccination information is collected through maternal recall, the caregiver/mother will be asked about each vaccine (per country-specific EPI guidelines) and the number of doses, with detailed prompts characterizing the vaccines to enhance the quality of the recall (e.g., describing oral polio vaccine as bitter drops; etc.). A sample of children with the health card available may be selected for the assessment of the verbal recall by the caregiver to enable the comparison between the written record and the recall and, therefore, allow for the validation of the verbal recall in this specific population. This information will be useful for estimating uncertainty of the vaccination coverage when the written records are supplemented by verbal recall. Additional information on the limited birth history (per DHS methodology) may be collected to estimate childhood mortality in the survey cluster, to serve as a source of validation for the impact objective.

Additionally, finger prick blood samples and measurements of the middle upper arm circumference (MUAC) will be collected in the first household survey to enable detection of *P. falciparum* infection using Rapid Diagnostic and assess the baseline nutritional status. Where the results of the malaria RDT are positive, antimalarial treatment will be offered in accordance with the national guidelines and national IRB requirements. Where the results of the MUAC indication undernutrition, referral to the nearest health facility will be offered in accordance with the national guidelines and national IRB requirements.

11.4 Data sources

The information will come from the Household Surveys.

11.5 Study size

A sample size of 100 houses per cluster will estimate the cluster-specific coverage of RTS,S/AS01 to within 10% (i.e. 95% CI from 40 to 60%) using a conservative estimate of 50% coverage and a high response rate above 95% in each cluster. Assuming a design effect of 1.5 between clusters, the overall precision in RTS,S/AS01 and coverage estimates of other vaccines over the pilot programme's implementation and comparison areas will be 2% (i.e. 95%CI 48% to 52%) in each country. The second household survey may be powered to generate coverage estimates in the evaluation vs. comparator areas, rather than in each cluster, to within ±2% of the true value.

11.6 Data management

Data will be captured electronically according to the standard approach in each country. Details of the system will be agreed with the research partners and presented in country-specific protocols. Information from the different countries will be harmonized and compiled into a single database.

11.7 Data analysis

The prevalence and corresponding 95% confidence intervals will be estimated for the different indicators, taking into account the clustered nature of the survey data. Descriptive statistics will describe the timeliness of vaccinations and breakdown key indicators (e.g., vaccine coverage) by gender. Comparison of the indicators between implementation and comparison areas will be based on the confidence intervals.

11.8 Quality control

Standard approaches to quality control will be implemented as is usually done by the DHS, MIS and/or MICS programmes in each country. Repeat and accompanied household interviews (as described in section 9.8), including in relation to the selection of households in the community, and in conjunction with internal consistency and logic checks of survey question responses, will assure the quality of household survey data. The CRO will review a 5% sample of informed consent forms.

11.9 Limitation of the research methods

Accepted approaches to selection of a representative sample of households will be used. Nevertheless, given the necessarily low household sampling fraction, it is possible that inaccurate estimates of the various parameters may be generated within individual clusters. This risk is ameliorated by the number of areas included in the pilot programme which should ensure overall robust parameter estimates in the evaluation and comparator areas.

11.10 Other aspects

None

12 Protection of human subjects

12.1 Regulatory and ethical considerations, including the informed consent process

The evaluation will be conducted in accordance with all applicable study participant privacy requirements and the guiding principles of the Declaration of Helsinki.

WHO will obtain favourable opinion/approval to conduct the evaluation prior to a site initiating study-related activities in any country, according to local requirements, or will document that neither a favourable opinion nor an approval to conduct the study is needed.

Implementation of the vaccine will be done by the Ministry of Health. Consent for administration of the vaccine will be implied by carers bringing their children to vaccination clinics and accepting the malaria vaccine. Individual written informed consent will not be sought for the administration of RTS,S/AS01 as (a) this is not standard practice when a new licensed vaccine is introduced; (b) the scale of the programme would make quality assurance of formal informed consent difficult to assure; and (c) the process of seeking consent would detract from the real-life nature of the programme and likely undermine the evaluation of feasibility and, as a result, impact. Signed consent will be sought from a parent or legal guardian of children who participate in household surveys, for verbal autopsies, and for the use of hospital data for research.

This master protocol will be submitted to the EMA, WHO and relevant national and institutional review boards to seek approval of the overall design of the evaluation. The WHO review board is guided by the CIOMS guidelines. The national review boards adheres to the protocol and all applicable local regulations.

Detailed country-specific protocols will be developed, including details of when and how informed consent will be sought, and submitted for review to the same ethics committees which review this master protocol. Informed consent forms will be modelled on standard forms for the conduct of verbal autopsies (Annex 14), the capture of non-routine data in hospitals and associated sample storage and processing (Annex 15), and for the household surveys (Annex 16).

Following the joint ethical review, WHO will prepare model ICFs for the various consent-requiring activities. These will embody the applicable ICH GCP or other applicable guidelines. While it is strongly recommended that this model ICF be followed as closely as possible, the informed consent requirements in the model consent are not intended to prevent inclusion of any local requirements. Clinical judgement, local regulations and requirements will guide the final structure and content of the local version of the ICF.

The in-country lead investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated and used by the investigators must be acceptable to WHO and approved (along with the protocol, and any other necessary documentation) by the relevant IRB/IECs.

Standard approaches will be taken to ensure the confidentiality and security of the data collected as part of this evaluation.

Where formal informed consent is required, freely given, written or witnessed/ thumbprinted informed consent will be obtained from each study participant’s parent(s)/LAR(s) or an impartial witness, as locally appropriate, prior to participation in the relevant evaluation component.

During household surveys, written/thumb-printed and witnessed informed consent will be sought from the heads of households, with verbal consent sought from the carers of children in the target age range for the evaluation.

The development of village-based mortality surveillance will only proceed with the approval of the locally-relevant community and associated administrative organisations. Before a verbal autopsy is attempted, written/thumb-printed and witnessed informed consent will be sought from parents/carers of children who have died in the eligible age range.

Assessments of safety in sentinel hospitals will be based on recommended medical practise. As such, written informed consent will not be requested for the collection of blood or CSF samples for routine investigation. However written/thumb-printed and witnessed informed consent will be sought from parents/carers of children before their samples are subject to additional laboratory investigation or longer term storage.

13 Management and reporting of adverse events/adverse reactions

Serious adverse events related to the routine administration of the RTS,S vaccine will be detected through the health system's national pharmacovigilance system, strengthened with support from the MVIP, and through the sentinel surveillance hospitals. Community-based mortality surveillance will capture fatal events and flag any which are considered possibly related to administration of RTS,S/AS01, or any other vaccine or medical intervention.

Standard medical case management will be provided for patients presenting with suspected serious adverse events at health facilities. In addition, at sentinel hospitals, a clinical algorithm will guide the systematic investigation and data capture for admitted children and support their management according to national guidelines.

Any child diagnosed with non-fatal meningitis or cerebral malaria will be invited to follow-up visits as described in section 10.3 to characterize the event further.

The local Principal Investigator will be responsible during the study for the detection and documentation of SAEs associated with study procedures. As the evaluation is observational, SAE reporting associated with administration of vaccines is not the responsibility of the PI, but will be reported through the health system's national pharmacovigilance system. No thresholds will be pre-specified for halting the programme on the grounds of safety concerns but data will be reviewed regularly at the local (monthly), national (quarterly) and international (6 monthly) level. Concerns at – or between - any of these reviews will be escalated and the Programme Advisory Group convened if the Data Safety and Monitoring Board recommends termination of the pilot programme.

13.1 Safety definitions

See also section 10.4.

13.1.1 Definition of an adverse event

An adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. If not rapidly and effectively dealt with, AEFIs can undermine confidence in a vaccine and have dramatic consequences for immunization coverage and disease incidence.

Adverse events will be routinely collected and reviewed during the MVPE through the health system's strengthened AEFI surveillance (for all vaccines), in place prior to RTS,S/AS01 administration.

13.1.2 Definition of a serious adverse event

Please refer to section 10.4.9.

13.2 Safety reporting

Safety reporting will comprise two main components:

(i) Data on AEFI, identified by the strengthened routine pharmacovigilance in all health facilities in the pilot implementation area. Reporting will be the responsibility of the health care system, under national supervision from the immunization programme and regulatory authority.

(ii) Information from the eight sentinel hospitals per country, focussed on meningitis and cerebral malaria. These data may flow through a specially augmented routine health information system or through a parallel, purpose-made reporting system. Details will be presented in country-specific protocols. In each case, an evaluation partner will be charged with assuring the completeness and accuracy of the relevant data.

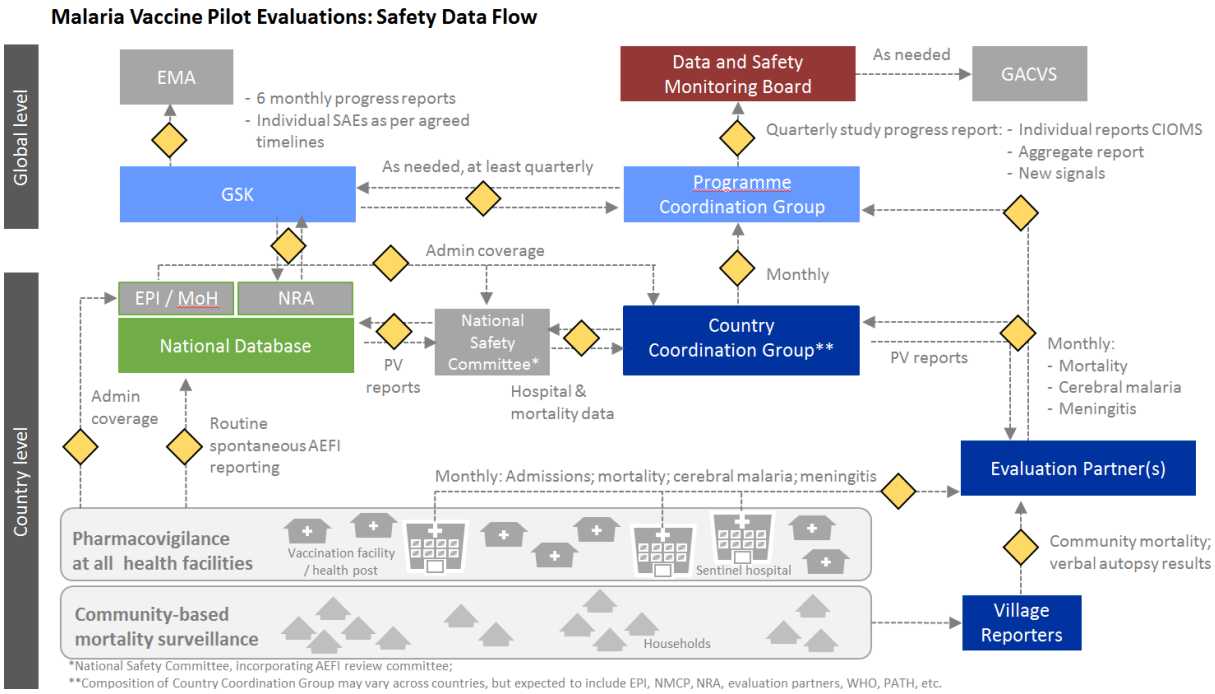
Further information on safety surveillance in sentinel hospitals is presented in Section 10. The approach to detecting and processing AEFI is described in the following sections (13.3-13.5). The safety data flow is described in section 10.15 and illustrated in Figure 5.

A national vaccine safety surveillance body will be designated by the MOH to review all serious AEFI and conduct causality assessments, according to procedures established by WHO (see section 13.3.2). This group will ensure access to AEFI reports by the immunization program and regulatory authority, and will also review data originating from the sentinel hospitals.

An information exchange mechanism will be established between the national vaccine safety surveillance body and GSK, with agreed, appropriate deadlines to communicate information according to the seriousness of the AEFI (see section 13.6). Details will be presented in country-specific protocols.

Following vaccine introduction, all AEFI, including cerebral malaria and meningitis cases, will be reported with other relevant information (e.g. numbers of vaccinations administered) on a monthly basis through the routine reporting systems. This information will be available to the pilot study's nationally designated vaccine safety surveillance body, the national Co-ordination Group, and to the DSMB, via the Programme Coordination team (figure 5).

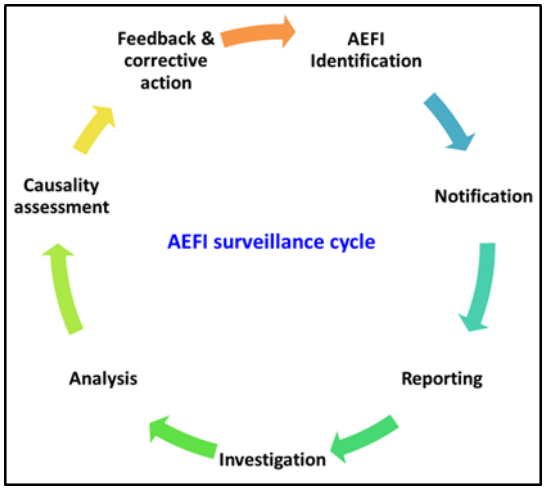
Figure 5: Overview of safety data flow



All AEFI will be reported to the agreed national body and all serious AEFI (defined in section 10.4.9) will be investigated within 24 hours (per routine systems). Investigation of non-serious AEFI will be decided on a case by case basis (see section 13.4) by the District Immunization Focal Person.

13.3 AEFI Detection

AEFI detection and reporting are the responsibility of the national pharmacovigilance system and MoH, and are described here and below (through section 13.9) for completeness. The parents/carers of immunized children, health providers at immunization facilities and other care staff in immunization facilities are most likely to recognize or detect AEFIs when they first occur. Any AEFI that is notified to or identified by a health provider will be reported to the District Immunization Focal Person (DIFP), through the fastest means possible, using a standard reporting form (see, for an example, Annex 17). The DIFP should be informed of any Serious AEFI cases (see definition in section 10.4.9) by telephone as soon as possible, followed immediately by completion and submission of the standard AEFI reporting form (Annex 17).



Health workers, including vaccination staff, from all health facilities in the pilot implementation area, will be trained to recognize and report AEFIs, and to communicate appropriately about AEFI with parents. Health care providers will be responsible for the management, including referral of AEFI, as needed.

13.4 Evaluation of initial AEFI report

The DIFP should review all AEFI reports and determine if criteria for a detailed investigation are met. If necessary the DIFP should contact the primary reporter and visit the locality of the event to interview relevant stakeholders for additional information.

AEFI reports case may be considered:

1. Not warranting detailed investigation

This applies to AEFI that are easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

The DIFP should indicate this on the reporting form and email/ fax this to the agreed authorities, including:

a. the concerned supervisor
b. the National Immunization Programme (e-mail address to be included in the country-specific protocol) and
c. the NRA (e-mail address to be included in the country-specific protocol).

The representatives of the national Immunization Programme and NRA will thus ensure AEFI reports are available to the National Safety Committee.

2. Warranting a detailed investigation.

This criterion is met for:

- Serious AEFI (see section 10.4.9)
- AEFI forming part of a cluster (defined as two or more cases of the same event, or similar events, related in time, geography, and/or the vaccine administered[30]) http://www.who.int/vaccine_safety/publications/aefi_manual.pdf
- AEFI forming part of a group of events above the expected rate/severity
- AEFI which reflect a suspected safety signal.

Other AEFI may be investigated in special cases, such as:

- AEFI that may have been caused by immunization error (e.g. bacterial abscess, severe local reaction, high fever or sepsis, toxic shock syndrome);
- Significant events of unexplained cause occurring up to 30 days after a vaccination (and that are not listed on the product label);
- Events causing significant parental or community concern.

The DIFP should discuss the initial AEFI report with any local experts and plan a detailed field investigation. Prior to initiating the investigation, the DIFP should e-mail the report (Annex 17) to the agreed authorities, as listed above.

13.5 Further investigation of an AEFI

If the DIFP considers that the investigation can be handled adequately at the local level, they should contact the appropriate member(s) of the local health care team reporting the AEFI and visit the patient together to initiate the detailed investigation. If assistance from the regional (or equivalent) or national levels is required for the investigation, the relevant people/agency should be contacted and assistance solicited. National investigations are expected to be led by a team from the national AEFI committee, supported by the National Immunization Program and the National Regulatory Authority. During field investigations, the AEFI investigation form (Annex 18) should be used as a guide to collect the relevant information.

Where an investigation is needed, more accurate information can be obtained by a single, coordinated and complete investigation than a series of partial investigations.

Specific activities in an AEFI investigation will include the following:

- Confirmation of the initial AEFI report. A unique report identifying number will be assigned, all details in the AEFI reporting form completed (in case any of them were missing when reporting) and the AEFI investigation initiated.

- Convening any local experts to plan the investigation.

- Visiting the patient, parents, immunisation clinic, reporting health worker, treating doctor, vaccine supply focal person, and others as needed. The visiting team should include local experts, the DIFP and the care provider(s) completing the initial report.

- Completion of the AEFI investigation form (Annex 18).

- Initiate collection of medical reports, a post-mortem report (if relevant), vaccine vials (if necessary, kept under cold chain conditions), logistic samples (e.g. syringes, needles, etc), and laboratory reports e.g. for CSF, serum or other biological products.

During the course of investigations the investigators should be careful to document any deficiencies in a generic way and suggest corrective measures, and not single out any individuals to blame.

Before the AEFI is attributed to any vaccine product, the investigator should rule out potential immunization errors, related to the storage, handling, reconstitution or administration of vaccines.

Obvious coincidental events should be identified, for example by reviewing hospital admissions for similar conditions during the same period and verifying their vaccination status. A rapid review of the morbidity pattern of similar conditions in previous years may suggest that the event is part of a cyclical pattern. The medical literature may also help if the estimated background incidence of various conditions is available in the published domain.

The completed AEFI investigation form (annex 18) along with the supporting documents (medical report, vaccine, logistic samples, laboratory reports, etc.) should be sent to the agreed authorities (as listed in section 13.4) within 7 days of the initial case notification. If this is not possible, at least a progress report should be made with details on when the completed report can be expected.

The District / State investigator should keep the National Immunization Program and the National Regulatory Authority, and thus the National Safety Committee, updated on the status and progress of the investigation. This is necessary as a national officer should be the spokesperson of the government to the media and the public about the investigation, if warranted.

13.5.2 Assessment of causality

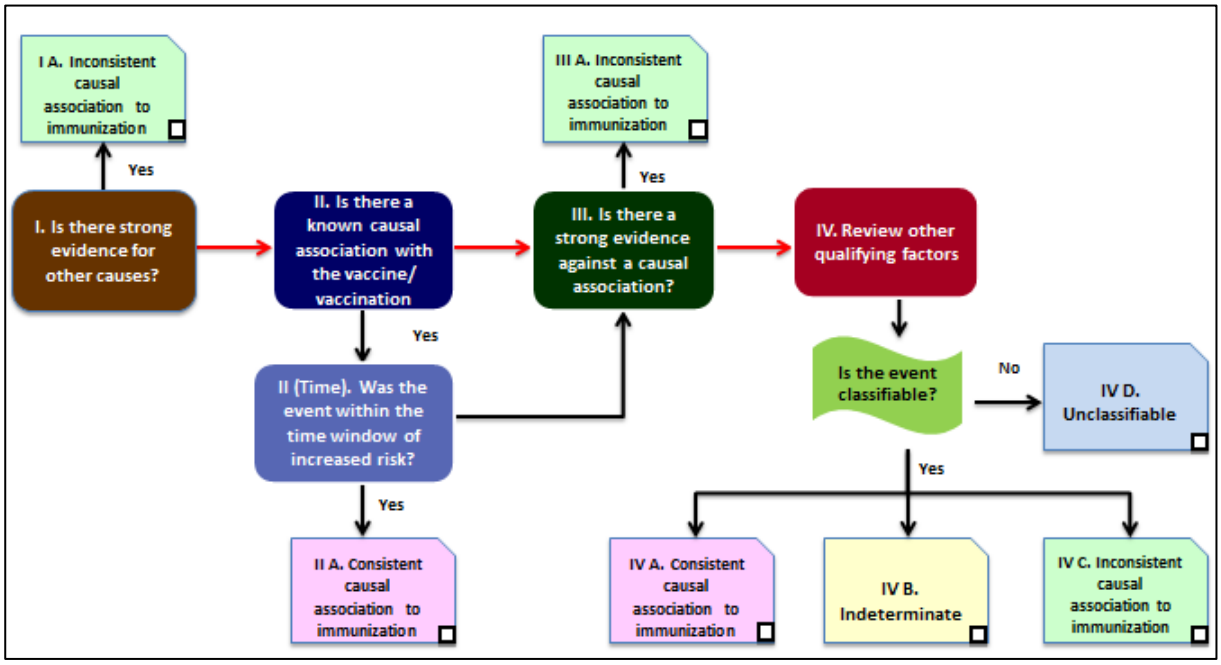
All cases warranting an investigation (see section 13.3.1 above) should have a causality assessment. Causality will be assessed according to WHO standards[32] and consider the following:

- Temporal relationship: vaccine exposure must precede the occurrence of the event.
- Availability of definitive proof that the vaccine caused the event (e.g. isolation of the BCG agent from a focus of osteomyelitis).
- Population-based evidence for causality. If there is no clear answer to the question at the population level, this will often lead to an indeterminate conclusion at the individual level.
- Biological plausibility.
- Consideration of alternative explanations (pre-existing illness, newly acquired illness, spontaneous occurrence of an event without known risk factors, emergence of a genetic disease).
- Other exposures to drugs or toxins prior to the event.
- Surgical or other trauma that leads to a complication.
- A manifestation of, or complication of, a coincidental infection that was present before or at the time of immunization, or was incubating, but was not apparent at the time of immunization.
- Prior evidence that the vaccine in question could cause a similar event.

