Safety of RTS,S/AS01$_E$ malaria vaccine up to 1 year after the third dose in Ghana, Kenya, and Malawi (EPI-MAL-003): a phase 4 cohort event monitoring study

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Summary

Background RTS,S/AS01$_E$ has been successfully administered to over two million children since 2019 through the Malaria Vaccine Implementation Programme (MVIP). In this Article, we report the safety results of a study evaluating RTS,S/AS01$_E$ safety and effectiveness in real-world settings.

Methods EPI-MAL-003 is an ongoing phase 4 disease surveillance study with prospective cohort event monitoring and hospital-based surveillance, done in the setting of routine health-care practice in Ghana, Kenya, and Malawi and fully embedded in the MVIP. The study design was dependent on the cluster-randomised vaccine implementation. In active surveillance, we enrolled children younger than 18 months from exposed (where RTS,S/AS01$_E$ was offered) and unexposed clusters. The coprimary endpoints were the occurrence of predefined adverse events of special interest and aetiology-confirmed meningitis. We report primary and secondary safety results up to 1 year after the primary vaccine schedule (three doses). The study is registered with ClinicalTrials.gov, NCT03855995.

Findings The first participant was enrolled on March 21, 2019. The cutoff date for the current analysis was 1 year after the third RTS,S/AS01$_E$ dose for each participant. In total, 44 912 children (19 993 in Ghana, 11 990 in Kenya, and 12 929 in Malawi) were included in the analysis set for the cluster-randomised comparison: 22 508 from exposed clusters and 22 404 from unexposed clusters. Incidence rates (expressed per 100 000 person-years) for generalised convulsive seizures and intussusception were similar between vaccinated and unvaccinated children. Aetiology-confirmed meningitis was reported in two children: one case of bacterial meningitis due to *Streptococcus pneumoniae* in an RTS,S/AS01$_E$-vaccinated child in the exposed clusters, and one case of viral meningitis due to human herpesvirus 6 in an unvaccinated child in the unexposed clusters. Both cases occurred within 12 months after vaccination in children in the cluster-design analysis set, leading to incidence rates of 4·1 (95% CI 0·1–23·0) per 100 000 person-years in RTS,S/AS01$_E$-vaccinated children and 4·0 (0·1–22·6) per 100 000 person-years in unvaccinated children, and a country-adjusted incidence rate ratio (IRR) of 0·96 (95% CI 0·06–15·34; p=0·98). Cerebral malaria cases were reported for four (<0·1%) of 20 639 RTS,S/AS01$_E$-vaccinated children in the exposed clusters and two (<0·1%) of 22 137 unvaccinated children in the unexposed clusters. These included three and two cases occurring within 12 months after the primary vaccination, in RTS,S/AS01$_E$-vaccinated children and unvaccinated children, respectively (IRR 1·43, 95% CI 0·24–8·58, p=0·70). Incidence rates for all-cause mortality were 659·7 (95% CI 561·5–770·3) in vaccinated children versus 724·5 (622·3–838·8) in unvaccinated children, with similar incidence rates for boys and girls.

Interpretation We found no evidence of vaccination being associated with an increased risk of meningitis, cerebral malaria, or mortality among vaccinated children, and no new safety risks were identified.

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Introduction

In 2023, approximately 263 million malaria cases occurred worldwide, leading to 597 000 deaths. Approximately 94% of cases and 95% of deaths (of which 76% were in children younger than 5 years) occurred in African countries.[1] Current malaria control measures include prevention of infection using insecticide-treated bed nets and indoor residual spraying to control the mosquito vector, and chemoprevention in pregnant people and children to reduce infection rates. Although these measures are effective in reducing malaria incidence, vector resistance to insecticides and parasite