An initial, preliminary, pre-investigation causality assessment will be made by the DIFP and relayed to the relevant national authorities.

Data will then be gathered, as shown in the causality assessment checklist (Annex 19), to generate the definitive causality assessment using the algorithm in figure 6:

Figure 6: WHO-recommended algorithm for AEFI causality classification



The WHO AEFI causality assessment software may be used to facilitate classification and reduce errors and is available at: http://www.who.int/vaccine_safety/causality-assessment-software-EN/en/.

13.5.2.1 Preparation for causality assessment

Prior to causality assessment, the AEFI case investigation should have been completed. All details of the case should be available, including the case report form (annex 17), the case investigation form (annex 18), the completed clinical case record, lab reports, autopsy report, details of field investigations etc..

There should be a "valid diagnosis" which is the extent to which the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease is defined.

Even with complete information the AEFI may be categorized as indeterminate due to the lack of clear evidence of a causal link, or conflicting evidence or other inconsistencies. Nevertheless, these assessments will be recorded because the reporting of more cases may lead to a stronger signal and a plausible hypothesis, or stronger refutation of any link.

13.5.2.2 AEFI Causality Assessment team

Causality assessment should be done by a national review team that:

- is independent of real or perceived conflicts of interest
- has broad expertise in the areas of infectious diseases, epidemiology, microbiology, pathology, immunology, neurology, vaccine program.

The committee will have written terms of reference (ToR).

13.5.2.3 Final Classification of AEFI Causality

The final classification will be based on the availability of adequate information (figure 7).

13.5.2.3.1 Case with adequate information for causality conclusion

A case with adequate information for causality conclusion can be classified as follows:

A. Consistent causal association with immunization

A1. Vaccine product-related reaction; or

A2. Vaccine quality defect-related reaction; or

A3. Immunization error-related reaction; or

A4. Immunization anxiety-related reaction.

B. Indeterminate

B1. The temporal relationship is consistent but there is insufficient definitive evidence that the vaccine caused the event (it may be a new vaccine-linked event). This is a potential signal and further investigation will be considered.

B2. Review of factors results in conflicting trends of consistency and inconsistency with a causal association with immunization (i.e. it may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other).

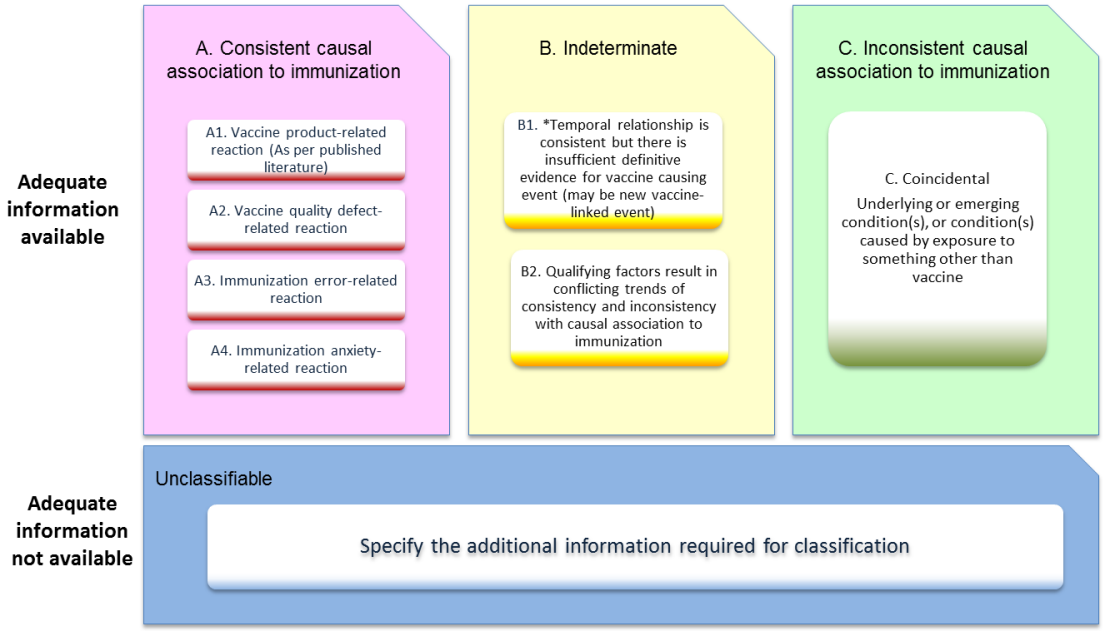
C. Inconsistent causal association with immunization (coincidental): This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine.

13.5.2.3.2 Case without adequate information for causality conclusion

This case is categorized as “unclassifiable” and requires additional information for further review of causality. The available information on unclassifiable cases will be placed in a database and reviewed periodically to check if additional information is available for classification and to perform analyses for signal identification.

The worksheet used for the causality assessment of an individual AEFI case is presented in Annex 19.

Figure 7: Summary of final causality classifications



*B1 : Potential signal and maybe considered for investigation

13.6 Follow up after causality assessment:

Responding to AEFI may involve immediate short-term activities or/and long-term follow-up. Follow-up should be based on findings of investigations, causality assessments and recommendations by the investigation/expert committees.

Proper and early treatment should be provided to patients regardless of the diagnosis. Case management and referral will vary depending on the seriousness. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. If parents return to seek medical attention, these cases should be documented and reported in the standard form. In case patients need hospitalization, a clear system for referral should be in place.

Table 9 summarises actions to be taken by the MoH upon completion of the investigation and causality assessment.

Table 9: Actions upon completion of the AEFI investigation

Type of AEFI	**Follow-up action**
Vaccine-related reactions	These will be reviewed monthly by the national safety committee and, along with data from other pilot countries, the multi-country Data Safety Monitoring Board(DSMB). The DSMB will recommend necessary actions for individual countries.
Immunization error related	Correct the cause of the error. This may mean one or more of the following: • Changing logistics for supply of the vaccine • Changing procedures at the health facility • Training of health workers • Intensifying supervision Whatever action is taken, it is important to review at a later date to check that the immunization error related events have been corrected.
Coincidental	The potential for coincidental events to harm the immunization programme through false attribution is immense. Present the evidence showing that there is no indication that the AEFI is a vaccine-related reaction or immunization-related error and that the most likely explanation is a temporal association between the event and vaccine/vaccination. Depending on the situation, for example if there is widespread belief that the event was caused by immunization, it may be useful to seek specialist communication advice, available through the Programme Coordination Team in Geneva. Further expert opinion (e.g from the DSMB) may be enlisted to reassure that the event was truly coincidental.

Depending on the nature of the event(s), the number of people affected, and community perceptions, a further investigation may be conducted.

13.6.1 Assessment of outcomes

The outcome of any SAE reported during the entire study will be assessed as one of the following:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal.
- Otherwise explained.
- Lost to follow-up.

13.7 Timeframes for reporting AEFI

Prompt notification of AEFI is essential so that the ethical responsibilities towards the safety of other potential RTS,S/AS01 recipients are met. These timelines are the responsibility of the MoH. WHO will support the MoH in the strengthening of pharmacovigilance to facilitate timely reporting.

When a DIFP has been informed of an AEFI, even where minimal information is available initially, it will still be important that an initial, preliminary causality assessment is made prior to submission of the SAE. The DIFP may change his/her opinion of causality in light of follow-up information and update the AEFI information accordingly. The initial causality assessment is important as this is one of the criteria used when determining regulatory reporting requirements.

Initial reports of possibly related AEFI will be submitted to the agreed authorities (as listed in section 13.4) within 24[7] hours of receipt/awareness of the relevant information by the DIFP.

Completed AEFI Investigation Forms should be submitted to the agreed authorities (as listed in section 13.4) within 7[7] days of the original notification to the DIFP.

A definitive assessment of causality should be made within 10[7] days of the original notification to the DIFP.

14 Reporting to GSK

Information exchange with GSK Biologicals will be defined as part of the risk management plan established at the time of registration in country.

15 Contact information for reporting serious adverse events

Name	Organisation	Role	e-mail	Telephone
TBC	National Regulatory Authority	Coordination Group member	**TBC**	**TBC**
TBC	National Immunization Program	Coordination Group member	**TBC**	**TBC**
Additional rows to be added as necessary				

[7] To be reviewed in country-specific protocols in light of national standards

16 Plans for disseminating and communicating ~~study~~ evaluation results

A communication strategy will be developed and maintained during the MVIP to ensure that all relevant stakeholders are provided with relevant information. Within the participating countries we will include specific efforts to reach the following groups:

- The national population and local communities of pilot implementation areas will be informed through appropriate means (e.g. mass media, meetings of district councillors, village meetings, posters at health facilities, etc.) that RTS,S/AS01 is being introduced and evaluated. This will help ensure acceptance of the results of the evaluation.

- National policy makers, malaria and vaccination programme implementers will be directly engaged within the national co-ordination group, which is expected to meet at monthly intervals throughout the programme.

- National regulatory authorities will also be directly engaged through the national co-ordination group. In addition, they will be furnished with mutually agreed reports documenting progress and summarising safety data on a 6-monthly basis.

- National and local ethical review committees will be updated according to a mutually agreed schedule and format.

In addition, the communication strategy will include efforts to inform key stakeholders beyond the countries involved in the pilot programme about the plans, progress and results of the pilot programme:

- MoH, EPI, NMCP and other key stakeholders in other malaria endemic countries.

- Regional and global policy makers will be provided with updates by the programme's central co-ordination team at meetings of WHO's MPAC and SAGE.

- Funders of the MVIP will be kept updated on progress through a specially-convened funders forum.

- Public health funders, especially vaccine and malaria programme funders, will be updated though participation in the Funders Forum, the MPAC and SAGE meetings and / or specific efforts by the programme to provide relevant information to them.

- The research community will be informed of the MVIP through presentations at national and international meetings and publications in peer-reviewed journals.

Following good research practice guidelines , the evaluation was registered on clinicaltrials.gov, as an observational study, NCT 03806465.

Analysis of safety, impact and feasibility endpoints will be performed at the end of the evaluation as described in the Analysis Plan, at earlier time points if sufficient data have accrued to inform decision making.

A final report will be written and submitted drawing together the overall results of the MVPE but not precluding publication of country-specific reports. The publication strategy will be agreed by in-country stakeholders and the Programme's Advisory Committee.

17 References

1. World Health Organization. Malaria vaccine: WHO position paper-January 2016. *Relevé Épidémiologique Hebd. Sect. Hygiène Secrétariat Société Nations Wkly. Epidemiol. Rec. Health Sect. Secr. Leag. Nations* **91,** 33–51 (2016).
2. World Health Organization, Global Malaria Programme & World Health Organization. *World Malaria Report 2015*. (2015).
3. Agnandji, S. T. *et al.* First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. *N. Engl. J. Med.* **365,** 1863–1875 (2011).
4. RTS,S Clinical Trials Partnership *et al.* A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. *N. Engl. J. Med.* **367,** 2284–2295 (2012).
5. The RTS,S Clinical Trials Partnership (2014) The RTS. Efficacy and Safety of the RTS,S/AS01 Malaria Vaccine during 18 Months after Vaccination: A Phase 3 Randomized, Controlled Trial in Children and Young Infants at 11 African Sites. *PLoS Med* **11,** e1001685 (2014).
6. The RTS,S Clinical Trials Partnertship. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *The Lancet* (2015). doi:10.1016/S0140-6736(15)60721-8
7. Penny, M. A. *et al.* Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *Lancet Lond. Engl.* **387,** 367–375 (2016).
8. Committe for Medicinal Products for Huma Use (CHMP), European Medicines Agency. Assessment Report. Mosquirix (TM). (2015).
9. World Health Organization. Meeting of Strategic Advisory Group of Experts on Immunization (SAGE), 20-22 October 2015. (2015).
10. Malaria vaccine: WHO position paper-January 2016. *Relevé Épidémiologique Hebd. Sect. Hygiène Secrétariat Société Nations Wkly. Epidemiol. Rec. Health Sect. Secr. Leag. Nations* **91,** 33–51 (2016).
11. Decade of Vaccines Collaboration. Global Vaccine Action Plan 2011-2020. *Global Vaccine Action Plan 2011-2020* Available at: http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/. (Accessed: 15th November 2016)
12. Snow, R. W. *et al.* Assembling a geo-coded repository of malaria infection prevalence survey data in Africa 1900-2014. (2015).
13. Ivers, N. M. *et al.* Allocation techniques for balance at baseline in cluster randomized trials: a methodological review. *Trials* **13,** 120 (2012).
14. Agnandji, S. T. *et al.* Evaluation of the Safety and Immunogenicity of the RTS,S/AS01E Malaria Candidate Vaccine When Integrated in the Expanded Program of Immunization. *J. Infect. Dis.* **202,** 1076–1087 (2010).
15. Asante, K. P. *et al.* Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. *Lancet Infect. Dis.* **11,** 741–749 (2011).
16. Mkumbo, E., Hanson, C., Penfold, S., Manzi, F. & Schellenberg, J. Innovation in supervision and support of community health workers for better newborn survival in southern Tanzania. *Int. Health* **6,** 339–341 (2014).
17. World Health Organization. Verbal autopsy standards: The 2016 WHO verbal autopsy instruments. (2016). Available at www.who.int/healthinfo/statistics/verbalautopsystandards/en/
18. InterVA. InterVA-4. (2016). Available at: http://www.interva.net/.
19. Institute for Health Metrics and Evaluation. Verbal Autopsy Tools. (2016). Available at:

http://www.healthdata.org/verbal-autopsy/tools.
20. Linard, C., Gilbert, M. & Tatem, A. J. Assessing the use of global land cover data for guiding large area population distribution modelling. *Geojournal* **76,** 525–538 (2011).
21. Linard, C., Gilbert, M., Snow, R. W., Noor, A. M. & Tatem, A. J. Population Distribution, Settlement Patterns and Accessibility across Africa in 2010. *PLOS ONE* **7,** e31743 (2012).
22. Mennis, J. Dasymetric Mapping for Estimating Population in Small Areas. *Geogr. Compass* **3,** 727–745 (2009).
23. VTS. The vaccination Tracking System (VTS) - Supporting polio erradication in Nigeria. (2016). Available at: http://vts.eocng.org/.
24. Tatem, A. J. Mapping the denominator: spatial demography in the measurement of progress. *Int. Health* **6,** 153–155 (2014).
25. Hayes, R. J. & Bennett, S. Simple sample size calculation for cluster-randomized trials. *Int. J. Epidemiol.* **28,** 319–326 (1999).
26. The World Bank. Mortality Rate, infant. Available at: http://data.worldbank.org/indicator/SP.DYN.IMRT.IN?view=chart. (Accessed: 24th October 2016)
27. The World Bank. Mortality rate, under-5. Available at: http://data.worldbank.org/indicator/SH.DYN.MORT?view=chart. (Accessed: 24th October 2016)
28. World Health Organization. Managing meningitis epidemics in Africa. A quick reference guide for health authorities and health-care workers. (2015).
29. World Health Organization. Dept. of Epidemic and Pandemic Alert and Response. *WHO recommended surveillance standards.* (WHO Press, 1999).
30. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 121, 1281–1286 (2008)..
31. Amarasinghe, A., World Health Organization & Global Advisory Committee on Vaccine Safety. *Global manual on surveillance of adverse events following immunization*. (2016).
32. World Health Organization. Causality assessment of adverse event following immunization (AEFI): user manual for the revised WHO classification. (2013).

Annex 1. List of stand-alone documents

Annex Number	Document reference number	Date	Title
1		18jul18	List of standalone documents
2		04mar17	ENCePP checklist for study protocols
3		28feb17	List of investigators, including contact details
4		14jul17	DRAFT Practical Operating Guide for the Malaria Vaccine Implementation Programme
5		10jul18	Governance and coordination structure for the RTS,S/AS01 Malaria Vaccine Pilot Evaluation
6		14jul17	Community engagement in the MVIP
7	ICD-10:v2016	2014	2014 cause of death list for verbal autopsy with corresponding ICD-10 codes
8	V1.4	2016	Verbal Autopsy for children aged four weeks to 11 years
9		28feb17	Village Reporter CRF
10		18jul18	CRF for impact evaluation
11		28feb17	Vaccination Registry
12		18jul18	Sentinel hospital CRF
13		18jul18	Household survey CRF
14		14jul17	Model informed consent for verbal autopsy
15		18jul18	Model informed consent for inpatient surveillance and long-term storage of samples
16		18jul18	Model informed consent for household survey
17		28feb17	Standard AEFI reporting form
18		28feb17	AEFI investigation form
19		28feb17	AEFI causality assessment worksheet
20		14jul17	CVs of Dr Mary Hamel and Dr David Schellenberg
21		14jul17	Preliminary budget estimate

Annex 2. ENCePP checklist for study protocols

Study title:
An evaluation of the randomised pilot implementation of RTS,S/AS01 through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa

Study reference number: RTSS_PIP_28.02.2017

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[8]	☒	☐	☐	6
1.1.2 End of data collection[9]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

No interim analyses are planned.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.6.5
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	7.6.2

[8] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[9] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.6.5
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7 10.12 11.7
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7 10.12
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	13.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	7.6.5 9.2.1 10.1 11.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	7.6.3
	4.2.2 Age and sex?	☒	☐	☐	7.6.5
	4.2.3 Country of origin?	☒	☐	☐	7.5
	4.2.4 Disease/indication?	☐	☐	☒	
	4.2.5 Duration of follow-up?	☒	☐	☐	7.6.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.5 7.6.5

Comments:

Evaluation of the malaria vaccine will involve monitoring of all-cause and cause-specific mortality and cause-specific admission to sentinel hospitals.

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	11.1.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	11.1.1
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	8.4.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	7

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.2 & 9.7 8.3 & 10.12 8.4 & 11.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.9 10.14 11.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Separate protocols will be developed to evaluate cost-effectiveness and potential effects on health care utilisation

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3 9.7 10.14
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	10.14
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.10 10.14
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Detailed analytical plans, in which issues of potential confounding, biases and covariates will be addressed, will be developed during the course of the evaluation.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.2.2

Comments:

The first secondary objective of the impact analysis will analyse gender/specific mortality effects. Detailed analytical plans will include additional potential effect modifiers.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	11.1.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4 10.7 11.3
9.1.3 Covariates?	☒	☐	☐	9.4 10.7 11.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	11.1.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4 10.7 11.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4 10.7 11.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3 Annex 5
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.3 10.12 10.14

Comments:

Linkage of endpoints to vaccination status will use documented vaccination status on children's health cards.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7 10.12 11.7
10.2 Are descriptive analyses included?	☒	☐	☐	10.12 11.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5 10.10 11.5

Comments:

It is not expected to have missing data at the cluster level, e.g data on deaths and population will be available from every cluster in the evaluation.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8 10.13 11.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8, 11.8 13.2 Annex 4

Comments:

Details of data management will vary between countries and will be presented in country-specific protocols.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	10.4
12.1.2 Information bias?	☒	☐	☐	9.9, 10.14
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.9 10.14

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	9.2.3 10.5 12.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	12.1

Comments:

Section 12.1 describes the approach to ensure the necessary and appropriate EC/IRB reviews are conducted and provides reassurance that data protection will be ensured.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Amendments will be captured in section 5 and any deviations documented as the study proceeds.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: David Schellenberg

Date: 4th March 2017

Signature: 

Annex 3. List of investigators, including contact details

Investigators: Ghana

Kintampo Health Research Centre (KHRC) is the lead organisation.

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Lead for Impact module: Dr Abraham Oduro, Navrongo Health Research Centre, Research and Development Division, Ghana Health Service

Lead for Feasibility module: Prof. Col. Edwin Andrews Afari (rtd.), School of Public Health, University of Ghana

Lead for Safety module: Prof. Daniel Ansong, Malaria Research Centre/Presbyterian Hospital, Agogo

Investigators: Kenya

Centers for Disease Control and Prevention (CDC) is the lead organisation.

Coordinating Investigator : Aaron Samuels, CDC-Kenya Malaria Research Program
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Lead for Impact module: Meghna Desai, Centers for Disease Control and Prevention (CDC)

Lead for Feasibility module: Dr. Nelli Westercamp, Centers for Disease Control and Prevention (CDC)

Lead for Safety module: Dr. Samuel Akech KEMRI-Wellcome Trust Research Program (KWTRP)

Investigators: Malawi

College of Medicine, School of Public Health, University of Malawi (COM) is the lead organisation.

Coordinating Investigator : Dr. Don Pascal Mathanga , College of Medicine, P/Bag 360, Chichiri, BT 3, Malawi. Contact telephone number: (+265) 1 870 145/878 Email: dmathang@mac.medcol.mw

Lead for Impact module: Dr Victor Mwapasa, College of Medicine, School of Public Health, University of Malawi

Lead for Feasibility module: Dr Atupele Kapito-Tembo, College of Medicine, School of Public Health, University of Malawi

Lead for Safety module: Dr. Tisungane Knox Titus Mvalo, University of North Carolina Project (UNCP) – Malawi.

The country-specific protocols include the extended investigator lists by country and collaborating institutions.

Annex 4. DRAFT Practical Operating Guide for the Malaria Vaccine Implementation Programme

Pilot Introduction of the RTS,S/AS01 Malaria Vaccine into the Routine Childhood Immunization Programmes in Ghana, Kenya and Malawi

Preliminary Version 14 July, 2017

Contents

Preface

This guide is intended for use by national expanded programme on immunization (EPI) managers and stakeholders involved in the programme.

The specific objectives of this guide are:

- To inform operational aspects for the sub-national pilot introduction of the RTS,S/AS01 malaria vaccine through the national routine EPI programme as a component of the WHO-coordinated Malaria Vaccine Implementation Programme (MVIP).
- To provide up-to-date references on the technical and strategic issues related to the introduction of the RTS,S/AS01 malaria vaccine through the EPI programme as part of the MVIP.

The guide draws from Principles and Considerations for adding a vaccine to a national immunization programme. From decision to implementation and monitoring 10, the experiences of many countries that have introduced new vaccines, and other training materials for health workers and mid-level managers.[11,12]

Introduction

Malaria Disease

Malaria, a parasitic disease transmitted by the anopheles mosquito, continues to be a major cause of childhood morbidity and death, especially in sub-Saharan Africa. Children are most vulnerable, and if not treated promptly, malaria can rapidly progress from fever to death. In high transmission areas, the most common manifestation of severe malaria is severe anaemia. Effective treatment and a reliable safe blood supply are required to treat severe malaria anaemia, but too frequently these interventions are inaccessible to children living in poor or rural communities. In 2015, WHO estimated that 214 million malaria episodes caused 438,000 deaths, the vast majority in young children in sub-Saharan Africa (SSA).

Malaria Control Strategies

WHO recommends a number of tools to reduce malaria transmission, morbidity and death. Insecticide treated nets, indoor residual spray, seasonal malaria chemoprophylaxis, intermittent treatment of malaria in pregnancy or for infants, and prompt effective treatment with artemisinin containing antimalarial treatment are all effective malaria control interventions. During the prior 15 years, considerable advances have been made with these malaria control tools, resulting in marked reduction in malaria illness and death across much of Africa. However, some areas continue to have high malaria burden despite good coverage with current tools. A vaccine could be an important addition to complement the tools we have, and reduce malaria further in areas with persistently high transmission.

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[10] Principles and considerations for adding a vaccine to a national immunization programme. From decision to implementation and monitoring.

http://www.who.int/immunization/programmes_systems/policies_strategies/vaccine_intro_resources/nvi_guidelines/en/

[11] WHO Vaccine Position Papers. http://www.who.int/immunization/documents/positionpapers/en/

[12] Controlled temperature chain (CTC) publications and guidance. http://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/index1.html

Malaria Vaccine Implementation Programme (MVIP)

The MVIP is a collaborative effort, coordinated by WHO, and designed to address outstanding questions on the public health use of the RTS,S/AS01 malaria vaccine. The goal of the MVIP is to provide key information to inform and update the WHO policy recommendation on the use of the RTS,S/AS01 malaria vaccine in young children in sub Saharan Africa. The MVIP encompasses all aspects of the pilot implementation of the malaria vaccine, including:

- Vaccine implementation led by the MOH and National Immunization Programme,
- The evaluations of feasibility, impact, and safety, including the main WHO-led evaluations and the PATH-led health utilisation study and economic analyses; and
- GSK-led Phase IV studies.

The RTS,S/AS01 Malaria Vaccine

The RTS,S/AS01 malaria vaccine, also known as Mosquirix™, is currently the only candidate malaria vaccine to have received a positive regulatory scientific opinion, which was issued by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP).[13] The vaccine development spanned a 30-year process, initiated in 1987 by scientists working at GlaxoSmithKline's (GSK) laboratories. At present, no regulatory authority in the African region has licensed RTS,S/AS01 for use as a malaria vaccine.[14]

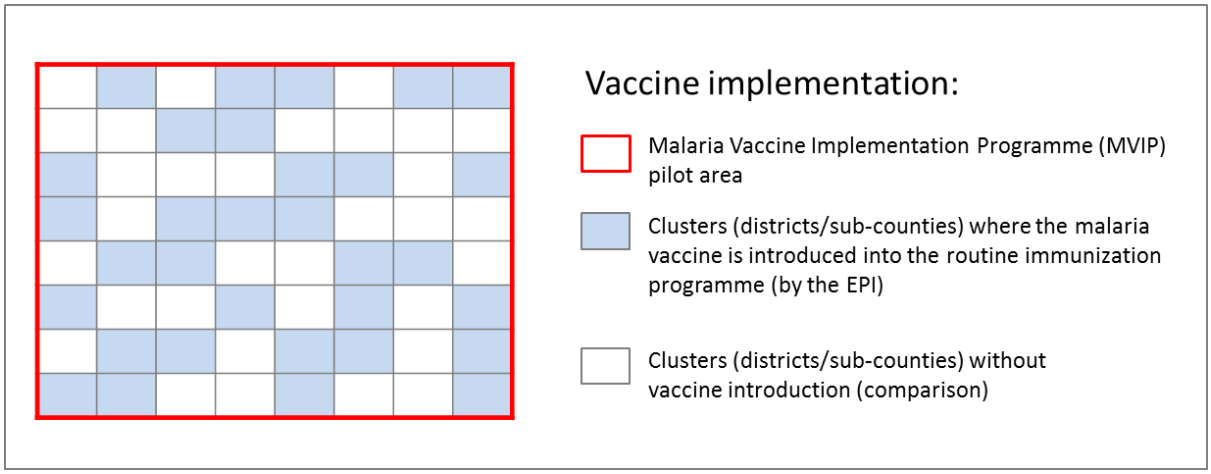
Sub-national pilot introduction of the RTS,S/AS01 malaria vaccine through the national EPI Programmes in MVIP Pilot Countries

The RTS,S/AS01 vaccine will be authorized by the respective National Regulatory Agencies (NRA) for use in the MVIP pilot areas of the three pilot countries. Vaccine introduction will be through the national EPI programmes, using the routine system for new vaccine introduction. Administrative areas, referred to as clusters, typically sub-counties or districts, will be randomized. Half of the areas will serve as vaccination and half as comparator clusters. Initially, the RTS,S/AS01 vaccine will be deployed only in the vaccination areas (see blue areas in figure below). Introduction in half of the clusters, while allowing the other half to serve as comparator areas allows a robust evaluation of feasibility, safety and impact. Cluster allocation (randomisation) will be led by the respective Ministries of Health. To facilitate this exercise, WHO will provide technical assistance using data provided by the country on agreed upon criteria to generate the list of options from which one option will be drawn at random. The selected option will be presented to the members at the country selection meeting (this will include membership from government and community leaders present as locally relevant) and messaging developed to share with stakeholders on how to best communicate the selection process and answer any questions. Following the cluster allocation process (randomization), the introduction and ongoing vaccine

[13] The RTS,S/AS01 vaccine has received a positive Scientific Opinion by EMA in accordance with Article 58 of Regulation (EC) No 726/2004 which allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with WHO, on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU). For more information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_ listing/document_listing_000157.jsp, accessed January 2016.

[14] WHO Questions and Answers on Malaria Vaccines: http://www.who.int/immunization/research/development/malaria_vaccine_qa/en/

delivery in the vaccination areas is the responsibility of the National Immunization Programme. After approximately 30 months of routine delivery in the vaccination clusters, the countries may begin delivery of the RTS,S/AS01 vaccine in the comparator clusters. The decision to expand will be that of the respective Ministries of Health, and will depend, among other things, on findings of feasibility and safety in the vaccination clusters. At the end of the MVIP evaluation, should the vaccine be recommended by WHO for broader use, every effort will be made to offer early introduction of the RTS,S/AS01 vaccine into the comparator areas.



Vaccine Characteristic and Cold Chain

The RTS,S/AS01 vaccine is a lyophilized vaccine that is reconstituted with a liquid adjuvant, AS01. RTS,S/AS01 is packaged as a two-dose vaccine, presented in two clipped vials. A Vaccine Vial Monitor (VVM) is adhered to the AS01 vial, and not to the AS01 adjuvant vial. After reconstitution, residual vaccine should be discarded after 6 hours. Storage of the vaccine is at +2°C to +8 °C for at least 3 years. Cold chain capacity assessment will occur as part of vaccine introduction planning, and the MVIP will provide support to ensure sufficient cold chain capacity to support the addition of RTS,S/AS01 to the EPI. A summary of product characteristics can be found at:

https://www.ema.europa.eu/en/documents/medicine-outside-eu/mosquirix-public-assessment-report_en.pdf

Product Characteristics: RTS,S/AS01 Malaria Vaccine

- Duration of protection: Wanes with no substantial protection after approximately 18 months after the 3rd dose of the vaccine, but efficacy is enhanced with the 4th dose and persists in the following 12 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

Vaccine safety

RTS,S/AS01 is associated with an increased risk of febrile seizures

In the large multi-country phase 3 trial, an additional safety signal of meningitis was observed rarely in children in the 5-17 month age-category who received the RTS,S/AS01vaccine. A causal relationship has not been established, and this may have been a chance finding.

A *post hoc* analysis of the same trial indicated an imbalance and potential increased risk of cerebral malaria and female mortality. These potential signals were on a background of reduced severe malaria overall and very low mortality. No deaths were associated with RTS,S/AS01 vaccination.

Post marketing surveillance is needed to assess the safety profile of the vaccine. Strengthening of routine pharmacovigilance and the establishment of sentinel hospitals to monitor for safety signals, with particular attention to those listed above, will be an important component of the pilot introduction of the vaccine.

Co-administration and multiple injections at one visit

RTS,S/AS01 can be given concomitantly with any of the following monovalent or combination vaccines: diphtheria (D), tetanus (T), whole cell pertussis (Pw), acellular pertussis (Pa), hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), oral polio (OPV), measles, yellow fever, rotavirus and pneumococcal conjugate vaccines (PCV). The co-administration of RTS,S/AS01 with PCV increases the risk of fever within 7 days post-vaccination.

Concomitant administration of rotavirus and pneumococcal conjugate vaccines with RTS,S/AS01 may reduce the antibody response to the circumsporozoite (CS) antigen of RTS,S/AS01. The impact of this observation on the level of protection induced by RTS,S/AS01 is currently unknown.

Multiple injections at one visit can be given as indicated in WHO recommendations, in particular if one cannot administer in separate limbs then WHO recommends separating the injections by at least 2.5 centimeters (an inch).[15]

It is important to avoid confusion of the RTS,S/AS01 diluent with that of other vaccines during the co-administration. The clipped vial presentation should mitigate this possibility.

WHO recommendations for RTS,S/AS01 vaccine in routine vaccination in MVIP Pilot Areas

A 4-dose schedule with routine vaccine administration beginning at 5 or 6 months of age administered in monthly doses for 3 doses, with a fourth dose provided 15-18 months after the third dose.

RTS,S/AS01 can be co-administered with other childhood vaccinations. Catch-up campaigns are not recommended as part of pilot implementation. Additional vaccination visits for the receipt of RTS,S/AS01 should be fully utilized as opportunities to provide other vaccines, vitamin A, antihelminth therapy or other nationally recommended childhood interventions that were previously missed.

Planning

A detailed planning process is underway in the three MVIP pilot countries. The target population, delivery strategy, vaccination schedule, and logistics are being carefully considered and a detailed introduction plan is under development. The introduction plan will outline all activities and steps required for the successful introduction of RTS,S/AS01 by programme component, identify government departments, institutions or external partners that are responsible for each activity, and will include a timeline and detailed budget.

Given the unique considerations for the RTS,S/AS01 vaccine pilot introduction and evaluation, it is critical that countries allow enough time for planning and implementation of all the specified introduction activities and that the introduction is not rushed. Sequencing activities in a detailed chronogram will highlight critical milestones necessary for the RTS,S/AS01 vaccine introduction to proceed smoothly.

Pilot countries are encouraged to refer to the checklist and tools contained in the WHO guide "Principles and considerations for adding a new vaccine to a national immunization programme: From decision to implementation and monitoring"[16], particularly the template for a new vaccine introduction plan and the new vaccine introduction checklist, activity list, and timeline.

[15] (SAGE meeting of April 2015 report. Session: administration of multiple injectable vaccines in a single visit, http://www.who.int/wer/2015/wer9022.pdf?ua=1)

[16] http://apps.who.int/iris/bitstream/10665/111548/1/9789241506892_eng.pdf

Microplanning

Micro-planning at the district level prior to introduction is essential. The randomized introduction of the RTS,S/AS01 vaccine presents unique challenges that will need to be anticipated and addressed. Engagement of stakeholders at all levels will be important, and clear communication and transparency about the MVIP will be needed to foster trust in the programme and the process.

Estimates of the target population will be done by the Ministries of Health with support from WHO. Naturally occurring events, such as agriculture migration or natural disasters, could influence population estimates. Seasonality could also be a factor if populations move when vaccinations are scheduled in local areas. Planning for these known seasonal migration patterns can help ensure more accurate projections. Conflict, famine, and political stability may also be localized events impacting the movement of people. Understanding if this situation is present can help inform the estimates of the target population as well.

Management of RTS,S/AS01 vaccine in local health centres should follow the same procedures as is done for any vaccine requiring continuous cold chain. A quality and recent effective vaccine management (EVM) assessment will inform if any health facilities require cold chain expansion, maintenance or strengthening in advance of RTS,S/AS01 vaccine pilot introduction.

Communication and Social Mobilization

Increasing awareness of communities through timely, complete and appropriate education and communication is the key to successful RTS,S/AS01 vaccine introduction.

The introduction of RTS,S/AS01 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,

respectively, which also require other control interventions[17]. 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 RTS,S/AS01 vaccination will be deployed at a sub-national level it will also be necessary to have IEC efforts address the potential for misunderstanding/rumours that RTS,S/AS01 vaccine introduction is an experimental research trial.

Given the safety signals for RTS,S/AS01 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.[18]

Details of the communication and social mobilization plans for the MVIP can be found in the accompanying document on communication and social mobilization.

Training

Health care staff in the MVIP pilot areas will receive specific training before introducing the RTS,S/AS01 vaccine. If prepared well, a three-day training should be sufficient to cover the necessary background information on the pilot implementation of RTS,S/AS01, the vaccine, its role in malaria control, operational issues, communication and key messages, pharmacovigilance and hands-on practice. If possible, the training for RTS,S/AS01 vaccine introduction could be included as a part of a regular annual or refresher training for health workers. Linking training with an annual micro-planning activity can also build efficiencies and allow for more integrated planning of vaccine delivery.

Service Delivery

Vaccination sessions for RTS,S/AS01 vaccine will be integrated into the routine vaccine immunization sessions. The main recording tools that are used for immunization will be adapted to include RTS,S/AS01 vaccine. At the service delivery level these include:

- Immunization register
- Tally sheet
- Immunization card or mother-child card or health passport
- Defaulter tracking system
- Vaccine stock record
- Integrated monthly report

As with other vaccines, immunization sessions should have all the necessary supplies and materials for effective delivery. Supplies include chair and table, water and soap or hand sanitizer,

[17] 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/

[18] 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)

safety boxes with closed lids, waste bags for garbage, and IEC materials. All forms and monitoring tools should be available at every vaccination session, including the vaccination logbook or register, tally sheets, vaccination cards, and AEFI forms in case of immediate reactions.

In addition to following all the basic requirements for any injectable vaccine, a few additional steps before and after are required to properly administer RTS,S/AS01 vaccine.

Safe injection practices

RTS,S/AS01 vaccine is freeze-dried and needs to be reconstituted before administration. The diluent attached to the vaccine vial must only be used. Each reconstituted vial contains 2 doses.

As with all other immunizations, RTS,S/AS01 vaccine should be delivered with good technique and following the best practices for safe injections:

- Always follow manufacturer recommendations for use, storage, and handling
- To minimize risk of injury, prepare work area so that:
- A trained vaccine administrator is on site
- Monitoring tools and safety boxes are easily accessible
- Each vaccinator has a designated safety box and can see the entrance hole when discarding needle
- Wash hands with soap and water and drip dry
- Prepare each dose immediately before administering. Do not prepare several syringes in advance
- Check the vaccine and diluent vials for condition, Vaccine vial monitor (VVM) status, and expiry date. Do not use if VVM has changed colour and indicates vaccine should not been used, packaging is punctured, torn, or damaged, or if vial contains particles or if there is discoloration
- Use a new reconstitution syringe for each vial of vaccine and diluent; Reconstitute only one vaccine vial at a time.
- After reconstitution, shake the vial gently upside down a few times, holding the neck for mixing appropriately. Do not hold the vial with the finger on the vial's septum.
- After reconstitution, immediately dispose of the reconstitution syringe in the safety box WITHOUT RECAPPING
- Record time of reconstitution on RTS,S/AS01 vaccine vial label. Use the reconstituted vaccine within 6 hours of reconstitution. Any unused reconstituted vaccine must be discarded after 6 hours.
- Using a new auto-disable syringe for each child fill the dose accurately
- DO NOT pre-fill syringes in advance – fill them only prior to each vaccine administration.
- Do not touch any part of the needle
- Inject entire content of the syringe by intramuscular injection, preferably in the deltoid muscle of the upper arm, using a perpendicular 90 degree angle

- Discard the syringe and needle directly (no recapping) into a safety box immediately after administering the vaccine
- Safety box should be a water-proof and tamper-proof container that is securely closed with only a small hole at the top large enough for syringe and needle to enter
- Do not overfill the safety box. Close the container and seal the opening when the box is ¾ full
- Keep safety boxes in a dry, safe place until they can be safely disposed
- Do not dispose of used syringe and needles in an open box or container

Adverse events following immunization (AEFI) monitoring

An adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. If not rapidly and effectively dealt with, AEFIs can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

Although an AEFI can be caused by the vaccine itself, reported AEFIs are more commonly either a coincident event that is not related to the vaccine, due to programmatic or human errors that compromise the vaccine quality, or allergic reactions to components in the vaccine.

AEFIs can be classified into 5 categories:

1. Vaccine product-related reaction
    - Caused or precipitated by inherent properties of the vaccine product
2. Vaccine quality defect-related reaction
    - Caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer
3. Immunization error-related reaction
    - Caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature, is preventable
4. Immunization anxiety-related reaction
    - Arising from anxiety about the immunization
5. Coincidental event
    - Caused by something other than the vaccine product, immunization error or immunization anxiety

The most commonly reported adverse reactions for RTS,S/AS01 vaccination were fever (27%), irritability (14%) and injection site reactions such as pain (16%) and swelling (7%). In clinical studies, the most serious adverse reaction associated with Mosquirix was febrile seizures (within 7 days post-vaccination) (0.1%).

The additional safety signals noted in the analysis from the large multi-country phase 3 trial, although causality is unknown, also needs to be monitored. These are specifically meningitis and cerebral malaria.

Monitoring and reporting of AEFI

Monitoring vaccine safety is of particular importance because RTS,S/AS01 is a new vaccine that has not been deployed in other settings. Consolidating the safety profile of the RTS,S/AS01 vaccine is an important outcome of the MVIP, and a three tiered approach is used as part of the MVIP to collect information on vaccine safety. This includes strengthening of the pharmacovigilance system, the establishment and support of sentinel hospitals in the pilot areas, and a community based mortality surveillance system. A functional pharmacovigilance system can provide the added effect of reassuring the public of a vaccine's safety, especially if effective groups opposed to vaccines for any reason initiate or perpetuate rumours of vaccine safety and spurious associations with coincident adverse events to discourage vaccination in the population.