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Research in context

Evidence before this study

We searched PubMed from database inception up to June 27, 2024, for any safety data for the RTS,S/AS01$_E$ malaria vaccine, using the search string ((RTS,S/AS01E[Title]) OR (RTS,S[Title])) AND ((safety signal) OR (risk)), with no language restrictions. Of the 47 manuscripts identified, 11 reported safety data after vaccination of children and infants from malaria-endemic regions with RTS,S/AS01$_E$ and previous formulations. Four papers reported data from phase 2 trials and five from phase 3 trials. Another manuscript reported data from the implementation of RTS,S/AS01$_E$ in national immunisation programmes 24 months after the cluster-randomised introduction of the vaccine, within the frame of the Malaria Vaccine Implementation Programme (MVIP) led by WHO and the respective Ministries of Health in three sub-Saharan countries (Ghana, Kenya, and Malawi). In the pivotal phase 3 trial, three safety signals were identified: increased incidence of meningitis and cerebral malaria in children vaccinated with RTS,S/AS01$_E$ and a higher mortality rate in girls who received RTS,S/AS01$_E$ compared with girls receiving control vaccine. These safety signals remained unexplained at the time, were considered a chance finding, had no temporal association with vaccination, and were not detected in any previous phase 2 studies, the other phase 3 studies, or 24 months after the introduction of RTS,S/AS01$_E$ in national immunisation programmes in Ghana, Kenya, and Malawi.

Added value of this study

The current phase 4 study was designed to monitor the safety and impact of RTS,S/AS01$_E$ after vaccine implementation by further investigating the safety signals previously observed in the pivotal phase 3 trial. The study is ongoing and is fully embedded within the MVIP. An evaluation of vaccine safety was done using enhanced surveillance in implementation and comparison areas. Results up to 1 year after third vaccine dose show that more than 80% of eligible children have received the primary three doses, with no evidence of the safety signals that were observed in the pivotal phase 3 clinical trial. Implementation of the vaccine in a real-world setting was associated with an 8% reduction in all-cause child death and a 14% reduction in death due to malaria during 12 months of follow-up after any vaccination. These results were observed in the context of relatively high vaccination coverage and during the COVID-19 pandemic.

Implications of all the available evidence

The analysis of available data up to 1 year after third RTS,S/AS01$_E$ dose shows that RTS,S/AS01$_E$ vaccination was not associated with any safety signals previously observed in the pivotal phase 3 trial, nor were any new safety concerns detected, in line with the MVIP data. These results support continued use of RTS,S/AS01$_E$ in children to reduce malaria-related disease and deaths in endemic countries.

resistance to chemotherapy are major threats for malaria control.[2] Despite wide implementation of measures, malaria control has stagnated in many endemic areas in Africa.[1] Vaccination, especially among young children, who bear the highest burden of disease, provides an additional tool to reduce malaria incidence and mortality.

The RTS,S/AS01$_E$ malaria vaccine was the first to be recommended by WHO. Since its pilot introduction in routine immunisation programmes within the Malaria Vaccine Implementation Programme (MVIP) in 2019, over 2 000 000 children from around 5 months of age from Ghana, Kenya, and Malawi were vaccinated with RTS,S/AS01$_E$.[3] In a pivotal phase 3 trial, which ran between 2009 and 2014 in seven sub-Saharan African countries, including Ghana, Kenya, and Malawi, 8922 children aged 5–17 months were enrolled. Children were provided with existing preventive and curative malaria interventions, and received primary vaccination with RTS,S/AS01$_E$ or a comparator vaccine (three doses administered 1 month apart) and a booster dose 18 months later.[4] Vaccine efficacy against clinical malaria over the 12 months after dose three was 51%,[5,6] and over a median follow-up of 48 months, vaccination with four doses showed 36% efficacy and averted, on average, 1774 cases of clinical malaria per 1000 vaccinated children.[4,5] Approximately 25% of children in the pivotal phase 3 trial had at least one serious adverse event; 0·3% had serious adverse events that were judged by investigators to be vaccine-related. An increased risk of febrile convulsions within the first 3 days after vaccination was reported.[7] Moreover, there was an increased number of clinically suspected meningitis cases and cerebral malaria in children who received RTS,S/AS01$_E$ compared with controls, and all-cause mortality was higher in vaccinated versus non-vaccinated girls; this imbalance was not observed in boys.[7] The imbalance between vaccinated and unvaccinated children for meningitis and malaria cases and all-cause mortality in girls were considered most likely to be chance findings[7] and the European Medicines Agency concluded that the benefits of the vaccine outweigh its risks.[8] However, based on a joint recommendation from the Strategic Advisory Group of Experts on Immunization and the Malaria Policy Advisory Group, WHO recommended further evaluation of vaccine safety in real-world settings before wide-scale deployment.[9] Therefore, GSK is conducting a series of studies within the framework of the MVIP, including an ongoing safety surveillance and vaccine effectiveness study (EPI-MAL-003).[10] Here, we report safety results of the EPI-MAL-003 study from a predetermined interim analysis done 1 year after dose three, including assessment of the safety signals of meningitis, cerebral malaria, and mortality in girls.

Methods

Study design and participants

EPI-MAL-003 is an ongoing phase 4 disease surveillance study with prospective cohort event monitoring and hospital-based surveillance, done in the setting of routine health-care practice in Ghana, Kenya, and Malawi. The study is done within the context of phased RTS,S/AS01$_E$ introduction under the MVIP, which used cluster-randomised vaccine implementation in the national Expanded Programmes on Immunisation (EPI) in each country. Cluster definition and randomisation in the MVIP were led by WHO and Ministries of Health in participating countries.[11] In the EPI-MAL-003 study, exposed clusters comprised study sites where RTS,S/AS01$_E$ was implemented and unexposed clusters were those where vaccination was not yet implemented at the time the study started (appendix p 1). As the study was done in real-life settings, some children from exposed clusters remained unvaccinated, and some in the unexposed clusters received the vaccine (in a different location, where vaccination was offered), depending on the parents' decision. The study design included active surveillance (home visits and continuous monitoring of outpatient visits and hospitalisations at all health-care facilities) and enhanced hospitalisation surveillance (continuous monitoring of hospitalisations in all children younger than 5 years) in both exposed and unexposed clusters (figure 1).

The interim analysis done on safety data up to 1 year after dose three included only children enrolled in active surveillance (ie, children younger than 18 months living in the geographical catchment areas of the study sites [exposed and unexposed clusters] and for whom written informed consent was provided by a parent or legally acceptable representative). Inclusion and exclusion criteria are provided in the appendix (p 2). Participants were identified at administration of diphtheria-tetanus-pertussis-hepatitis B-*Haemophilus influenzae* type B (DTP/HepB/Hib) vaccine within the EPI (usually given at 6, 10, and 14 weeks of age) or at hospitalisation before administration of the third DTP/HepB/Hib vaccine dose. To include all children who would receive RTS,S/AS01$_E$ from the start of vaccine implementation, children identified at first RTS,S/AS01$_E$ dose administration who either received all DTP/HepB/Hib doses before study start or received at least one DTP/HepB/Hib dose and were older than the age corresponding to the third DTP/HepB/Hib dose at study start, were also included.

This study is done in accordance with Good Clinical Practice, Good Pharmacoepidemiology Practices, and the principles of the Declaration of Helsinki. The study protocol was approved by national, regional, or investigational independent ethics committees or institutional review boards in each country. The study is registered with ClinicalTrials.gov, NCT03855995.

See Online for appendix

Procedures

In the period covered by this analysis, home visits were done approximately 1 week after each RTS,S/AS01$_E$ dose, and 6 weeks and 6 months after administration of the third dose. Unvaccinated children were visited at equal points in time according to their age, using a simulated vaccination schedule (figure 1).

At each home visit, the following information was recorded: vaccination status (any vaccine); any outpatient visits or hospitalisations at any health-care facility; body temperature and overall wellbeing of the child; any detected signs or symptoms; information about malaria control measures, health-care seeking behaviour, drug use, and exposure to environmental hazards; and developmental milestone delays (after the first and third dose).

For all hospitalised children suspected of having an adverse event of special interest or meningitis, a blood sample (approximately 5 mL) was collected and tested by