The monitoring and reporting of AEFI should be included in the regular AEFI reporting and monitoring system. A system in place should facilitate prompt reporting and investigation of AEFIs. The NRA and the National Immunization Technical Advisory Group (NITAG) should take a proactive role in investigation of reports of serious adverse events to verify any link to vaccine and develop communication messages to address rumours. Clear procedures for what should be reported and how are necessary elements of any AEFI reporting system should be in place. Health workers will be trained on the recognition of adverse events, completion of the AEFI reporting form, and appropriate notification of supervisors and the district/county health officer, according to established protocols. Countries should ensure that vaccine adverse event monitoring is fully incorporated within the national AEFI guidelines prior to national introduction.

Supportive supervision

Once the RTS,S/AS01 vaccine is introduced, implementation should be monitored through supportive supervision, which includes "on-the-job training." Supportive supervision strengthens the capacities of health workers and improves performance; visits can be used to provide feedback, update health staff on this and other vaccinations, enhance motivation, and identify training needs.

Supervisor schedules and integrated checklist tools will be adapted to include the RTS,S/AS01 vaccine. During supervisory visits, staff should be specifically asked about vaccine coverage and any problems (supply or demand) that they face with this vaccine.

Administrative method to calculate vaccine coverage

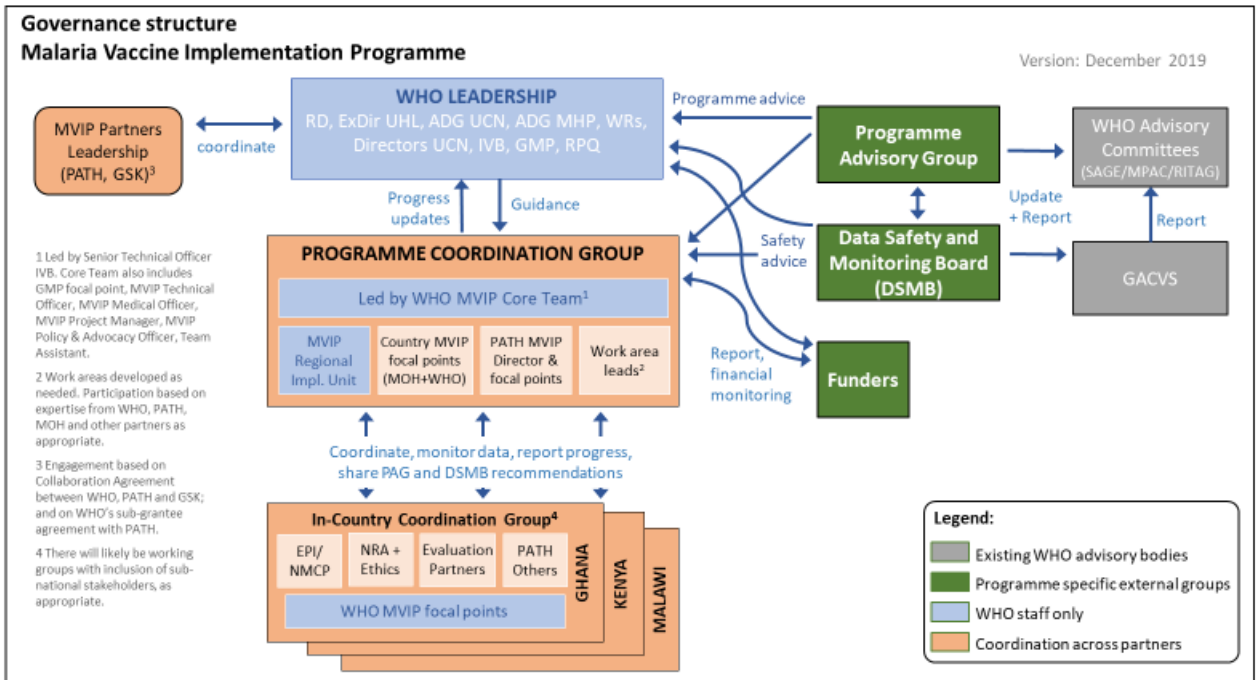
Calculating RTS,S/AS01 vaccine coverage is necessary for monitoring the impact of vaccine on a population, as well as for evaluating the performance of a vaccine programme toward meeting objectives. As with other EPI vaccines, administrative coverage will be supplemented by coverage surveys that will be conducted as part of the MVIP.

RTS,S/AS01 vaccine coverage monitoring will rely on the monthly data compilation of number of doses, dose number and age. Following established practices, the child's date of birth or age, date of vaccine administration, and the dose should be recorded in the immunization register and

on the child's home-based vaccination record (immunization card) each time a vaccine is administered.

A coverage monitoring wall chart for RTS,S/AS01 vaccination should be maintained and displayed in the health facility. This chart should include the target population of children at the health facility or catchment area, and record the number of children vaccinated per month, per dose, over time, until the target is reached.

Annex 5: Governance and coordination structure for the RTS,S/AS01 Malaria Vaccine Pilot Evaluation



Abbreviations

ADGs	Assistant Director Generals in WHO
FWC	Family, Women's and Children's health cluster
HTM	HIV, TB and Malaria cluster in WHO
AFRO	WHO Regional Office for Africa
DIRs	Directors in WHO
IVB	Department of Immunizations, vaccines and biologicals
GMP	Global Malaria Programme
CRO	Clinical Research Organization
EMP	Essential Medicines and Health Products
EPI	Expanded Programme on Immunization
GACVS	Global Advisory Committee on Vaccine Safety
MoH	Ministry of Health
MPAC	Malaria Policy Advisory Committee
NMCP	National Malaria Control Programme
NPV	National Pharmacovigilance
NRA	National Regulatory Agency
RD AFRO	Regional Director of the WHO Regional Office for Africa
SAGE	Strategic Advisory Group of Experts on immunization
WHO	World Health Organization

Entity	Function (high-level description)	Composition
Programme Leadership Team	Decision-making on design, management and implementation of the MVIP, informed by progress reports from PCT and guidance from the PAC.	WHO: Assistant Director-Generals of FWC and HTM and AFRO RD; Directors of IVB and GMP and AFRO Directors PATH leadership GSK leadership*
Programme Coordination Team	Coordinates and provides technical, managerial and administrative support to the Programme. Sets up and coordinates technical working groups Receives, processes and delivers information from countries to PLT and PAC.	Mid-senior level technical staff WHO: IVB, GMP, EMP + AFRO PATH
Country Co-ordination Group	Coordinates activities across all MVIPcomponents within a country - regulatory, vaccine implementation, evaluations -to ensure progress according to plans and protocols Reviews reports from national safety data review committee	Mid-senior level technical staff Chaired by MoH Representatives from national EPI, NMCP, evaluation partners, NPV/NRA, and others as appropriate WHO and PATH country offices focal points
Programme Advisory Group	Monitors programme activities and provides scientific, technical and programmatic advice to PLT No executive, regulatory or decision-making function. Reports to SAGE & MPAC	~10 people, including members of SAGE, MPAC, GACVS. Experts shall serve in their personal capacity.
Funders Forum	Reviews progress, including financial monitoring Advises on funding outlook Facilitates coordination of MVIP with other ongoing or	Representatives of donor organizations financially contributing to MVIP (Gavi, UNITAID, Global Fund , BMGF) Observers: key donors to immunization / malaria without direct contribution to MVIP

	future activities by funding agencies	
Data and Safety Monitoring Board	Reviews safety data from the MVPE and the GSK Phase IV study on an ongoing basis in order to monitor and rapidly identify any accumulating safety signals from across the programme. Provides updates to the GACVS Can recommend to the PLT for the pilots to be stopped or altered in the event there is evidence of harm	Experts in cerebral malaria and meningitis, as well as experts in vaccine safety Involves representatives of the safety monitoring groups in each country.

Annex 6. Community engagement in the MVIP

Engagement and sensitization of community stakeholders will be an essential component of the Malaria Vaccine Implementation Programme (MVIP). Community engagement will be important both for the vaccine introduction and implementation activities, and for the various components of the evaluation. In all efforts, the principles of the Good Participatory Practice[i] guidelines will guide efforts to ensure communities are engaged respectfully to build mutual understanding, to ensure integrity, transparency, accountability and ensure the autonomy of the community stakeholders.

Comprehensive communication plans are under development by Ministries of Health in the three MVIP pilot countries to support vaccine introduction, including plans to guide community engagement. Community engagement will be focused at all relevant levels, including at the community and district/county levels within the MVIP pilot areas. In accordance with WHO guidance on implied consent for vaccination,[ii] community engagement procedures will be designed to provide sufficient information to allow parents and caretakers to make informed decisions on whether to bring age-eligible children to clinics to receive the RTS,S/AS01 vaccine or whether to "opt-out" of RTS,S/AS01 vaccination.

Engagement within the MVIP will be informed by data-driven communications plans and strategies that emphasize interactive communication approaches. For increased effectiveness, these plans will be informed by sociocultural data collected from African communities where malaria is a major public health issue. Working with countries and in collaboration with WHO, PATH has supported literature reviews that summarized sociocultural factors influencing decisions around the use of malaria prevention tools and care seeking behavior and vaccination uptake in sub-Saharan Africa. Additionally, PATH and country partners have conducted formative research, including within the MVIP countries of Ghana, Kenya and Malawi, to understand perceptions of malaria and vaccines and how those perceptions might affect the acceptability and uptake of a malaria vaccine.[iii] Findings from the literature review and from the formative research are informing national communications and community mobilization strategies and the development of key messages.

Communication plans under development include the identification of key stakeholders, especially those groups who will constitute critical audiences for community engagement within the MVIP. Key among these groups are those who make decisions on whether to bring young children for vaccination (parents and other caregivers). Other main audiences include those who have the potential to inform vaccination decisions (including health care workers, community health workers, grandparents, religious and traditional leaders, traditional healers, local government administrators, and nongovernmental organization representatives). Health workers will receive training on how to communicate effectively with caregivers, and will be provided information so that they accurately relay information on the benefits and risks of vaccination with RTS,S.

Communication activities will address information gaps related to the RTS,S/AS01 malaria vaccine and will aim to increase understanding of the MVIP. Simple, evidence-based messages that provide information about the vaccine in the local languages will be developed. This information will include an explanation of who is the target population for vaccination and why that group; the

potential health benefits of the vaccine; the possible side effects; and simple information on how the vaccine works, what it does, and its role in the overall malaria control strategy. Messages will emphasize the partial efficacy of the vaccine (specifically, that vaccinated child will have fewer episodes of malaria, but still can become sick with malaria) and the need to continue to use malaria preventive measures, including insecticide treated bednets, and to seek care promptly for fever. Messages to community members and health workers will emphasize the need to continue to test for malaria with a diagnostic tool, even among children who have received the RTS,S/AS01 vaccine. Where possible, messages will be packaged within the context of established child welfare programs.

Communications plans and strategies for the MVIP will build on familiar practices already in use to engage communities and deliver information. Countries will have their own distinct processes for delivering health information, but familiar, interactive channels across countries include the use of gatherings called by chiefs and other senior community members (such as durbars in Ghana and barazas in Kenya), workshops, and vehicles with megaphone message-delivery.

In conclusion, the community engagement activities supported as part of the MVIP are designed to ensure that caregivers of eligible children have the necessary information to make decisions on whether to receive the RTS,S/AS01 malaria vaccine. Communication plans are being developed in the three MVIP pilot countries to ensure effective delivery of key messages that will support families to make informed decisions on vaccination with RTS,S. Activities will be conducted by MoH staff involved in the vaccination programs, and will be carried out within a timeframe that allows adequate time to address concerns and misconceptions.

[i]https://www.avac.org/good-participatorypractice

[ii]World Health Organization (WHO). (2014) Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old. WHO Press: Geneva.

[iii]Ojakaa DI, Ofware P, Machira YW, Yamo E, Collymore Y, et al. (2011) Community perceptions of malaria and vaccines in the South Coast and Busia Regions of Kenya. *Malar J* 10: 147. doi:10.1186/1475-2875-10-147.

[iv] Menaca A, Tagbor H, Adjei R, Bart-Plange C, Collymore Y, et al. (2014) Factors Likely to Affect Community Acceptance of a Malaria Vaccine in Two Districts of Ghana: A Qualitative Study. *PLoS ONE* 9(10): e109707. doi:10.1371/journal.pone.0109707.

Annex 7. 2014 cause of death list for verbal autopsy with corresponding ICD-10 codes

Source: Verbal autopsy standards. The 2014 WHO verbal autopsy instrument.[17]

Appendix 1. Column 1 contains the code for the verbal autopsy entity. Column 2 lists the related titles. Column 3 lists the ICD-10 codes that would be used if the condition labeled by column 2 were coded to ICD-10. Column 4 lists the ICD-10 categories that need to be grouped to match the content of the relevant VA entity.

Verbal autopsy code	Verbal autopsy title	ICD-10 code (to ICD)	ICD-10 codes (from ICD)
VAs-01 Infectious and parasitic diseases			
VAs-01.01	Sepsis	A41	A40-A41
VAs-01.02	Acute respiratory infection, including pneumonia	J22/J18	J00-J22
VAs-01.03	HIV/AIDS related death	B24	B20-B24
VAs-01.04	Diarrheal diseases	A09	A00-A09
VAs-01.05	Malaria	B54	B50-B54
VAs-01.06	Measles	B05	B05
VAs-01.07	Meningitis and encephalitis	G03;G04	A39; G00-G05
VAs-01.08	Tetanus **Excludes:** ***Neonatal tetanus VAs-10.05***	A35 (obstetrical A34)	A33-A35
VAs-01.09	Pulmonary tuberculosis	A16	A15-A16
VAs-01.10	Pertussis	A37	A37
VAs-01.11	Haemorrhagic fever	A99	A92-A99
VAs-01.12	Dengue fever	A90;A91	A90-A91
VAs-01.99	Unspecified infectious disease	B99	A17-A19 A20-A38; A42-A89; B00-B19; B25-B-49; B55-B99

Non-communicable diseases

Note:
This group covers all non-communicable conditions. Any infection of the systems that are listed in this section should be assigned to the suitable infectious disease category. Any maternal and perinatal condition should be assigned to the maternal and perinatal causes below.

VAs-98	Other and unspecified non-communicable disease Note: ***This group covers all non-communicable conditions that could not be assigned to another category in this section. There is a separate category for cases where the cause of death is unknown.***	R99	D55-D89; E00-E07; E15-E35; E50-E90; F00-F99; G06-G09 G10-G37; G50-G99; H00-H95; J30-J39; J47-J99; K00-K31; K35-K38 K40-K93; L00-L99; M00-M99; N00-N16; N20-N99; R00-R09 R11-R94
VAs-02 Neoplasms			
VAs-02.01	Oral neoplasms	C06	C00-C06
VAs-02.02	Digestive neoplasms	C26	C15-C26
VAs-02.03	Respiratory neoplasms	C39	C30-C39
VAs-02.04	Breast neoplasms	C50	C50
VAs-02.05	Female reproductive neoplasms	C57	C51-C58
VAs-02.06	Male reproductive neoplasms	C63	C60-C63
VAs-02.99	Other and unspecified neoplasms	C80	C07-C14 C40-C49 C60-D48

VAs-03 Nutritional and endocrine disorders			
VAs-03.01	Severe anaemia	D64	D50-D64
VAs-03.02	Severe malnutrition	E46	E40-E46
VAs-03.03	Diabetes mellitus	E14	E10-E14

VAs-04 Diseases of the circulatory system			
VAs-04.01	Acute cardiac disease	I24 (acute ischemic)	I20-I25
VAs-04.02	Stroke	I64	I60-I69
VAs-04.03	Sickle cell with crisis	D57	D57
VAs-04.99	Other and unspecified cardiac disease	I99	I00-I09 I10-I15 I26-I52 I70-I99
VAs-05 Respiratory disorders			
VAs-05.01	Chronic obstructive pulmonary disease (COPD)	J44	J40-J44
VAs-05.02	Asthma	J45 (J46)	J45-J46
VAs-06 Gastrointestinal disorders			
VAs-06.01	Acute abdomen	R10	R10
VAs-06.02	Liver cirrhosis	K74	K70-K76
VAs-07 Renal disorders			
VAs-07.01	Renal failure	N19	N17-N19
VAs-08 Mental and nervous system disorders			
VAs-08.01	Epilepsy	G40	G40-G41

VAs-09 Pregnancy-, childbirth and puerperium-related disorders			
VAs-09.01	Ectopic pregnancy	O00	O00
VAs-09.02	Abortion-related death	O06	O03-O08
VAs-09.03	Pregnancy-induced hypertension	O13 (or O15 for eclampsia)	O10-O16
VAs-09.04	Obstetric haemorrhage	O46 (ante partum) O72 (post partum)	O46; O67; O72
VAs-09.05	Obstructed labour	O66	O63-O66
VAs-09.06	Pregnancy-related sepsis	O753 (ante partum) O85 (post partum)	O85; O75.3
VAs-09.07	Anaemia of pregnancy	O99	O99.0
VAs-09.08	Ruptured uterus	O71	O71
VAs-09.99	Other and unspecified maternal cause	O05	O01-O02; O20-O45; O47-O62; O68-O70; O73-O84; O86-O99
VAs-10 Neonatal causes of death			
VAs-10.01	Prematurity	P07	P05-P07
VAs-10.02	Birth asphyxia	P21	P20-P22
VAs-10.03	Neonatal pneumonia	P23	P23-P25
VAs-10.04	Neonatal sepsis	P63	P36
VAs-10.05	Neonatal tetanus	A33	A33
VAs-10.06	Congenital malformation	Q89	Q00-Q99
VAs-10.99	Other and unspecified perinatal cause of death	P96	P00-P04; P08-P15; P26-P35; P37-P94; P96

VAs-11 Stillbirths			
VAs-11.01	Fresh stillbirth	P95	P95
VAs-11.02	Macerated stillbirth	P95	P95
VAs-12 External causes of death Note: ***The list of questions contains sub questions that allow for more specificity for accidents.***			
VAs-12.01	Road traffic accident	V89	V01-V89
VAs-12.02	Other transport accident	V99	V90-V99
VAs-12.03	Accidental fall	W19	W00-W19
VAs-12.04	Accidental drowning and submersion	W74	W65-W74
VAs-12.05	Accidental exposure to smoke, fire and flames	X09	X00-X19
VAs-12.06	Contact with venomous animals and plants	X29	X20-X29
VAs-12.07	Accidental poisoning and exposure to noxious substance	X49	X40-X49
VAs-12.08	Intentional self-harm	X84	X60-X84
VAs-12.09	Assault	Y09	X85-Y09
VAs-12.10	Exposure to force of nature	X39	X30-X39
VAs-12.99	Other and unspecified external cause of death	X59	S00-T99; W20-W64; W75-W99; X50-X59; Y10-Y98
VAs-99	Cause of death unknown	R99	R95-R99

Annex 8: Verbal Autopsy for children aged four weeks to 11 years, adapted for MVIP impact evaluation

Source: Verbal autopsy standards. The 2016 WHO verbal autopsy instrument.[17]

2016 WHO VERBAL AUTOPSY SAMPLE QUESTIONNAIRE

V1.4

Death of a child aged four weeks to 11 years

DK= answer means 'don't know'
Ref= answer means 'refused to answer'

World Health Organization

No.	Questions and filters	Answer		Skip	
	1) INFORMATION ABOUT THE PREVALENCE OF MALARIA AND HIV				
10002	Is this an area of high HIV/AIDS prevalence?	High	☐		
		Low	☐		
		Very low	☐		
10003	Is this a region of high malaria prevalence?	High	☐		
		Low	☐		
		Very low	☐		
10004	During which season did (s)he die	Wet	☐		
		Dry	☐		
		DK	☐		
	2) INFORMATION ABOUT THE RESPONDENT, CONSENT AND TIME OF INTERVIEW				
10007	What is the name of the VA respondent?				
	_____				
10008	What is the respondent's relationship to the deceased?	Parent	☐		
		Child	☐		
		Other	☐		
		family member	☐		
		Friend	☐		
		Health worker	☐		
		Public official	☐		
		Another relationship	☐		
10009	Did the respondent live with the deceased in the period leading to her/his death?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10010	What is the name of the VA interviewer				
	_____				
10011	Time at start of interview	hh:mm 24h _____			