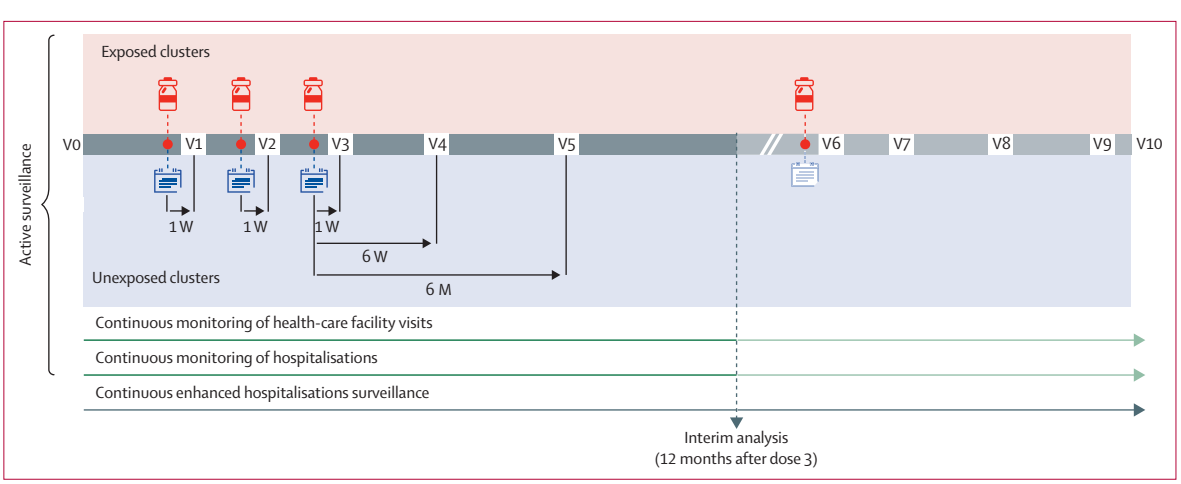

Figure 1: **Study design**

Exposed indicates children from sites where RTS,S/AS01$_E$ was administered. Unexposed indicates children from sites where RTS,S/AS01$_E$ was not administered. Vials symbolise vaccination with RTS,S/AS01$_E$. The calendar symbolises the simulated vaccination schedule for children in unexposed clusters, at equal points in time according to their ages. Shaded elements are not in the scope of this analysis. M=months. V=study visit. W=week(s).

an external reference laboratory. Hospitalisation was defined as spending at least one night at a health-care facility, which included children with non-severe disease who lived too far to be sent home on the same day and stayed overnight for monitoring purposes. For all cases of suspected neurological adverse events of special interest or meningitis, where a cerebrospinal fluid sample was taken as part of routine practice and sufficient sample volume was available, the sample was also tested by an external reference laboratory.

In case of death, the cause was systematically documented through verbal autopsy using the INDEPTH Standard Verbal Autopsy Questionnaire[12] for children who died at home or based on medical records for children who died at a primary health-care facility or hospital.

To ensure accurate case detection and diagnosis, several measures were implemented before and during the study, ranging from enhanced periodic and refresher trainings for site staff and medical and non-medical health-care workers on pharmacovigilance and diagnosis of adverse events of special interest and meningitis, to the provision of job aids for adverse event of special interest identification (appendix p 14).

Outcomes

Study objectives and endpoints are presented in the appendix (pp 3–4). Here, we report safety results only. The coprimary endpoints of the study were the incidence of adverse events of special interest and the occurrence of aetiology-confirmed meningitis. Secondary safety endpoints included the occurrence of probable meningitis, clinically suspected meningitis, cerebral malaria, mortality (overall and by sex), febrile convulsions (during the 3-day and 7-day period following each RTS,S/AS01$_E$ vaccination), and other adverse events leading to hospitalisation. Risk periods and case definitions used for safety endpoints are detailed in the appendix (pp 5–13).

Cluster design comparison

	Exposed (six clusters)	Unexposed (six clusters)	Total
Enrolled	22564	22436	45000*
Excluded from the analyses	56	31	87
Eligibility criteria not met	5	0	5
Inclusion not done according to procedure or acceptable timeframe	51	31	82
Analysis set	22508	22404*	44912

Before–after comparison

	Exposed (three clusters; EPI-MAL-003 study)	Unexposed (three sites; EPI-MAL-002 study)	Total
Analysis set	12992	16733	29725

Figure 2: **Participant flowchart**
Exposed indicates children from sites where RTS,S/AS01$_E$ was administered. Unexposed indicates children from sites where RTS,S/AS01$_E$ was not administered. *A child who was enrolled by mistake in active surveillance was not included in the analysis set.

Statistical analysis

The number of children targeted for enrolment in active surveillance was at least 22500 (with at least 20250 vaccinated) in the exposed clusters and at least 22500 in the unexposed clusters (45000 children in total). The precision of estimates for the coprimary objectives under different assumptions is provided in the appendix (p 15).

Incidence rates were computed by dividing the number of first events reported during the at-risk period after each dose (appendix p 5) by the accumulated person-time during the at-risk period after each of the three (RTS,S/AS01$_E$ or simulated) vaccine doses, with censoring of children when they received the following dose. Incidence rates were estimated for vaccinated children in exposed clusters and unvaccinated children in unexposed clusters with exact Poisson 95% CIs and expressed per 100000 person-years. Incidence rate ratios (IRRs) were calculated using Poisson regression or negative binomial regression in case of overdispersion (ie, variance value of data greater than the mean value), with country as a fixed effect and unvaccinated or unexposed status as a reference. IRRs were estimated with 95% Wald CIs.