		__			
10012	Date of interview	DAY	☐☐		
		MONTH	☐☐		
		YEAR	☐☐		
10013	Did the respondent give consent?	YES	☐		
		NO	☐		
	3) INFORMATION ABOUT THE DECEASED				
	3a) Socio-demographic information				
10017	What was the first or given name(s) of the deceased?				
	_____				
10018	What was the surname or family name(s) of the deceased?				
	_____				
10019	What was the sex of the deceased?	MALE	☐		
		FEMALE	☐		
10020	Is the date of birth known?	YES	☐		
		NO	☐	➡	10022
		REF	☐	➡	10022
10021	When was the deceased born?	DAY	☐		
		MONTH	☐		
		YEAR	☐		
10022	Is the date of death known?	YES	☐		
		NO	☐	➡	AAAA
		REF	☐	➡	AAAA
10023	When did (s)he die?	DAY	☐☐		
		MONTH	☐☐		
		YEAR	☐☐		
AAAA	Please indicate the age of the child in months or years	Months	☐☐		
		Years	☐		

			☐		
age_group	What age group corresponds to the deceased?	Neonate	☐		
		Child	☐		
		Adult	☐		
10058	Where did the deceased die?	Hospital	☐		
		Other health facility	☐		
		Home	☐		
		On route to facility or hospital	☐		
		Other	☐		
		DK	☐		
		Ref.	☐		
10051	Is there a need to collect civil registration data on the deceased?	YES	☐		
		NO	☐	➡	10069

10052	What was her/his citizenship / nationality?	Citizen at birth	☐		
		Naturalized citizen	☐		
		Foreign national	☐		
		DK	☐		
10053	What was her/his ethnicity?				
	_____				
10054	What was his/her place of birth?				
	_____				
10055	What was his/her place of usual residence (the place where the person lived most of the year)?				
	_____				
10056	What was his/her place of usual residence 1 to 5 years before death?				
	_____				
10057	Where did death occur?(specify country, province, district, village)				
	_____				

10061	What was the name of the father?				
	Surname				
	_____				
	Name				
	_____				
10062	What is the name of the mother?				
	Surname				
	_____				
	Name				
	_____				
10063	What was her/his highest level of schooling?	no formal education	☐		
		primary school	☐		
		Doesn't know	☐		
		Refused to answer	☐		
10064	Was (s)he able to read and write? (select 'yes' also if only one of either reading or writing is known to the respondent)	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10065	What was her/his economic activity status in year prior to death?	Mainly unemployed	☐		
		Mainly employed	☐		
		Home-maker	☐		
		Pensioner	☐		
		Student	☐		
		Other	☐		
		DK	☐		
		Ref.	☐		
10066	What was her/his occupation, that is, what kind of work d (s)he mainly do?				
	_____				

	3b) Civil registration information				
10069	Is there a need to collect civil registration numbers on the deceased?	YES	☐		
		NO	☐	➡	10077
10070	Death registration number/certificate				
	_____				
10071	Date of registration	DAY	☐☐		
		MONTH	☐☐		
		YEAR	☐☐		
10072	Place of registration				
	_____				
10073	National identification number of deceased				
	_____				
	4) HISTORY AND DETAILS OF INJURIES/ ACCIDENTS				
10077	Did (s)he suffer from any injury or accident that led to her/his death?	YES	☐		
		NO	☐	➡	10120
		DK	☐	➡	10120
		Ref.	☐	➡	10120
10079	Was it a road traffic accident?	YES	☐		
		NO	☐	➡	10082
		DK	☐	➡	10082
		Ref.	☐	➡	10082

10080	What was her/his role in the road traffic accident?	Driver or passenger in bus or heavy vehicle	☐		
		Driver or passenger in a car or light vehicle	☐		
		Driver or passenger on a	☐		

		motorcycle			
		Driver or passenger on a pedal cycle	☐		
		Pedestrian	☐		
10081	What was the counterpart that was hit during the road traffic accident?	Pedestrian	☐		
		Stationary object	☐		
		Car or light vehicle	☐		
		Bus or heavy vehicle	☐		
		Motorcycle	☐		
		Pedal cycle	☐		
		Other	☐		
10082	Was (s)he injured in a non-road traffic accident?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10083	Was (s)he injured in a fall?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10084	Was there any poisoning?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10085	Did (s)he die of drowning?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10086	Was (s)he injured by a bite or sting of venomous animal?	YES	☐	➡	10088
		NO	☐		

		DK	☐		
		Ref.	☐		
10087	Was (s)he injured by an animal or insect (non-venomous)	YES	☐		
		NO	☐	➡	10089
		DK	☐	➡	10089
		Ref.	☐	➡	10089
10088	What was the animal/insect?	Dog	☐		
		Snake	☐		
		insect or scorpion	☐		
		Other	☐		
		DK	☐		
10089	Was (s)he injured by burns/fire?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10090	Was (s)he subject to violence (homicide, abuse)?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10091	Was (s)he injured by a fire arm?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10092	Was (s)he stabbed, cut or pierced?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10093	Was (s)he strangled?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10094	Was (s)he injured by a blunt force?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10095	Was (s)he injured by a force of nature?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10096	Was it electrocution?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10097	Was (s)he injured by some other injury?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10098	Was the injury accidental?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10099	Was the injury or accident self-inflicted?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10100	Was the injury or accident intentionally inflicted by someone else?	Yes	☐		
		No	☐		
		DK	☐		
		Ref	☐		
	5) MEDICAL HISTORY ASSOCIATED WITH THE FINAL ILLNESS				
	5a) Duration of final illness				
10120	For how long was (s)he ill before (s)he died?	Days:	☐ ☐		

		Weeks:	☐ ☐		
		Months:	☐ ☐		

10123	Did (s)he die suddenly?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
	5b) History of diseases likely to be associated with or the cause of death				
10125	Was there any diagnosis by a health professional of tuberculosis?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10126	Was a HIV test ever positive?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10127	Was there any diagnosis by a health professional of AIDS?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10128	Did (s)he have a recent positive test by a health professional for malaria?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10129	Did (s)he have a recent negative test by a health professional for malaria?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10130	Was there any diagnosis by a health professional of dengue fever?	YES	☐		
		NO	☐		

		DK	☐		
		Ref.	☐		
10131	Was there any diagnosis by a health professional of measles?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10133	Was there any diagnosis by a health professional of heart disease?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10134	Was there any diagnosis by a health professional of diabetes?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10135	Was there any diagnosis by a health professional of asthma?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10136	Was there any diagnosis by a health professional of epilepsy?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10137	Was there any diagnosis by a health professional of cancer?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10142	Was there any diagnosis by a health professional of sickle cell disease?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10143	Was there any diagnosis by a health professional of kidney disease?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10144	Was there any diagnosis by a health professional of liver disease?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

	5c) General signs and symptoms associated with final illness				
10147	Did (s)he have a fever?	YES	☐		
		NO	☐	➡	10152
		DK	☐	➡	10152
		Ref.	☐	➡	10152
10148	For how many days did the fever last?	Days:	☐ ☐		
10149	Did the fever continue until death?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10150	How severe was the fever?	Mild	☐		
		Moderate	☐		
		Severe	☐		
10151	What was the pattern of the fever?	Continuous	☐		
		On and off	☐		
		Only at night	☐		
		DK	☐		
		Ref.	☐		
10152	Did (s)he have night sweats?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10153	Did (s)he have a cough?	YES	☐		
		NO	☐	➡	10159
		DK	☐	➡	10159
		Ref.	☐	➡	10159
10154	For how many days did (s)he have a cough?	DAYS	☐ ☐		
10155	Was the cough productive, with sputum?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10156	Was the cough very severe?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10157	Did (s)he cough up blood?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10158	Did (s)he make a whooping sound when coughing?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10159	Did (s)he have any difficulty breathing?	YES	☐		
		NO	☐	➡	10166
		DK	☐	➡	10166
		Ref.	☐	➡	10166
10161	For how many days did the difficulty breathing last?	DAYS	☐ ☐		
10165	Was the difficulty continuous or on and off?	Continuous	☐		
		On and off	☐		
		DK	☐		
		Ref.	☐		

10166	During the illness that led to death, did (s)he have fast breathing?	YES	☐		
		NO	☐	➡	10168
		DK	☐	➡	10168
		Ref.	☐	➡	10168
10167	For how many days did the fast breathing last?	DAYS	☐ ☐		
10168	Did (s)he have breathlessness?	YES	☐		
		NO	☐	➡	10172
		DK	☐	➡	10172
		Ref.	☐	➡	10172
10169	For how many days did (s)he have breathlessness?	DAYS	☐ ☐		
10172	Did you see the lower chest wall/ribs being pulled in as the child breathed?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10173	During the illness that led to death did his/her breathing sound like any of the following:	Stridor	☐		
		Grunting	☐		
		Wheezing	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10174	Did (s)he have chest pain?	YES	☐		
		NO	☐	➡	10181
		DK	☐	➡	10181
		Ref.	☐	➡	10181
10176	How many days before death did (s)he have chest pain?	DAYS	☐☐		
10181	Did (s)he have more frequent loose or liquid stools than usual?	YES	☐		
		NO	☐	➡	10186
		DK	☐	➡	10186
		Ref.	☐	➡	10186
10182	For how many days did (s)he have frequent loose or liquid stools?	DAYS	☐☐		
10183	How many stools did the baby or child have on the day that loose liquid stools were most frequent?	NUMBER OF STOOLS:	☐☐		
10184	How many days before death did the frequent loose or liquid stools start?	DAYS	☐☐		
10185	Did the frequent loose or liquid stools continue until death?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10186	At any time during the final illness was there blood in the stools?	YES	☐		
		NO	☐	➡	10188
		DK	☐	➡	10188
		Ref.	☐	➡	10188
10187	Was there blood in the stool up until death?	YES	☐		
		NO	☐		
		DK	☐		

		Ref.	☐		
10188	Did (s)he vomit?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10189	Did (s)he vomit in the week preceding death?	YES	☐		
		NO	☐	➡	10193
		DK	☐	➡	10193
		Ref.	☐	➡	10193
10191	Did (s)he vomit blood?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10192	Was the vomit black?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10193	Did (s)he have any belly (abdominal) problem?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10194	Did (s)he have belly (abdominal) pain?	YES	☐		
		NO	☐	➡	10200
		DK	☐	➡	10200
		Ref.	☐	➡	10200
10195	Was the belly (abdominal) pain severe?	YES	☐		
		NO	☐	➡	10200
		DK	☐	➡	10200
		Ref.	☐	➡	10200
10196	For how long before death did (s)he have severe abdominal pain?	HOURS	☐ ☐		

10197	For how many days before death did (s)he have severe abdominal pain?	DAYS	☐☐		
		WEEKS	☐☐		
10198	For how many months before death did (s)he have severe abdominal pain?	MONTHS	☐☐		

10199	Was the pain in the upper or lower abdomen?	Upper abdomen	☐		
		Lower abdomen	☐		
		Upper and lower abdomen	☐		
		DK	☐		
		Ref.	☐		
10200	Did (s)he have a more than usually protruding abdomen?	YES	☐		
		NO	☐	➡	10204
		DK	☐	➡	10204
		Ref.	☐	➡	10204
10201	For how many days did (s)he have a more than usually protruding abdomen?	DAYS	☐☐		
10202	For how many months did (s)he have a more than usually protruding abdomen?	MONTHS	☐☐		
10203	How rapidly did (s)he develop the protruding abdomen?	Rapidly	☐		
		Slowly	☐		
10204	Did (s)he have any mass in the abdomen?	YES	☐		
		NO	☐	➡	10207
		DK	☐	➡	10207
		Ref.	☐	➡	10207
10205	For how many days before death did (s)he have a mass in the abdomen?	DAYS	☐☐		
10206	For how many months before death did (s)he have a mass in the abdomen?	MONTHS	☐☐		
10207	Did (s)he have a severe headache?	YES	☐		

		NO	☐		
		DK	☐		
		Ref.	☐		
10208	Did (s)he have a stiff neck during illness that led to death?	YES	☐		
		NO	☐	➡	10210
		DK	☐	➡	10210
		Ref.	☐	➡	10210
10209	For how many days before death did (s)he have stiff neck?	DAYS	☐☐		
10210	Did (s)he have a painful neck during the illness that led to death?	YES	☐		
		NO	☐	➡	10214
		DK	☐	➡	10214
		Ref.	☐	➡	10214

10211	For how many days before death did (s)he have a painful neck?	DAYS	☐☐		
10214	Was (s)he unconscious during the illness that led to death?	YES	☐		
		NO	☐	➡	10219
		DK	☐	➡	10219
		Ref.	☐	➡	10219
10215	Was (s)he unconscious for more than 24 hours before death?	YES	☐	➡	10217
		NO	☐		
		DK	☐		
		Ref.	☐		

10216	How many hours before death did unconsciousness start?	Hours	☐☐		
10217	Did the unconsciousness start suddenly, quickly (at least within a single day)?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10218	Did the unconsciousness continue until death?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10219	Did (s)he have convulsions?	YES	☐		
		NO	☐	➡	10223
		DK	☐	➡	10223
		Ref.	☐	➡	10223
10220	Did (s)he experience any generalized convulsions or fits during the illness that led to death?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10221	For how many minutes did the convulsions last?	MINUTES:	☐☐		
10222	Did (s)he become unconscious immediately after the convulsion?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10223	Did (s)he have any urine problems?	YES	☐		
		NO	☐	➡	10227
		DK	☐	➡	10227
		Ref.	☐	➡	10227
10224	Did (s)he stop urinating?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10225	Did (s)he go to urinate more often than usual?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10226	During the final illness, did (s)he ever pass blood in the urine?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10227	Did (s)he have sores or ulcers anywhere on the body?	YES	☐		
		NO	☐	➡	10230
		DK	☐	➡	10230
		Ref.	☐	➡	10230
10229	Did the sores have clear fluid or pus?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10230	Did (s)he have an ulcer (pit) on the foot?	YES	☐		
		NO	☐	➡	10233
		DK	☐	➡	10233
		Ref.	☐	➡	10233
10231	Did the ulcer on the foot ooze pus?	YES	☐		
		NO	☐	➡	10233

		DK	☐	➡	10233
		Ref.	☐	➡	10233
10232	For how many days did the ulcer on the foot ooze pus?	DAYS	☐ ☐		

10233	During the illness that led to death, did (s)he have any skin rash?	YES	☐		
		NO	☐	➡	10238
		DK	☐	➡	10238
		Ref.	☐	➡	10238
10234	For how many days did (s)he have the skin rash?	DAYS	☐ ☐		
10235	Where was the rash?	Face	☐		
		Trunk or abdomen	☐		
		Extremities	☐		
		Everywhere	☐		
10236	Did (s)he have measles rash (use local term)?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10238	During the illness that led to death did his/her skin flake off in patches?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10239	During the illness that led to death did he/ she have areas of skin that turned black?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10240	During the illness that led to death did he/ she have areas of the skin with redness or swelling?	YES	☐		
		NO	☐		

		DK	☐		
		Ref.	☐		
10241	During the illness that led to death, did (s)he bleed from anywhere?	YES	☐		
		NO	☐	➡	10243
		DK	☐	➡	10243
		Ref.	☐	➡	10243
10242	Did (s)he bleed from the nose, mouth or anus?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10243	Did (s)he have noticeable weight loss?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10244	Was (s)he severely thin or wasted?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10245	During the illness that led to death, did s/he have a whitish rash inside the mouth or on the tongue?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10246	Did (s)he have stiffness of the whole body or was unable to open the mouth?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10247	Did (s)he have puffiness of the face?	YES	☐		
		NO	☐	➡	10249
		DK	☐	➡	10249

		Ref.	☐	➡	10249
10248	For how many days did (s)he have puffiness of the face?	DAYS	☐☐		
10249	During the illness that led to death, did (s)he have swollen legs or feet?	YES	☐		
		NO	☐	➡	10252
		DK	☐	➡	10252
		Ref.	☐	➡	10252
10250	How many days did the swelling last?	DAYS	☐☐		
10251	Did (s)he have both feet swollen?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10252	Did (s)he have general puffiness all over his/her body?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10253	Did (s)he have any lumps?	YES	☐		
		NO	☐	➡	10258
		DK	☐	➡	10258
		Ref.	☐	➡	10258
10255	Did (s)he have any lumps on the neck?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10256	Did (s)he have any lumps on the armpit?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10257	Did (s)he have any lumps on the groin?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10258	Was (s)he in any way paralysed?	YES	☐		
		NO	☐	➡	10261
		DK	☐	➡	10261
		Ref.	☐	➡	10261
10259	Did s(he) have paralysis of only one side of the body?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10260	Which were the limbs or body parts paralysed?	Right side	☐		
		Left side	☐		
		Lower part of body	☐		
		Upper part of body	☐		
		One leg only	☐		
		One arm only	☐		
		Whole body	☐		
		Other	☐		

10261	Did (s)he have difficulty swallowing?	YES	☐		
		NO	☐	➡	10264
		DK	☐	➡	10264
		Ref.	☐	➡	10264
10262	For how many days before death did (s)he have difficulty swallowing?	DAYS	☐ ☐		
10263	Was the difficulty with swallowing with solids, liquids, or both?	Solids	☐		
		Liquids	☐		
		Both	☐		
10264	Did (s)he have pain upon swallowing?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10265	Did (s)he have yellow discoloration of the eyes?	YES	☐		
		NO	☐	➡	10267
		DK	☐	➡	10267
		Ref.	☐	➡	10267
10266	For how many days did (s)he have the yellow discoloration?	DAYS	☐ ☐		
10267	Did her/his hair change in colour to a reddish or yellowish colour?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10268	Did (s)he look pale (thinning/lack of blood) or have pale palms, eyes or nail beds?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10269	Did (s)he have sunken eyes?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10270	Did (s)he drink a lot more water than usual?	YES	☐		

		NO	☐		
		DK	☐		
		Ref.	☐		

	5d) Signs and symptoms relevant for neonatal and child deaths				
	NOTE THE NEXT SECTION UP TO ID10418 SHOULD ONLY BE ASKED IF THE DECEASED WAS ONE YEAR OLD OR LESS				
10271	Was the baby able to suckle or bottle-feed within the first 24 hours after birth?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10272	Did the baby ever suckle in a normal way?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10273	Did the baby stop suckling?	YES	☐		
		NO	☐	➡	10275
		DK	☐	➡	10275
		Ref.	☐	➡	10275
10274	How many days after birth did the baby stop suckling?	Days:	☐☐		
10275	Did the baby have convulsions in the first 24 hours of life?	YES	☐	➡	10277
		NO	☐		
		DK	☐		
		Ref.	☐		
10276	Did the baby have convulsions starting more than 24 hrs after birth?	YES	☐		
		NO	☐		
		DK	☐		

		Ref.	☐		
10277	Did the baby's body become stiff, with the head arched backwards?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10278	During the illness that led to death did the baby have a bulging or raised fontanelle?	YES	☐	➡	10281
		NO	☐		
		DK	☐		
		Ref.	☐		
10279	During the illness that led to death did the baby have a sunken fontanelle?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10281	During the illness that led to death, did the baby become unresponsive or unconscious?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10282	Did the baby become unresponsive or unconscious soon after birth, within less than 24 hours?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10283	Did the baby become unresponsive or unconscious more than 24 hours after birth?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10352	How many years old was the child when the fatal illness started?	YEARS:	☐☐		
10354	Was the child part of a multiple birth?	YES	☐		
		NO	☐	➡	10356
		DK	☐	➡	10356

		Ref.	☐	➡	10356
10355	Was the child the first, second, or later in the birth order?	First	☐		
		Second or later	☐		
10356	Is the mother still alive?	YES	☐	➡	10360
		NO	☐		
		DK	☐		
		Ref.	☐		
10357	Did the mother die during or after the delivery?	During delivery	☐	➡	10360
		After delivery	☐		
10358	How many months after delivery did the mother die?	Months:	☐☐		
10359	How many days after delivery did the mother die?	Days:	☐☐		

10360	Where was the deceased born?	Hospital	☐		
		Other health facility	☐		
		Home	☐		
		On route to hospital or facility	☐		
		Other	☐		
		DK	☐		
		Ref	☐		
10361	Did the mother receive professional assistance during the delivery?	YES	☐		
	(ask only up to one year)	NO	☐		
		DK	☐		
		Ref.	☐		
10362	At birth was the baby of usual size?	YES	☐	➡	10365
		NO	☐		
		DK	☐		

		Ref.	☐		
10363	At birth was the baby smaller than usual (weighing under 2.5 kg)?	YES	☐		
		NO	☐	➡	10365
		DK	☐	➡	10365
		Ref.	☐	➡	10365
10364	At birth was the baby very much smaller than usual (weighing under 1 kg)?	YES	☐	➡	10366
		NO	☐	➡	10366
		DK	☐	➡	10366
		Ref.	☐	➡	10366
10365	At birth was the baby larger than usual (weighing over 4.5 kg)?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10366	What was the weight in grammes of the deceased at birth?	GRAMMES	☐☐☐		
	Note 1kg = 1000 grammes	Don't Know	☐		
10367	How many months long was the pregnancy before birth?	Months:	☐☐		
	(ask only up to one year)	Don't Know	☐		

10368	Were there any complications in the late part of the pregnancy (defined as the last 3 months before labour)?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10369	Were there any complications during labour or delivery?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10370	Was any part of the baby physically abnormal at time of delivery?	YES	☐		
	(for example body part too large or too small)	NO	☐	➡	10418
		DK	☐		
		Ref.	☐		
10371	Did the baby/child have swelling or a defect on the back at time of birth?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10372	Did the baby/child have a very large head at time of birth?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10373	Did the baby/child have a very small head at time of birth?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10408	Before the illness that led to death was the baby/ child growing normally?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
	5e) Health service and contextual factors				
10418	Did (s)he receive any treatment for the illness that led to death?	YES	☐		
		NO	☐	➡	10428

		DK	☐	➡	10428
		Ref.	☐	➡	10428

10419	Did (s)he receive oral rehydration salts?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10420	Did (s)he receive (or need) intravenous fluids (drip) treatment?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10421	Did (s)he receive (or need) a blood transfusion?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10422	Did (s)he receive (or need) treatment/food through a tube passed through the nose?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10423	Did (s)he receive (or need) injectable antibiotics?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10424	Did (s)he receive (or need) antiretroviral therapy (ART)?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10425	Did (s)he have (or need) an operation for the illness?	YES	☐		
		NO	☐	➡	10427
		DK	☐	➡	10427
		Ref.	☐	➡	10427
10426	Did (s)he have the operation within 1 month before death?	YES	☐		

		NO	☐		
		DK	☐		
		Ref.	☐		

10427	Was (s)he discharged from hospital very ill?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10428	Had (s)he received immunisation?	YES	☐		
		NO	☐	➡	10432
		DK	☐	➡	10432
		Ref.	☐	➡	10432
10429	Do you have the child's vaccination card? (If no vaccination card, ascertain vaccinations through verbal recall)	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10430	Can I see the vaccination card (and note the vaccines the child received)? (If vaccination card can not be seen, ascertain vaccinations through verbal recall)	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10431	Note vaccines here (including RTS,S)				
	_____				
	_____				
	_____				
	_____				
10432	Was care sought outside the home while (s)he had this illness?	YES	☐		
		NO	☐	➡	10450
		DK	☐	➡	10450
		Ref.	☐	➡	10450

10433	Where or from whom did you seek this care?	traditional healer	☐		

		homeopath	☐		
		religious leader	☐		
		governmen t hospital	☐		
		governmen t health centre or clinic	☐		
		private hospital	☐		
		community -based practitioner associated with health system	☐		
		trained birth attendant	☐		
		private physician	☐		
		Relative, friend (outside household)	☐		
		pharmacy	☐		
		Doesn't know	☐		
		Refused to answer	☐		
10434	Record the name and address of any hospital health centre or clinic where help was sought:				
	_____				
	_____				
	_____				
	_____				
10435	Did a health care worker tell you the cause of death?	YES	☐		
		NO	☐	➡	10437
		DK	☐	➡	10437
		Ref.	☐	➡	10437
10436	What did the health care worker say?				
	_____				

	_____				
	_____				
	_____				

10437	Do you have any health care records that belonged to the deceased?	YES	☐		
		NO	☐	➡	10445
		DK	☐	➡	10445
		Ref.	☐	➡	10445
10438	Can I see the health records?	YES	☐		
		NO	☐	➡	10445
		DK	☐	➡	10445
		Ref.	☐	➡	10445
10439	Record the date of the most recent (last) visit	Day	☐☐		
		Month	☐☐		
		Year	☐☐		
10445	Has the deceased's (biological) mother ever been tested for HIV?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10446	Has the deceased's (biological) mother ever been told she had HIV/AIDS by a health worker?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10450	In the final days before death, did s/he travel to a hospital or health facility?	YES	☐		

		NO	☐	➡	10455
		DK	☐	➡	10455
		Ref.	☐	➡	10455
10451	Did (s)he use motorised transport to get to the hospital or health facility?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10452	Were there any problems during admission to the hospital or health facility?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

10453	Were there any problems with the way (s)he was treated (medical treatment, procedures, interpersonal attitudes, respect, dignity) in the hospital or health facility?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10454	Were there any problems getting medications, or diagnostic tests in the hospital or health facility?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10455	Does it take more than 2 hours to get to the nearest hospital or health facility?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10456	in the final days before death were there any doubts about whether medical care was needed?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10457	in the final days before death, was traditional medicine used?	YES	☐		
		NO	☐		

		DK	☐		
		Ref.	☐		
10458	In the final days before death, did anyone use a telephone or cell phone to call for help?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		
10459	Over the course of illness, did the total costs of care and treatment prohibit other household payments?	YES	☐		
		NO	☐		
		DK	☐		
		Ref.	☐		

	5f) Information from death certificate	YES	☐		
10462	Was a death certificate issued?	NO	☐	➡	10481
		DK	☐	➡	10481
		Ref.	☐	➡	10481
10463	Can I see the death certificate?	YES	☐		
		NO	☐	➡	10481
		DK	☐	➡	10481
		Ref.	☐	➡	10481
10464	Record the immediate cause of death from the certificate (line 1a)				
	_____				
10465	Duration (1a)				
	_____				
10466	Record the first antecedent cause of death from the certificate (line 1b)				
	_____				
10467	Duration (1c)				
	_____				
10468	Record the second antecedent cause of death from the certificate (line 1c)				
	_____				
10469	Duration (1c)				
	_____				

10470	Record the third antecedent cause of death from the certificate (line 1d)				
	_____				
10471	Duration (1d)				
	_____				
10472	Record the contributing cause(s) of death from the certificate (part 2)				
	_____				
10473	Duration (part 2)				
	_____				

	6) NARRATIVE DESCRIPTION OF FINAL ILLNESS				
10476	NARRATIVE DESCRIPTION				
	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____				
	_____ _____ _____ _____ _____ _____				
	7) CHECK LIST OF KEY INDICATORS FROM THE NARRATIVE DESCRIPTION				
10478	Are any of the following words of interest mentioned in the above narrative?	Abdomen	☐		
		Cancer	☐		
		Dehydration	☐		
		Dengue fever	☐		
		Diarrhoea	☐		

		Fever	☐		
		Heart problems	☐		
		Jaundice (yellow skin or eyes)	☐		
		Pneumonia	☐		
		Rash	☐		
		None of the above words were mentioned	☐		
		Don't know	☐		
10481	Time at end of interview _____				

Annex 9. Village Reporter CRF

A. DETAILS OF THE DECEASED

0.	District / Sub-District /Community	
1.	Serial number	
2.	Full name of deceased	
3.	Date of birth (day/month/year)	
4.	Sex of deceased	
5.	Date of death (day/month/year)	
6.	Place of death	
7.	Usual place of residence	
8.	RTS,S status (if feasible)	

B. DETAILS OF THE INFORMANT

1.	Full name of informant	
2.	Address	
3.	Telephone number	
4.	Date of reporting	

Note: This is not a burial permit or a death certificate.

DECLARATION

I …….. do hereby declare

that I have been notified of the death of

…… and permission is hereby

granted for the burial of the deceased after the registration of the death with the Birth

and Death Registry.
Name: …….
Title: ……

Signature ……
Date (D AY/MONTH/YEAR) ……

Annex 10. CRF for impact evaluation

Variable format/type	Question
Select one GHA/KEN/MLW	Country
Select one YES or NO	Was consent obtained ?
Alphanumeric	If Y, then include unique identifier of consent form
Death reported	
day/month/year	Date death reported
Alphanumeric	ID of the VR
Demographics	
Drop down	Cluster
Drop down list	Village name
Text	Name of respondent
Drop down list	Relation of respondent
Date	Date of VA interview
XX:XX hrs	Time of VA interview
Text	Compound head name (KENYA ONLY)
Text	What was the first or given name(s) of the deceased?
Text	What was the surname (or family name) of the deceased?
Text	Initials of the deceased
Select one MALE or FEMALE	What was the sex of the deceased?
Select one YES or NO	Is the date of birth known?
Date	When was the deceased born?
Select one YES or NO	Is the date of death known?
Date	When did (s)he die?
Number	How old was the deceased when they died (Age at death in months)
Select LOCATION from drop down list	What was her/his place of death?
Select HOME or HEALTH FACILITY or OTHER	Where was her/his place of death?
Select IMPLEMENTING or COMPARATOR cluster	What was her/his place of usual residence? (the place where the person lived most of the year)
Drop down list	Cluster of residence
Period (months)	How long had the deceased lived there?
Longitude	Longitude GPS coordinates of the household

Latitude	Latitude GPS coordinates of the household
Select one YES or NO	Did the deceased receive any vaccinations since birth?
Select one YES or NO	Is there a vaccination record available
Photo taken YES or NO	If YES to vaccination record available, take a photograph of the vaccine record
Select one HEALTH RECORD OR MATERNAL RECALL or HEALTH FACILITY REGISTER	Record vaccines received
Date	BCG
Date	OPV 0
Date	OPV 1
Date	OPV 2
Date	OPV 3
Date	IPV
Date	Pentavalent 1
Date	Pentavalent 2
Date	Pentavalent 3
Date	PCV 1
Date	PCV 2
Date	PCV 3
Date	RTS,S 1
Date	RTS,S 2
Date	RTS,S 3
Date	RTS,S 4
Date	Rotavirus vaccine 1
Date	Rotavirus vaccine 2
Date	Measles 1
Date	Measles 2
Date	Meningitis A vaccine
Date	Yellow fever vaccine
Select one YES or NO	Was VA form completed
Number	Provide the VA form ID
Alphanumeric	Unique ID of person conducting VA

Alphanumeric	Unique ID of person reviewing VA

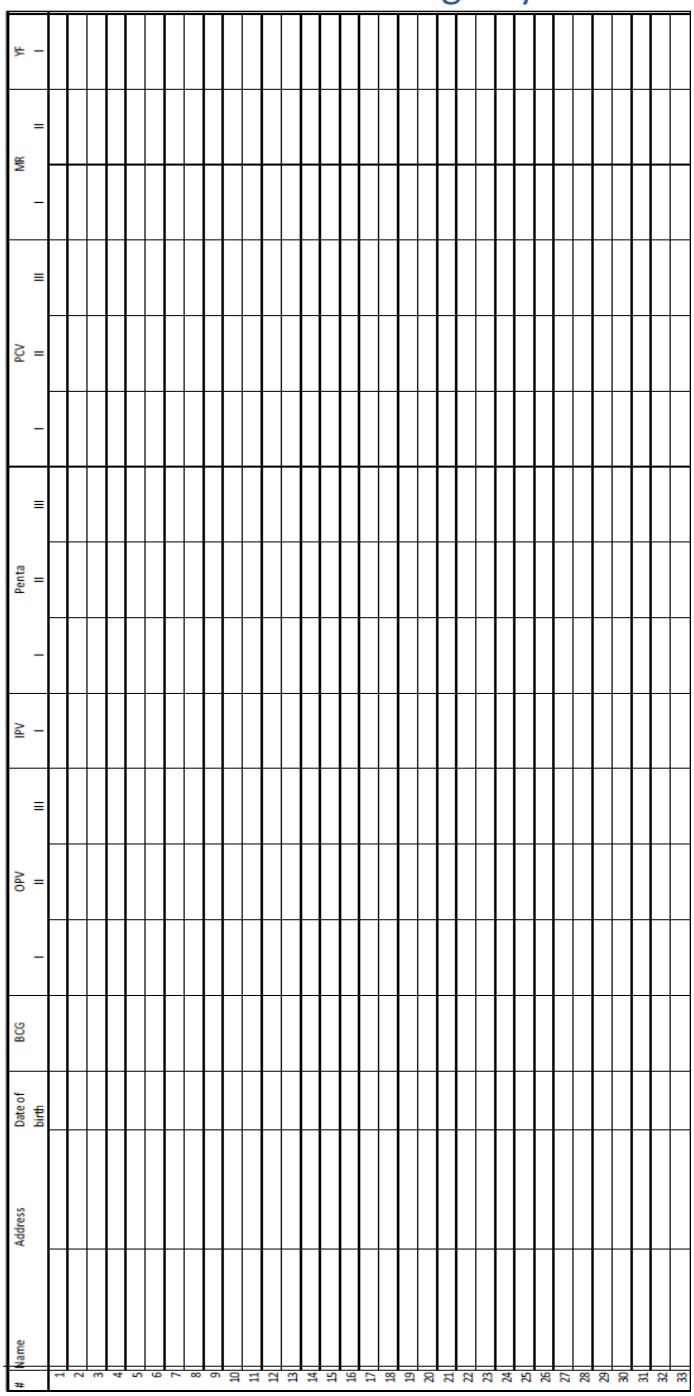
Question on the variable list	Instructions and notes
Time of VA start	For QA purposes
Time of VA end	For QA purposes

Select one YES or NO	If YES to death registration certificate, take a photograph
Photo taken YES or NO	Do you have a death registration certificate?
Select one YES or NO	Was VA form coded
Select interVA or SmartVA or InsilicoVA	If coded, provide name of algorithm
Select one YES or NO	Was cause of death classified
Select ICD group	What was the ICD 10 group
Select ICD cause of death	What was the ICD 10 cause of death

Notes for mortality CRF

What was the surname (or family name) of the deceased?	Only record for data triangulation exercise on the ground, but strip before sending data further up the chain
When was the deceased born?	Use local event calendar?? Verify date of birth using card/some other documentation? This variable should allow for month/year as well (in case doesn't know day)
How old was the deceased when they died (Age at death in months)	Use local event calendar?? Verify date of birth using card/some other documentation? This variable should allow for month/year as well (in case doesn't know day)
Record vaccines received	If not available on MCH or maternal record, get from health facility register and indicate source of register
Was VA form completed	The VA form completed should be the 2016 WHO verbal autopsy instrument for children aged 4 weeks to 11 years

Annex 11. Vaccination Registry



#	Name	Address	Date of birth	BCG	OPV			IPV	Penta			PCV			MR		YF
					I	II	III	I	I	II	III	I	II	III	I	II	I
1																	
2																	
3																	
4																	
5																	
6																	
7																	
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33																	

Annex 12. Sentinel hospital CRF

Type	Question	
Select one GHA/KEN/MLW	Country	
Select one YES or NO	Has consent been obtained ?	
Alphanumeric	If Y, then include unique identifier of consent form	
Drop down list	Name of sentinel hospital	
Number	Indicate the inpatient number for this admission	
Text	What is the first or given name(s) of the child ?	
Text	What is the surname (or family name) of the child?	
Text	Initials of the child (use 3 letters)	
Demographics		
Select IMPLEMENTING or COMPARATOR cluster	What is her/his place of usual residence? (the place where the person lived most of the year)	
Text or drop down	Cluster of residence	
Select one YES or NO	Have the child been resident in this location during this illness?	
Select one MALE or FEMALE	What is the sex of the child?	
Select one YES or NO	Is the date of birth known?	
YYYY	When is the child born?	
MMM	When is the child born?	
DD	When is the child born?	
DDMMMYYYY	What is the date of this admission ?	
Number	Age at admission (months)	
Select one YES or NO	Is this the first admission ?	
Number	If not the first admission, indicate number of previous admissions in the last 12 months	
YYYY	If not the first admission, indicate the date of the last admission	
MMM	If not the first admission, indicate the date of the last admission	
DD	If not the first admission, indicate the date of the last admission	
Select one YES or NO	Is the child enrolled in a clinical or intervention trial ?	

Select one YES or NO	Does the child have a bed net ?	
Select one YES or NO	Does the child sleep under a bed net on the night before admission?	
Select one YES or NO	At any time in the last 12 months has anyone sprayed the interior walls of your dwelling against mosquitoes ?	
Vaccinations	For all children, just record RTS,S status; then if there is a meningitis or cerebral malaria, record all vaccines.	
Select one YES or NO	Did the child receive any vaccinations since birth?	
Select one YES or NO	Is there a vaccination record available	
Confirm if photo taken YES or NO	If vaccination record is available, take a photograph	
Select one HEALTH RECORD OR MATERNAL RECALL	Record vaccines received	
Date	BCG	
Date	OPV 0	
Date	OPV 1	
Date	OPV 2	
Date	OPV 3	
Date	IPV	
Date	Pentavalent 1	
Date	Pentavalent 2	
Date	Pentavalent 3	
Date	PCV 1	
Date	PCV 2	
Date	PCV 3	
Date	RTS,S 1	
Date	RTS,S 2	
Date	RTS,S 3	
Date	RTS,S 4	
Date	Rotavirus vaccine 1	
Date	Rotavirus vaccine 2	
Date	Measles 1 or Measles Rubella 1	
Date	Measles 1 or Measles Rubella 2	
Date	Meningitis A vaccine	
Date	Yellow fever vaccine	

This admission		
History		
Select one YES or NO	Has the child had fever in the last 7 days ?	
Date	Indicate the date the fever started	
Number	How many days has the child had fever	
Select one YES or NO	Have you sought treatment for the fever in the last 7 days ?	
Select one YES or NO	If sought treatment, was an antibiotic given?	
Drop down list	If Yes to antibiotic, which antibiotic was used ?	
Select one YES or NO	If sought treatment, was an antimalarial given?	
Drop down list	If Yes to antimalarial, which antimalarial was used ?	
Select one YES or NO	Does this child have any pre-existing illnesses?	
Select one HIV, Congenital heart disease, Sickle cell disease, Severe malnutrition, other	Indicate the pre-existing illnesses	
Select one YES or NO	Has the child had difficulty in breathing during this illness?	
Select one YES or NO	Has the child had altered consciousness during this illness?	
Select one YES or NO	Has the child had convulsions during this illness?	
Select one YES or NO	If yes to convulsions, number in the last 24 hours?	
Number	Has the child had more than 1 convulsion or atypical convulsion during this illness?	if yes, do LP.
Examination		
Number (_ _._ C)	What was the body temperature on admission?	
Number (_ _ Breaths per min)	What was the respiratory rate on admission?	
Number (_ _._ kg)	What was the weight taken on admission?	
Number (_ _._ cm)	What was the MUAC taken on admission?	
Number (1-5)	What was the total Blantyre coma score on admission?	if total score is 3 or less, do LP
Number (0, 1 or 2)	Motor component	
Number (0, 1 or 2)	Verbal component	

Number (0 or 1)	Eye component	
Select one YES or NO	Was there presence of deep breathing on admission?	
Select one YES or NO	Was there presence of lower chest indrawing on admission?	
Select one YES or NO	Was there a bulging fontanelle on admission? For children less than 12 months of age	if yes, do LP
Select one YES or NO	Was there neck stiffness on admission?	if yes, do LP
Select one YES or NO	Was the child eligible for a lumbar puncture ? Contraindications for LP include needing resusitation, Poor pupillary responses to light, papilloedema, cranial nerve lesions, lateralising signs, Skin infection at LP site	Review for contraindicatio ns to LP, then if not present, do LP
Text	If eligible for LP but not done, describe reasons.	
Tests		
Select one YES or NO or not done	Was an RDT or malaria slide performed ?	
Select one YES or NO or not done	Results of the RDT or malaria slide	
Select one YES or NO or not done	Was an Haemoglobin or haematocrit test performed ?	
Number (_ _._ or _ _ %)	Results of the haemoglobin or haematocrit test	
Select one YES or NO or not done	Was an Blood glucose test performed ?	If BCS is less than 3
Number (_ _._ mmol/L)	Results of the blood glucose test	
Select one YES or NO or not done	Was a lumbar puncture performed ?	Review criteria for LP
Date	Date of lumbar puncture	
Alphanumeric	ID of person performing LP	
Select one YES or NO	Had antibiotics been used in the 7 days before LP?	If yes, refer to question above for antibiotics used
Select reason: Contraindication for LP, parental refusal, dead, absconded, discharge against medical advice, referral to another facility, no resources	If no LP was performed with criteria present	
Select one YES or NO or not done	Was CSF collected ?	