The analysis set included all evaluable study participants who met all eligibility criteria and complied with all protocol-defined procedures. Two types of comparisons were planned. A contemporaneous, cluster-design comparison was done between vaccinated children from exposed clusters and unvaccinated children from unexposed clusters in the current study. A temporal, before–after comparison was also done using data collected in the pre-RTS,S/AS01$_E$ implementation study EPI-MAL-002 (NCT02374450; done between January, 2016, and July, 2022[13]). For the before–after comparison, children in exposed clusters at three study sites (Kintampo, Navrongo, and Kombewa) in the EPI-MAL-003 study were compared with children at the same sites in the EPI-MAL-002 study. These sites (the only ones common to both studies) were unexposed in the EPI-MAL-002 study and became exposed in the EPI-MAL-003 study.

All statistical analyses were done with SAS v9.4, without adjustment for multiplicity.

Role of the funding source

The study sponsor was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

The first participant was enrolled on March 21, 2019. The cutoff date for the current analysis was 1 year after the third RTS,S/AS01$_E$ dose for each participant. In total,

	Cluster design comparison		Before–after comparison	
	Exposed (n=22 508)	Unexposed (n=22 404)	Exposed (n=12 992)	Unexposed (n=16 733)
Age at informed consent, months	3·07 (1·88)	2·41 (1·27)	3·34 (2·13)	3·16 (2·98)
Sex				
Girls	11 130 (49·4%)	11 255 (50·2%)	6377 (49·1%)	8252 (49·3%)
Boys	11 378 (50·6%)	11 149 (49·8%)	6615 (50·9%)	8481 (50·7%)
RTS,S/AS01$_E$ vaccination status, doses received				
None	1869 (8·3%)	22 137 (98·8%)	672 (5·2%)	16 733 (100%)
One	633 (2·8%)	44 (0·2%)	..	..
Two	894 (4·0%)	35 (0·2%)	..	..
At least three*	19 112 (84·9%)	188 (0·8%)	..	..
Any dose	20 639 (91·7%)	267 (1·2%)	12 320 (94·8%)	..
Number of people living in household	5·9 (2·6)	5·6 (2·5)	6·4 (2·9)	6·1 (2·8)
Neighbourhood of residence				
Urban	2317 (10·3%)	4077 (18·2%)	1956 (15·1%)	2641 (15·8%)
Semi-rural	1598 (7·1%)	2026 (9·0%)	1280 (9·9%)	2602 (15·6%)
Rural	18 593 (82·6%)	16 301 (72·8%)	9756 (75·1%)	11 490 (68·7%)
Closest health-care facility				
Approximate distance <5 km	17 121 (76·1%)	16 141 (72·0%)	11 810 (90·9%)	15 360 (91·8%)
Type				
Primary health-care facility	17 144 (76·2%)	13 699 (61·1%)	10 152 (78·1%)	12 347 (73·8%)
Hospital	5364 (23·8%)	8705 (38·9%)	2840 (21·9%)	4386 (26·2%)

Data are mean (SD) or n (%). Exposed indicates children from sites where RTS,S/AS01$_E$ was administered. Unexposed indicates children from sites where RTS,S/AS01$_E$ was not administered. *At the time of database freeze, most of these children had already received the fourth dose.

Table 1: **Participant characteristics (analysis set)**

44 912 children (19 993 in Ghana, 11 990 in Kenya, and 12 929 in Malawi) were included in the analysis set for the cluster-randomised comparison: 22 508 from exposed clusters and 22 404 from unexposed clusters. 38 571 (85·9%) of 44 912 children in the cluster-randomised comparison were still in the study at 12 months after dose three. For the before–after comparison, the analysis set included 12 992 exposed children from the current study and 16 733 unexposed children from the EPI-MAL-002 study (figure 2).

Overall, participant characteristics were balanced between the exposed and unexposed clusters. In the cluster analysis set, children in the exposed clusters were slightly older than in unexposed clusters. In the exposed clusters, 19 112 (84·9%) of 22 508 children received at least three RTS,S/AS01$_E$ doses (table 1). All but 33 doses (recalled by parents) were documented in vaccination cards.