Alphanumeric	CSF sample number	
Select CLEAR, TURBID, PURULENR, BLOODY, OTHER	Macroscopic appearance of the CSF	
Select one YES or NO or not done	Was CSF WCC counted ?	
Number (_ _ _)	Results of CSF WCC count	
Select one YES or NO or not done	Was a CSF aliquot frozen?	
To be inputted from the ref lab	CSF result from reference laboratory	
Diagnosis		
ICD 10 classification code	Final primary diagnosis	
If final primary diagnosis is not consistent with clinical algorithm, record reason for discrepancy (e.g. severe malaria anemia or cerebral malaria with negative blood slide because treated confirmed malaria prior day, or low BCS with parasites, but not CM)		
ICD 10 classification code	Secondary diagnosis 1	
If final secondary diagnosis 1 is not consistent with clinical algorithm, record reason for discrepancy		
ICD 10 classification code	Secondary diagnosis 2	
If final secondary diagnosis 2 is not consistent with clinical algorithm, record reason for discrepancy		
ICD 10 classification code	Secondary diagnosis 3	
If final secondary diagnosis 3 is not consistent with clinical algorithm, record reason for discrepancy		
Select ALIVE; DEAD, REFERRED or ABSCONDED	Outcome	
QA		
Alphanumeric	ID of person completing admission form	
Alphanumeric	ID of person reviewing/finalising inpatient form	

Notes for safety CRF

Question for safety variables	Notes
Has consent been obtained ?	Who and how is consent attained.
What is the first or given name(s) of the child ?	Only record for data linkage but strip before sending data further up the chain

What is the surname (or family name) of the child?	Only record for data linkage but strip before sending data further up the chain
Initials of the child (use 3 letters)	Only record for data linkage but strip before sending data further up the chain
Vaccinations	Record all vaccines. Enter only DPT3/Pentavalent 3 doses and all RTSS doses
If sought treatment, was an antimalarials given?	Possibility to have a picture of common antibiotics for parents to identify. Refer to the health record
If sought treatment, was an antibiotic given?	Possibility to have a picture of common antimalarials for parents to identify. Refer to the health record
Was an RDT or malaria slide performed ?	Malaria test to be performed on all admissions.
Results of the RDT or malaria slide	Important if BCS less than 3 to rule out malaria as well.
ID of person performing LP	Only record for QA on the ground, but strip before sending data further up the chain
ID of person completing admission form	Only record for QA on the ground, but strip before sending data further up the chain
ID of person reviewing/finalising inpatient form	Only record for QA on the ground, but strip before sending data further up the chain

Annex 13. Household Survey CRF

	Reference is DHS/ questionnaires for samples
Type	**Question**
Select one GHA/KEN/MLW	**Country**
Select one YES or NO	**Has consent been obtained ?**
Alphanumeric	**If Y, then include unique identifier of consent form**
X X:X X hrs	**Interview start time**
Demographics	
Select one GHA/KEN/MLW	Country
Drop down list from the randomisation list	Region/ County/ District
Alphanumeric	Randomisation cluster ID
Drop down list from the randomisation list	Randomisation cluster name
Date	Interview date
Alphanumeric	Household number
Alphanumeric	Survey cluster ID
Longitude	Longitude GPS coordinates of the household
Latitude	Latitude GPS coordinates of the household
Select one Completed/Refused/No person to consent	Outcome
Number	Household members children aged 5- 48 months
Number	TOTAL ELIGIBLE CHILDREN AGED 12-23 MONTHS
Number	TOTAL ELIGIBLE CHILDREN AGED 27-38 MONTHS
Wealth quintile	**Each country should include validated PCA variables for this section to calculate wealth quintiles**
Select one YES or NO	
	Does your household have:
Select one YES or NO	Electricity
Select one YES or NO	A radio
Select one YES or NO	A television
Select one YES or NO	A mobile phone
Select one YES or NO	A bicycle
Select one YES or NO	A car or truck
Select one YES or NO	A motor bike
Select one YES or NO	A boat with a motor
Select one YES or NO	Does any member of this household own a bank account ?

Select one YES or NO	Does any member of this household own any agricultural land ?
Use the DHS drop list	Observe the main material of the floor of the dwelling. Record
Use the DHS drop list	Observe the main material of the roof of the dwelling. Record
Use the DHS drop list	Observe the main material of the exterior walls of the dwelling. Record
Select POOR or LOW , AVERAGE, ABOVE AVERAGE, WEALTHY	In relation to others in this community, what would you say is your wealth status in this community
Malaria control	
Select one YES or NO	At any time in the last 12 months has anyone sprayed the interior walls of your dwelling against mosquitoes ?
Months (number)	How many months ago did your household get sprayed against mosquitoes?
Select one YES or NO	Does your household have any mosquito nets?
Name	DID (NAME of eligible child sleep under this mosquito net last night? if yes, show the net, then record the specifics of that net
Select LLIN or OTHER	Observe or ask the type of mosquito net ?
Mother	
Name	Identify mother of target child
MM YYYY	In what month and year were you born?
select one YES or NO	Have you ever attended school?
Select PRIMARY or SECONDARY or HIGHER	What is the highest level of school you attended?
Number	What is the highest [GRADE/FORM/YEAR] you completed at that level?
	Check highest level of school attended, if PRI or SEC, perform reading test below
Use the DHS drop list	Now I would like you to read this sentence to me. SHOW CARD TO RESPONDENT. IF RESPONDENT CANNOT READ WHOLE SENTENCE, PROBE: Can you read any part of the sentence to me?
Use the DHS drop list	What is your ethnic group?
Use the DHS drop list	What is your religion?

Use the DHS drop list	What is your occupation?
Father	
Name	Identify father of target child (Is this the natural father of NAME?)
MM YYYY	In what month and year were you born?
select one YES or NO	Have you ever attended school?
Select PRIMARY or SECONDARY or HIGHER	What is the highest level of school you attended?
Number	What is the highest [GRADE/FORM/YEAR] you completed at that level?
	Check highest level of school attended, if PRI or SEC, perform reading test below
Use the DHS drop list	Now I would like you to read this sentence to me. SHOW CARD TO RESPONDENT. IF RESPONDENT CANNOT READ WHOLE SENTENCE, PROBE: Can you read any part of the sentence to me?
Use the DHS drop list	What is your ethnic group?
Use the DHS drop list	What is your religion?
Use the DHS drop list	What is your occupation?
	Reference is DHS/ questionnaires for samples
Type	**Question**
Select one GHA/KEN/MLW	**Country**
Select one YES or NO	**Has consent been obtained ?**
Alphanumeric	**If Y, then include unique identifier of consent form**
Demographics	
Select one GHA/KEN/MLW	Country
Drop down list from the randomisation list	Region/ County/ District
Alphanumeric	Randomisation cluster ID
Drop down list from the randomisation list	Randomisation cluster name
Date	Interview date
Alphanumeric	Household number

Alphanumeric	Survey cluster ID
Select one Completed/Refused/No person to consent /postponed / dwelling not found	Response outcome
Number	Household members children aged 5- 48 months
Number	TOTAL ELIGIBLE CHILDREN AGED 12-23 MONTHS
Number	TOTAL ELIGIBLE CHILDREN AGED 27-38 MONTHS
	Enumerate each child aged 5-48 months separately to collect the following information
Text	**Name of the child**
Text	Relationship to Head of Household
Name	Identify mother of target child
Select one YES or NO	Are you the primary caregiver of target child
YYYY	Date of birth
MMM	Date of birth
DD	Date of birth
Number	Age
Select one MALE or FEMALE	Gender
Malaria control	
Name	DID (NAME of eligible child sleep under this mosquito net last night? if yes, show the net, then record the specifics of that net
Select LLIN or OTHER	Observe or ask the type of mosquito net ?
Child health	
Vaccine status	
5-48 months	Name of the child in the target age group

Hospital OR Clinic OR Outreach	In which facility/clinic does this child receive their vaccines?
YES or NO or DK	Do you have a card or other document where (NAME)'s vaccinations are written down?
YES or NO or DK	Did you ever have a vaccination card for (NAME)?
Card/record seen YES or NO	May I see the card or other document where (NAME)'s vaccinations are written down?
Confirm if photo has been taken	Take a photo of the card or record if available
Vaccine record OR Maternal recall	How is vaccination status ascertained?
	The following questions will be asked in the following circumstances: 1) In a subset of children where the card is available to assess the comparability of maternal recall and card history. Ask the questions first, then request the card and take a picture and fill in the dates. 2) If the vaccine record is not available.
YES or NO or DK	Has (NAME) ever received a BCG vaccination against tuberculosis, that is, an injection in the arm or shoulder that usually causes a scar?
YES or NO or DK	Within 24 hours after birth, did (NAME) receive a Hepatitis B vaccination, that is, an injection in the thigh to prevent Hepatitis B?
YES or NO or DK	Has (NAME) ever received oral polio vaccine, that is, about two drops in the mouth to prevent polio?
YES or NO or DK	Did (NAME) receive the first oral polio vaccine in the first two weeks after birth or later?

Number	How many times did (NAME) receive the oral polio vaccine?
YES or NO or DK	The last time (NAME) received the polio drops, did (NAME) also get an IPV injection in the arm to protect against polio?
YES or NO or DK	Has (NAME) ever received a pentavalent vaccination, that is, an injection given in the thigh sometimes at the same time as polio drops?
Number	How many times did (NAME) receive the pentavalent vaccine?
YES or NO or DK	Has (NAME) ever received a pneumococcal vaccination, that is, an injection in the thigh to prevent pneumonia?
Number	How many times did (NAME) receive the pneumococcal vaccine?
YES or NO or DK	Has (NAME) ever received a rotavirus vaccination, that is, liquid in the mouth to prevent diarrhea?
Number	How many times did (NAME) receive the rotavirus vaccine?
YES or NO or DK	Has (NAME) ever received a measles vaccination, that is, an injection in the arm to prevent measles?
	Has (NAME) ever received the measles vaccine at 1 and half years after?
	Has (NAME) ever received the measles vaccine at 9 months or soon after?
Number	How many times did (NAME) receive the measles vaccine?
YES or NO or DK	Has (NAME) ever received a yellow fever vaccination, that is, an injection in the arm to prevent YELLOW FEVER?

YES or NO or DK	Has (NAME) ever received a meningitis vaccination, that is, an injection in the arm to prevent MENINGITIS, AROUND 1 1/2 YEAR OF AGE?
YES or NO or DK	Has (NAME) ever received a malaria vaccination, that is, an injection in the arm/thigh to prevent malaria?
Number	How many times did (NAME) receive the malaria vaccine?
YES or NO or DK	In addition to what is recorded on (this document/these documents), did (NAME) receive any other vaccinations, including vaccinations received in campaigns or immunization days or child health days?
Use drop down list	If incomplete vaccine status for age, probe reasons for not receiving the vaccine - stock outs, illness, religious reasons, etc
Other preventive interventions	
YES or NO or DK	In the last six months, was (NAME) given a vitamin A dose like [this/any of these]?
YES or NO or DK	Was (NAME) given any drug for intestinal worms in the last six months?
Health seeking behaviour	
Fever	
YES or NO or DK	Has (NAME) been ill with a fever at any time in the last 2 weeks?
YES or NO or DK	At any time during the illness, did (NAME) have blood taken from (NAME)'s finger or heel for testing?
use DHS drop down list	Did you seek advice or treatment for the illness from any source?
use DHS drop down list	Where did you seek advice or treatment? Anywhere else?

use DHS drop down list	If sought treatment from multiple sources, indicate the initial source of treatment here
use DHS drop down list	Where did you first seek advice or treatment?
YES or NO or DK	How many days after the illness began did you first seek advice or treatment for (NAME)?
Treatment	
YES or NO or DK	At any time during the illness, did (NAME) take any drugs for the illness?
use DHS drop down list	What drugs did (NAME) take? Any other drugs?
use DHS drop down list	How long after the fever started did (NAME) first take an artemisinin combination therapy?
use DHS drop down list	How long after the fever started did (NAME) first take SP/Fansidar?
use DHS drop down list	How long after the fever started did (NAME) first take chloroquine?
use DHS drop down list	How long after the fever started did (NAME) first take amodiaquine?
use DHS drop down list	How long after the fever started did (NAME) first take quinine?
use DHS drop down list	How long after the fever started did (NAME) first take artesunate?
use DHS drop down list	How long after the fever started did (NAME) first take (OTHER ANTIMALARIAL)?
Biomarker testing	
Text	Confirm child's name in the target age
YES or NO	Confirm consent for the child in the target age
Number (months)	Age
Number with 1 decimal point	Mid upper arm circumference in cm taken
Select one POS or NEG	Record Rapid malaria test results here
Initials	Enter the measurers code here

Notes for Feasibility

Questions	**Notes or instructions**
Age	Calculate using date of birth and interview date or estimate stating age if date of birth is not known.
Identify mother of target child	If not available, organise to meet her when available
Is this the target mother? Is this the target/natural father ?	Complete the mother and father module
Total eligible children aged 27-38 months	This should only be collected in the 3rd HHS
Has (NAME) ever received a malaria vaccination, that is, an injection in the arm/thigh to prevent malaria?	Only for the second and third HHS
Take a photo of the card or record if available	Take a photograph of the all the pages where vaccinations have been recorded including vaccination stickers
Biomarker testing	Only for the first HHS
Record Rapid malaria test results here	If positive, provide antimalarials as per the national guidelines
Within 24 hours after birth, did (NAME) receive a Hepatitis B vaccination, that is, an injection in the thigh to prevent Hepatitis B?	Only use this question if a birth dose of Hep B is given in the national schedule
Has (NAME) ever received a BCG vaccination against tuberculosis, that is, an injection in the arm or shoulder that usually causes a scar?	Check for scar
Was (NAME) given any drug for intestinal worms in the last six months?	Age dependent. Follow country guidelines
Wealth quintile	Each country should include validated PCA variables for this section to calculate wealth quintiles. These questions can be adapted to country specific questions.

Annex 14: Model informed consent statement for verbal autopsy

Hello. My name is _____ and I am working with [AGENCY].

I am an interviewer. I have been informed that a child in your household died. I am very sorry to hear this. Please accept my sympathy.

We are collecting information on the causes of recent deaths of children aged less than 5 years in the community. I would like to talk to the adult person in your house who took care of [say the child's name] during his/her illness before death, or who was present at the time of his/her death.

We would very much appreciate your participation in this effort.

We want to ask you about the illness and events leading to the death of [say the child's name]. We would also like to ask about vaccinations s/he received and take a photograph of his/her vaccination card.

Confidential information, including your child's name, will not be shared with anyone. We will share other information with the Ministry of Health, with investigators in [pilot country] and [pilot country], where similar assessments are being done, and with the World Health Organization, which is sponsoring this work, and with other individuals or groups approved by WHO. However, no information identifying you or the deceased will ever be released to anyone outside this information-collection activity.

Participation in this survey is voluntary and you can choose not to answer any individual question or all of the questions. You may also stop the interview completely at any time without any consequences at all. However, we hope that you will participate in this survey. This will contribute to a better understanding of the causes of deaths in children in this area, as the authorities work to improve health services.

At this time, do you want to ask me anything about the purpose or content of this interview?

May I begin the interview now?

Signature of interviewer

Annex 15: Model Informed consent form for Inpatient Surveillance

15.1 Model ICF for Inpatient Surveillance

Title: An evaluation of the cluster-randomised pilot implementation of RTS, S/AS01 through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa

[Institutional Letterhead]

Informed consent for the primary caretaker of a child between the ages of 5 months and 59 months who live in the MVIP pilot areas, who we are asking to participate in the MVIP sentinel hospital surveillance.

[Name of Principal Investigator]

[Name of Organization]

Sponsor: World Health Organization

[Name of Proposal and version]

This Informed Consent Form has two parts:

• Information Sheet (to share information about the survey with you)

• Certificate of Consent (for signatures if you agree that your child may participate)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

Good morning/afternoon. I am [ ] working for [ ] research institute. The Ministry of Health, in collaboration with [research institutions] and the World Health Organization, are collecting information at this and [enter number] other hospitals in [area] to understand how well the malaria vaccine that is provided in some [counties/districts] works to prevent severe malaria and to gather more information on the vaccine's safety. I am sorry that your child has been hospitalized and I understand this is a stressful time. If you are able to talk, I would like to give you information and invite you to have your child participate in this research, which will consist of some questions to you, and possibly some tests for your child. We will tell you about any tests we want to do before doing them. The results of any test we do here will be given to your child's doctor to be used in your child's care. You do not have to decide today whether or not you agree that your child may participate in the research. Before you decide, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me.

Purpose

Malaria is one of the most common and dangerous childhood diseases in this region. There are important ways to prevent malaria in children, including insecticide treated nets, and indoor residual spray, [IPTi if recommended in country]. A new vaccine against malaria is being introduced into some [counties/districts/areas/] in [name MVIP pilot areas] and in selected areas in [other MVIP countries] as part of a pilot introduction. By collecting information from parents of children who are admitted to hospital, and finding out whether or not the child received the malaria vaccine, the Ministry of Health can learn how well the vaccine is working to prevent severe malaria. We can also learn more about the safety of the malaria vaccine. This information will allow the Ministry of Health to understand whether the malaria vaccine should be introduced more widely in [country].

Surveillance

We are gathering information through hospital surveillance, meaning that we would like to

gather information on your child's current illness and the tests done. Some of this information will come from speaking with you, some from your child's medical records, and some from the laboratory results of tests done. In addition we will ask to see the vaccination record of your child and to take a photograph of the vaccination record so as to have a record of the vaccines received and the dates they were given. We might ask for additional tests to be done, but will discuss this with you before doing any additional tests.

Participant selection

We have chosen children from 5-59 months of age, because this is the age group who is likely to benefit from the malaria vaccine, which will be given to children in [country] who are [5 or 6 months of age].

Voluntary Participation

Your decision to have your child participate in this research is entirely voluntary. If you choose not to consent, there will be no negative consequences and your child will still receive the usual standard of care at this hospital. You may also choose to change your mind later and stop participating, even if you agreed earlier, and that is fine.

Procedures and Protocol

We will ask you a series of questions about your child's recent illness, and will ask to see the child's vaccination records. We will ask that you allow us to take a photograph of your child's vaccination record and collect the information fromyour child's medical records, including any tests done. Depending on your child's illness, we may ask for additional tests to be done performed. Some of those tests will be performed here, and the results will be provided to your doctor to help with your child's care. If your child needs an assessment of the fluid from around the spinal cord, the cerebral spinal fluid, to check to see if he or she has meningitis, we will send the remaining fluid to a laboratory outside [country], to a laboratory in either South Africa or the The Gambia. There we will be able to look closely for bacteria or viruses that might be causing your child's illness. These results will be provided to your doctor, but will not be available in time to direct treatment. However, they will help us to know if your child has meningitis, and to understand the different germs that cause meningitis in children in this area.

Duration

The questions we will ask you should take about 20 minutes.

Risks or Discomforts

Few risks are associated with participating in hospital surveillance. The tests that will be done for your child are those that should usually be done for children who are sick. If we ask to do additional blood tests, your child may have pain where the needle enters the skin or a bruise. The pain usually resolves within a day and the bruise is not long lasting.

Benefits

If your child participates in this research, he/she will have the following benefits: he/she will receive diagnostic tests to help determine what is causing his/her illness free of charge. There may not be any other benefit for your child but his/her participation is likely to help us find the answer to the research question which could benefit the community.

Reimbursements

You will not be provided any incentive to take part in this research. Where follow-up visits are requested, appropriate fare compensation would be provided.

Confidentiality

The information that we collect from this research will be kept confidential. Information about your child that will be collected from the survey will be put away and no-one but the

researchers will be able to see it. Any information about your child will have a number on it instead of his/her name. Only the researchers will know what his/her number is and we will lock that information up. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, CRO, etc].)

Sharing of the results

[The knowledge that we get from this study will be shared through small meetings in the community before it is made widely available to the public]. Information collected will also be shared with other investigators in [pilot country] and [pilot country] where similar assessments are being done, as well as with the World Health Organization, which is sponsoring the work, and with other individuals or groups approved by WHO. Confidential information, including your child's name, will not be shared. Afterwards, we will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to agree to your child taking part in this research if you do not wish to do so.

You may stop your child from participating in the research at any time that you wish.

Who to Contact

[Provide the name and contact information of someone who is involved, informed and accessible (a local person who can actually be contacted.) State also that the proposal has been approved and how.]

(If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail]

This proposal has been reviewed and approved by [name of the IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact [name, address, telephone number.])

PART II: Certificate of Consent

Certificate of Consent

I have been invited to have my child participate in hospital surveillance research to understand how well the recently introduced malaria vaccine prevents severe malaria, and to gather more information on the vaccine safety. I have read the foregoing information or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study. I consent for samples from my child to be sent to a laboratory in The Gambia or South Africa.