Cumulatively, during the entire period of follow-up covered by this analysis, 16 (0·1%) of 20 639 vaccinated children in the exposed clusters had at least one confirmed adverse event of special interest diagnosed at hospitalisation: generalised convulsive seizures (in 13 children) and intussusception (three children). In the unexposed clusters, 15 (0·1%) of 22 137 unvaccinated children had at least one adverse event of special interest: generalised convulsive seizures (in nine children), intussusception (four children), juvenile chronic arthritis (one child), and thrombocytopenia (one child; table 2).

In the cluster-design analysis set, no cases of intussusception were reported within 2 weeks after RTS,S/AS01$_E$ vaccination, compared with one case in unvaccinated children (incidence rate 38·5, 95% CI 1·0–214·7 per 100 000 person-years). Six generalised convulsive seizures were reported within 2 weeks after RTS,S/AS01$_E$ vaccination, leading to an incidence rate of 247·4 (90·8–538·5) per 100 000 person-years; no cases were reported in unvaccinated children. In the before–after analysis set, two cases of intussusception were reported within 2 weeks after vaccination, both in unvaccinated children (incidence rate 101·8, 2·3–367·6 per 100 000 person-years). One case of generalised convulsive seizures (incidence rate 67·5, 1·7–376·3 per 100 000 person-years) occurred within 2 weeks after vaccination in vaccinated children, and none in unvaccinated children (table 3).

Aetiology-confirmed meningitis was reported in two children: one case of bacterial meningitis due to *Streptococcus pneumoniae* in an RTS,S/AS01$_E$-vaccinated child in the exposed clusters, and one case of viral meningitis due to human herpesvirus 6 in an unvaccinated child in the unexposed clusters. Both cases occurred within 12 months after vaccination in children in the cluster-design analysis set, leading to incidence rates of 4·1 (95% CI 0·1–23·0) per 100 000 person-years in RTS,S/AS01$_E$-vaccinated children and 4·0 (0·1–22·6) per 100 000 person-years in unvaccinated children, and a

	Exposed clusters		Unexposed clusters	
	Vaccinated (n=20 639)	Unvaccinated (n=1869)	Vaccinated (n=267)	Unvaccinated (n=22 137)
Any adverse event of special interest	16 (0·1%)	0	0	15 (0·1%)
General convulsive seizures	13 (0·1%)	0	0	9 (<0·1%)
Intussusception	3 (<0·1%)	0	0	4 (<0·1%)
Juvenile chronic arthritis	0	0	0	1 (<0·1%)
Thrombocytopenia	0	0	0	1 (<0·1%)
Any meningitis	26 (0·1%)	1 (0·1%)	3 (1·1%)	45 (0·2%)
Aetiology-confirmed meningitis	1 (<0·1%)	0	0	1 (<0·1%)
Clinically suspected meningitis	4 (<0·1%)	1 (0·1%)	0	9 (<0·1%)
Probable meningitis	1 (<0·1%)	0	0	0
Any malaria	5410 (26·2%)	176 (9·4%)	59 (22·1%)	6368 (28·8%)
Uncomplicated malaria	5352 (25·9%)	172 (9·2%)	55 (20·6%)	6288 (28·4%)
Severe malaria	94 (0·5%)	5 (0·3%)	5 (1·9%)	142 (0·6%)
Cerebral malaria	4 (<0·1%)	0	0	2 (<0·1%)
Febrile convulsions	10 (<0·1%)	0	0	8 (<0·1%)
Anaemia	999 (4·8%)	52 (2·8%)	10 (3·7%)	1127 (5·1%)
Severe anaemia	169 (0·8%)	11 (0·6%)	2 (0·7%)	179 (0·8%)
Hospitalisation, all-cause	1826 (8·8%)	93 (5·0%)	28 (10·5%)	2097 (9·5%)
Due to adverse event of special interest	15 (0·1%)	0	0	14 (0·1%)
Due to malaria	570 (2·8%)	43 (2·3%)	10 (3·7%)	749 (3·4%)
Due to meningitis	6 (<0·1%)	1 (0·1%)	0	10 (<0·1%)
Death, all-cause	161 (0·8%)	34 (1·8%)	2 (0·7%)	179 (0·8%)
Girls	81 (0·8%)	17 (0·9%)	0	88 (0·4%)
Boys	80 (0·8%)	17 (0·9%)	2 (0·7%)	91 (0·4%)
Due to adverse event of special interest	1 (<0·1%)	0	0	4 (<0·1%)
Due to malaria	22 (0·1%)	1 (0·1%)	0	23 (0·1%)
Due to meningitis	1 (<0·1%)	0	0	4 (<0·1%)
Other adverse event leading to hospitalisation	1786 (8·7%)	90 (4·8%)	28 (10·5%)	2056 (9·3%)
Gastroenteritis	653 (3·2%)	42 (2·2%)	11 (4·1%)	783 (3·5%)
Anaemia	601 (2·9%)	46 (2·5%)	10 (3·7%)	797 (3·6%)
Sepsis	521 (2·5%)	37 (2·0%)	8 (3·0%)	676 (3·1%)
Iron deficiency anaemia	457 (2·2%)	8 (0·4%)	1 (0·4%)	382 (1·7%)
Pneumonia	403 (2·0%)	26 (1·4%)	12 (4·5%)	523 (2·4%)
Bacterial pneumonia	123 (0·6%)	1 (0·1%)	0	22 (0·1%)

Exposed children are from sites where RTS,S/AS01$_E$ was administered. Unexposed children are from sites where RTS,S/AS01$_E$ was not administered. Data shown are the number of children reporting the event at least once. All adverse events are shown, except adverse events of special interest, meningitis, or malaria, based on Medical Dictionary for Regulatory Activities preferred term. Only the most frequent preferred terms are presented here.

Table 2: **Adverse events reported starting from dose one and up to 1 year after the third dose (analysis set)**

country-adjusted IRR of 0·96 (95% CI 0·06–15·34; p=0·98). The before–after analysis set included one RTS,S/AS01$_E$-vaccinated and two unvaccinated children with aetiology-confirmed meningitis within 12 months after vaccination, with an estimated IRR of 0·62 (95% CI 0·06–6·85; p=0·70; table 3). Cumulative numbers for secondary safety endpoints and the corresponding incidence rates and IRRs (when estimable) within the at-risk periods are reported in tables 2 and 3.

Cerebral malaria cases were reported for four (<0·1%) of 20 639 RTS,S/AS01$_E$-vaccinated children in the exposed clusters and two (<0·1%) of 22 137 unvaccinated children in the unexposed clusters (table 2), including three and two cases occurring within 12 months after vaccination, in RTS,S/AS01$_E$-vaccinated children and unvaccinated children, respectively. Country-adjusted IRRs were 1·43 (95% CI 0·24–8·58; p=0·70) in the cluster-design comparison and 1·88 (0·31–11·25; p=0·49) in the before–after comparison (table 3).

All-cause death was reported for 161 (0·8%) of 20 639 vaccinated and 34 (1·8%) of 1869 unvaccinated children in exposed clusters and two (0·7%) of 267 vaccinated children and 179 (0·8%) of 22 137 unvaccinated children in unexposed clusters. The proportions of vaccinated and unvaccinated children with fatal events were similar between girls and boys (table 2). Incidence rates for