Print Name of Participant_____

Print Name of Parent or Guardian_____

Signature of Parent or Guardian _____

Date _____

Day/month/year

If Parent or Guardian illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the consent form to the parent of the potential participant and the individual has had the opportunity to ask questions. I confirm that

the individual has given consent freely.
Print name of witness_____AND Thumb print of parent
Signature of witness _____
Date _____
Day/month/year
Statement by the researcher/person taking consent
I have accurately read out the information sheet to the parent of the potential participant, and to the best of my ability made sure that the person understands the components of the research.
I confirm that the parent was given an opportunity to ask questions about the study, and all the questions asked by the parent have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent and the consent has been given freely and voluntarily.
A copy of this ICF has been provided to the participant.
Print Name of Researcher/person taking the consent_____
Signature of Researcher /person taking the consent_____
Date _____
Day/month/year

15.2 Model ICF for Long term storage of samples

Additional Consent to an evaluation of the cluster-randomised pilot implementation of RTS,S/AS01 through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa
This Statement of Consent consists of two parts:
• Information Sheet (to share information about storage of unused samples with you)
• Certificate of Consent (to record your agreement)
You will be given a copy of the full Statement of Consent
Part 1. Information Sheet
As part of the information that we are collecting through hospital surveillance, we might collect blood, cerebrospinal fluid and other samples for tests to understand the cause of your child's illness. Where necessary, we might ask for additional tests to be done, but we will discuss this with you before doing any additional tests. You may choose to have your samples only used for the current research or for research as well. Some of the samples might be sent abroad to laboratories in The Gambia or South Africa for further analysis and/or quality assurance.
Once the tests are done, there may be a small volume of unused sample leftover. We request permission to store your child's leftover samples for possible future use in research looking at public health problems. If any blood or body fluid samples are taken during your child's hospitalization, we ask that you allow us to store any leftover samples for up to 15 years. You can decide not to allow us to store left over samples and still participate in this research. For future research, we would request permission from the ethics committee, as appropriate
It is possible that genetic tests may be undertaken on your child's samples. This will not be linked directly to your child but may help understand the mechanisms of malaria as affected by inherited traits. If you do not wish for your child's sample to be used in this or any other type of research, please let us know.

The leftover samples can be traced to your child while in the hospital and this allows us to feedback results which have immediate clinical relevance. However during long term storage, we would remove all identifying information that could trace the sample back to your child. This would allow us to protect your child's identity but would not allow us to give back individual results in the long term.
Your child's sample will only be used for research purposes, where appropriate approvals have been obtained as described above.
Right to Refuse and Withdraw
Your decision to have your child's samples kept for research is entirely voluntary. If you

□ I give permission for my (TYPE OF SAMPLE) sample to be stored and used in future research
but only on the same subject as the current research project : [give name of current research]
□ I give my permission for my [TYPE OF SAMPLE] sample to be stored and used in future research of any type which has been properly approved
□ I give permission for my [TYPE OF SAMPLE] sample to be stored and used in future research
except for research about [NAME TYPE OF RESEARCH]
choose not to consent, there will be no negative consequences and your child will still receive
the usual standard of care at this hospital and can still participate in the inpatient surveillance study. You may also choose to change your mind later and stop participating, even if you agreed earlier, and that is fine.
Confidentiality
We will remove all identifiers that could trace the sample back to your child in the long term. This means that you will not receive any further individual results.
You can ask me any more questions about any part of the information provided above? Do you have any questions?
Part II. Certificate of Consent
Long Term Storage of samples
If any of the blood or body fluid I have provided for this research project is unused or leftover when the project is completed (Tick one choice from each of the following boxes)
□ I wish my [TYPE OF SAMPLE] sample to be destroyed immediately.
□ I want my [TYPE OF SAMPLE] sample to be destroyed after ____ years.
□ I give permission for my [TYPE OF SAMPLE] sample to be stored indefinitely
AND (if the sample is to be stored)
AND
□ I want my identity to be removed from my (TYPE OF SAMPLE) sample.
□ I want my identity to be kept with my (TYPE OF SAMPLE) sample.

I have read the information, or it has been read to me. I have had the opportunity to ask questions about it and my questions have been answered to my satisfaction. I consent voluntarily to have my samples stored in the manner and for the purpose indicated above.
Print Name of Participant_____
Signature of Participant _____
Date _____

Day/month/year
If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.
I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.
Print name of witness_____ AND Thumb print of participant
Signature of witness _____
Date _____
Day/month/year
Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1.
2.
3.
I confirm that the participant was given an opportunity to ask questions about the nature and manner of storage of the samples, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.
A copy of this ICF has been provided to the participant.
Print Name of Researcher/person taking the consent_____
Signature of Researcher /person taking the consent_____
Date _____
Day/month/year

Annex 16: Model informed consent statement for household surveys

Hello. My name is _____. I am working with [NAME OF ORGANIZATION]. We are conducting a survey about vaccine use, malaria and other topics in
this area of [NAME OF COUNTRY]. This information will allow the Ministry of Health to understand whether the malaria vaccine should be introduced more widely in [country] and how to introduce the malaria vaccine. Your household was selected for this survey.
I would like to ask you some questions about your household. In addition we will ask to see the
vaccination record of your child and take a photograph of the vaccination record so we can check the dates vaccines were received. The questions usually take about 20 to 30 minutes.

Confidentiality

The information that we collect from this survey will be kept confidential. Information about your child will be put away and no-one but the researchers will be able to see it. Any information about people living in your household will have a number on it instead of their name. Only the researchers will know what their numbers are and we will lock that information
up. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, CRO, etc].)

Sharing of the results

The knowledge that we get from this study will be shared through community meetings and government meetings before it is made widely available to the public. Information collected will
also be shared with other investigators in [pilot country] and [pilot country] where similar assessments are being done, as well as with the World Health Organization, which is sponsoring
these work, and with other individuals or groups approved by WHO. Confidential information,
including peoples' names, will not be shared. Afterwards, we will publish the results in order that other interested people may learn from this research.

Right to refuse or withdraw

You don't have to be in the survey, but we hope you will agree to answer the questions since your views and experiences are important. If I ask you any question you don't want to answer,
just let me know and I will go on to the next question. You can stop the interview at any time.
At this time, do you want to ask me anything about the purpose or content of this interview? In
case you need more information about the survey, you may contact the person listed on this card.
Do you have any questions? May I begin the interview now?

Signature of interviewer:

Signature of Parent of CHILD:

Biomarker and MUAC (for children aged 5-48 months in baseline survey only)

As part of this survey, we are asking children aged 5 to 48 months to have a test to see if they have malaria. Malaria is a serious illness caused by a parasite transmitted by a mosquito bite.

Malnutrition is a serious illness caused by not enough or unbalanced diet, problems with digestion or absorption or certain medical conditions. This information on nutrition status and malaria will help us understand how the population that receives routine vaccines are affected by these conditions. This information will be shared with the government to include in their programs to prevent and treat malaria and malnutrition. These procedures usually take about 5 to 10 minutes.

We ask that all children who are aged 5 to 48 months take part in malaria testing in this survey and give a few drops of blood from a finger or heel. The equipment used to take the blood is clean, safe and has not been used on anyone before: it will be thrown away after each test.

One blood drop will be tested for malaria immediately, and the result will be told to you right away. If the malaria test is positive, appropriate treatment will be offered following the government's guidelines.

Measurement of the arm will be done using a tape measure. If your child is found to be malnourished, they will be referred to the nearest health facility for nutritional rehabilitation.

Your child's result will be kept strictly confidential and will not be shared with anyone other than members of our survey team and appropriate health care workers.

Do you have any questions? You can say yes or no. It is up to you to decide.

Will you allow (NAME OF CHILD) to participate in the malaria test and nutrition assessment?

Signature of interviewer:

Signature of Parent of CHILD:

Annex 17: Standard AEFI reporting form

AEFI reporting ID number:

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

***Patient Name*:** ***Patient's full Address*:** Telephone: Sex: ☐ M ☐ F ***Date of birth* : _ _ /_ _ /_ _** *OR Age at onset:* ☐☐ *Years* ☐☐ *Months* ☐☐☐ *Days* *OR Age Group at onset:* ☐ *<1 Year* ☐ *1 to 5 Years* ☐ *>5 Years*	***Reporter's Name*:** Institution: Designation & Department: Address: Telephone & E-mail: Date patient notified event to health system: _ _ /_ _ /_ _ Today's date : _ _ /_ _ /_ _

Health facility (place or vaccination centre) name & address:

Vaccine						*Diluent (if applicable)*			
Name of vaccine	***Date of vaccination***	***Time of vaccination***	Dose (1st, 2nd, etc.)	***Batch /Lot number***	Expiry date	Name of diluent	***Batch /Lot number***	Expiry date	Date and time of reconstitution

Adverse event(s): ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever ≥38°C ☐ Other (specify).....	Date AEFI started : _ _ /_ _/_ _ Time __ __:__ __ Describe AEFI (Signs & Symptoms):

Serious: Yes / No; ➔ If Yes ☐ Death ☐ Life threatening ☐ Persistent or significant disability ☐ Hospitalization ☐ Congenital anomaly
☐ Other important medical event (specify).....

Outcome: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Died If Died, date of death : _ _ /_ _ /_ _ Autopsy done: ☐Yes ☐No ☐Unknown

Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases). *Use additional sheets if needed:*

First Decision making level to complete:

Investigation needed: ☐ Yes ☐ No	If Yes, date investigation planned : _ _ /_ _ /_ _

National level to complete:

Date report received at National level _ _ /_ _ /_ _	AEFI worldwide unique ID :
Comments:	

Compulsory field

Page 1 of 2

January 2016

Description of elements in the AEFI reporting form (revised Jan 2016)

	Reporting element	Description
	AEFI reporting ID number	Unique number assigned to the AEFI case as per the national guidelines
Patient identifier	*Patient's Name	The name of the patient or initials as decided by the country
	*Patient's full Address	Geographic location of the case (address), please try to provide landmarks
	Telephone	Number to contact to provide or receive additional information
	Sex	Male or Female
	*Date of birth	Date** patient was born
	Age at onset	If date of birth is not known, this may be considered as first alternative
	Age Group at onset	If date of birth and age at onset is not known, this may be considered as second alternative
Reporter details	*Reporter´s Name	Name of person who has reported this AEFI to the healthcare system and also completed this form
	Institution	The place where the reporter is working or is affiliated to
	Designation & Department	Reporter's designation and his/her section of work
	Address	Reporters full address - Please add the name of the country here as well
	Telephone	Reporter's phone number
	E-mail	Reporter's e-mail address
	Date patient notified event to health system	The date** when the event was first brought to the notice of the healthcare system
	Today's date	Date** when the report was compiled by the reporter (this can be different from the date of notification (above))
Details of vaccination, vaccine(s) and diluent(s)	Vaccination centre or place of vaccination - name & address	Name and address of the place where the child received the vaccine - provide details (e.g. mobile clinic, home etc.)
	*Name of vaccine	The vaccine that is suspected to have caused the AEFI (provide brand name, if possible)
	Name (of other vaccines)	Other vaccines that were administered at the same time (provide brand name, if possible)
	*Date of vaccination	Date** when the vaccine was administered
	*Time of vaccination	Time** when vaccine was administered - try to be as accurate as possible
	*Batch/Lot number (of vaccine)	Batch number/lot number of each of the vaccines mentioned above
	Dose (1st, 2nd, etc.)	Dose number of the vaccine for the vaccinee e.g. 2nd dose of DTP or 5th Dose of OPV etc.
	Expiry date	The date** of expiry for each vaccine
	*Batch/Lot number (of diluent)	The batch/lot number of diluent (if applicable)
	Expiry date (of diluent)	The date** of expiry of the diluent
	Time of reconstitution	Time when the vaccine was reconstituted with the diluent
Adverse event(s)	*Adverse event(s)	The details of the events suspected to be caused by immunization. Multiple events can occur in a single patient. They need to be documented here
	Date & Time AEFI started	Date** and time** the event was first noticed
	Describe AEFI (Signs & Symptoms)	Description of the events in chronological order
	*Serious: Yes / No	If the case is serious, mark "Yes" and indicate one or several options: Death, Life threatening, Persistent or significant disability, Hospitalization, Congenital anomaly or Other important medical event that may jeopardize the patient or may require intervention to prevent one of the outcomes mentioned here
	*Outcome	Outcome of the reaction(s). Indicate status of the patient at the time of reporting: Recovering, Recovered, Recovered with sequelae, Not Recovered, Unknown or Died
	Died	Provide date of death and details of autopsy, if available
	Past medical history	Please include history of similar reaction or other allergies, concomitant medication and other relevant information (e.g. other cases in the locality or among those vaccinated)
Response	First Decision making level to complete	This section has to be completed by the decision maker for a detailed field AEFI investigation.
	Investigation needed	Decision on detailed field AEFI investigation.
	Date investigation planned	Date** when detailed investigation (including field investigation) is planned to start.
	National level to complete	This section has to be completed by the National level to decide on the next steps.
	Date report received at National level	Date** this report was received at the National level
	AEFI worldwide unique ID	Unique ID number (e.g. regulatory authority's case report number) for the AEFI case automatically generated for electronic transmission from National level to International level
	Comments	Please add additional details that will help with processing this report. Please include other documents as attachments, if necessary

** Compulsory field* — *Items marked with an asterix (*) have to be completed*

** Please use the local convention for the format e.g. DD/MM/YY or MM/DD/ YY or YY/MM/DD, for time use a 12 or 24 hours format

Annex 18: AEFI investigation form

AEFI INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A Basic details

Province/State **District** **Case ID**

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐ Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

Date of investigation: __ __ / __ __ / __ __ __ __
Date of filling this form: __ __ / __ __ / __ __ __ __

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐ M ☐ F

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

OR *Age at onset:* __ __ *years* __ __ *months* __ __ __ *days* ***OR*** *Age group:* ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years*

Patient's full address with landmarks *(Street name, house number, locality, phone number etc.)*:

Name of vaccines/diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom *(hh/mm)*: __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐ Unknown

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *(hh/mm)*: __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B Relevant patient information prior to immunization

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event	Yes / No / Unkn	
Adverse event after previous vaccination(s)	Yes / No / Unkn	
History of allergy to vaccine, drug or food	Yes / No / Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause	Yes / No / Unkn	
Patient currently on concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unkn	

For adult women
- Currently pregnant? Yes (weeks) _____ / No / Unknown
- Currently breastfeeding? Yes / No

For infants
The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

Section C	**Details of first examination** of serious AEFI case**		
Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy** ☐ **Other**_____ *If from verbal autopsy, please mention source* _____			
Name of the person who first examined/treated the patient:_____ Name of other persons treating the patient: _____ Other sources who provided information (specify): _____			
Signs and symptoms in chronological order from the time of vaccination:			
Name and contact information of person completing these clinical details:	Designation:	Date/time	

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D	**Details of vaccines provided at the site linked to AEFI on the corresponding day**										
Number immunized for each antigen at session site. Attach record if available.	Vaccine name										
	Number of doses										

a)	When was the patient immunized? (✓ the ☐ below and respond to ALL questions)	
	☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown	
	In case of multidose vials, was the vaccine given ☐ within the first few doses of the vial administered? ☐ within the last doses of the vial administered? ☐ unknown?	
b)	Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c)	Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d)	Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes* / No / Unable to assess
e)	Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes* / No / Unable to assess
f)	Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes* / No / Unable to assess
g)	Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes* / No / Unable to assess
h)	Number immunized from the concerned vaccine vial/ampoule	
i)	Number immunized with the concerned vaccine in the same session	
j)	Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k)	Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes* / No / Unable to assess
l)	Could this event be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes* / No / Unable to assess
m)	Is this case a part of a cluster?	Yes* / No / Unkn
	i. If yes, how many other cases have been detected in the cluster?	
	a. Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
	b. If no, number of vials used in the cluster (enter details separately)	

*__It is compulsory for you to provide explanations for these answers separately__

Section E Immunization practices at the place(s) where concerned vaccine was used

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn
If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____	
Specific key findings/additional observations and comments:	

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			

Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)

• Correct dose and route?	Yes / No

• Time of reconstitution mentioned on the vial? (in case of freeze dried vaccines)	Yes / No
• Non-touch technique followed?	Yes / No
• Contraindications screened prior to vaccination?	Yes / No
• How many AEFI were reported from the centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If Yes, specify the date of last training _____)	Yes / No
Specific key findings/ additional observations and comments?	

Section F **Cold chain and transport** *(Complete this section by asking and/or observing practice)*	
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality?
Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

Other comments:

Section H Other findings/observations/comments

Annex 19: AEFI Causality Assessment Worksheet

Step 1: Eligibility

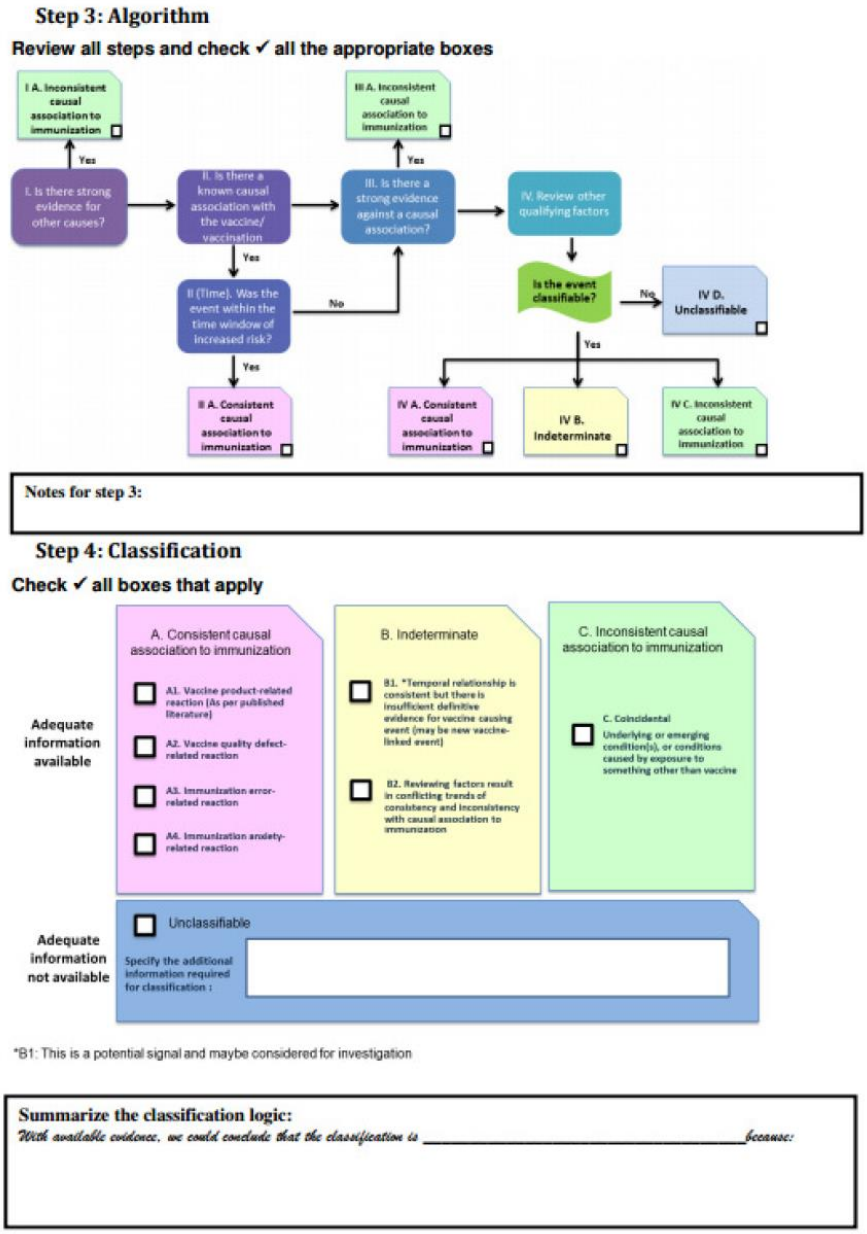
Name of the patient	Name of one or more vaccines administered before this event	What is the valid diagnosis?	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine/vaccination caused _____? (The event is for review in step 2)

I. Is there strong evidence for other causes?	**Y N UK NA**	**Remarks**
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐☐☐☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐☐☐☐	
Immunization error		
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐☐☐☐	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	☐☐☐☐	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
Did the event occur within an appropriate time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	☐☐☐☐	
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	☐☐☐☐	
Could the event be a manifestation of another health condition?	☐☐☐☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐☐☐☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐☐☐☐	
Was there acute illness prior to the event?	☐☐☐☐	
Did the event occur in the past independently of vaccination?	☐☐☐☐	
Was the patient taking any medication prior to vaccination?	☐☐☐☐	
Is there a biological plausibility that the vaccine could cause the event?	☐☐☐☐	

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable.



Source: Causality assessment of adverse event following immunization (AEFI): User manual for the revised WHO classification. World Health Organization. 2013. ISBN 978 92 4 150533 8. www.who.int/vaccine_safety/publications/gvs_aefi/en/