	Number of children with at least one event	Number of first events after each dose reported	Person-years	Incidence rate per 100 000 person-years (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI)
Cluster design comparison						
Adverse events of special interest						
Generalised convulsive seizures, at-risk 2 weeks						
Vaccinated	6*	6	2425·0	247·4 (90·8–538·5)	NE	NE
Unvaccinated	0	0	2595·6	0·0 (0·0–142·1)	..	..
Intussusception, at-risk 2 weeks						
Vaccinated	0	0	2425·1	0·0 (0·0–152·1)	NE	NE
Unvaccinated	1	1	2595·6	38·5 (1·0–214·7)	..	..
Aetiology-confirmed meningitis, at-risk 12 months						
Vaccinated	1*	1	24 251·8	4·1 (0·1–23·0)	1·02 (0·06–16·29); p=0·99	0·96 (0·06–15·34); p=0·98
Unvaccinated	1	1	24 705·3	4·0 (0·1–22·6)	..	..
Any meningitis, at-risk 12 months						
Vaccinated	6*	6	24 251·1	24·7 (9·1–53·9)	0·61 (0·22–1·68); p=0·34	0·59 (0·21–1·62); p=0·31
Unvaccinated	10	10	24 703·6	40·5 (19·4–74·4)	..	..
Cerebral malaria, at-risk 12 months						
Vaccinated	3*	3	24 250·7	12·4 (2·6–36·2)	1·53 (0·26–9·15); p=0·65	1·43 (0·24–8·58); p=0·70
Unvaccinated	2	2	24 705·3	8·1 (1·0–29·2)	..	..
Death, all-cause, at-risk 12 months						
Vaccinated	160*	160	24 251·9	659·7 (561·5–770·3)	0·91 (0·74–1·13); p=0·39	0·92 (0·74–1·13); p=0·43
Unvaccinated	179	179	24 705·4	724·5 (622·3–838·8)	..	..
Girls						
Vaccinated	80	80	11 945·7	669·7 (531·0–833·5)	0·94 (0·70–1·28); p=0·71	0·95 (0·70–1·28); p=0·72
Unvaccinated	88	88	12 405·6	709·4 (568·9–873·9)	..	..
Boys						
Vaccinated	80	80	12 306·1	650·1 (515·5–809·1)	0·88 (0·65–1·19); p=0·40	0·89 (0·66–1·20); p=0·44
Unvaccinated	91	91	12 299·8	739·8 (595·7–908·4)	..	..
Death, due to malaria, at-risk 12 months						
Vaccinated	21	21	24 251·9	86·6 (53·6–132·4)	0·93 (0·51–1·68); p=0·81	0·92 (0·51–1·67); p=0·79
Unvaccinated	23	23	24 705·4	93·1 (59·0–139·7)	..	..
Any hospitalisation due to other adverse events						
30 days						
Vaccinated	547	567	4907·4	11 554·0 (10 622·5–12 545·4)	1·12 (1·00–1·26); p=0·056	1·10 (0·98–1·24); p=0·11
Unvaccinated	514	543	5271·7	10 300·2 (9451·9–11 204·1)	..	..
12 months						
Vaccinated	1778	1934	23 493·7	8232·0 (7869·2–8607·2)	0·88 (0·83–0·93); p<0·001	0·86 (0·81–0·91); p<0·001
Unvaccinated	2051	2226	23 761·3	9368·2 (8983·0–9765·6)	..	..
Hospitalisation due to anaemia†, at-risk 30 days						
Vaccinated	316	320	4918·5	6506·0 (5812·6–7259·4)	1·21 (1·04–1·43); p=0·017	1·19 (1·01; 1·39); p=0·035
Unvaccinated	275	283	5283·1	5356·7 (4750·7; 6018·5)	..	..
Hospitalisation due to pneumonia‡, at-risk 30 days						
Vaccinated	174	176	4924·2	3574·2 (3065·7–4143·0)	1·28 (1·03–1·59); p=0·028	1·28 (1·03–1·59); p=0·029
Unvaccinated	145	148	5288·8	2798·4 (2365·7–3287·3)	..	..
Before–after comparison						
Adverse events of special interest						
Generalised convulsive seizures, at-risk 2 weeks						
Vaccinated	1	1	1480·5	67·5 (1·7–376·3)	NE	NE
Unvaccinated	0	0	1965·6	0·0 (0·0–187·7)	..	..

(Table 3 continues on next page)

	Number of children with at least one event	Number of first events after each dose reported	Person-years	Incidence rate per 100 000 person-years (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI)
(Continued from previous page)						
Intussusception, at-risk 2 weeks						
Vaccinated	0	0	1480·5	0·0 (0·0–249·2)	NE	NE
Unvaccinated	2	2	1965·5	101·8 (12·3–367·6)	..	..
Aetiology-confirmed meningitis, at-risk 12 months						
Vaccinated	1	1	15 376·7	6·5 (0·2–36·2)	0·61 (0·06–6·76); p=0·69	0·62 (0·06–6·85); p=0·70
Unvaccinated	2	2	18 860·0	10·6 (1·3–38·3)	..	..
Any meningitis, at-risk 12 months						
Vaccinated	2	2	15 376·3	13·0 (1·6–47·0)	0·41 (0·08–2·03); p=0·28	0·43 (0·09–2·12); p=0·30
Unvaccinated	6	6	18 857·2	31·8 (11·7–69·3)	..	..
Cerebral malaria, at-risk 12 months						
Vaccinated	3		15 375·5	19·5 (4·0–57·0)	1·84 (0·31–11·01); p=0·51	1·88 (0·31–11·25); p=0·49
Unvaccinated	2		18 860·3	10·6 (1·3–38·3)	..	..
Death, all-cause, at-risk 12 months						
Vaccinated	90	90	15 376·8	585·3 (470·6–719·4)	0·75 (0·58–0·98); p=0·032	0·76 (0·59–0·99); p=0·045
Unvaccinated	147	147	18 861·2	779·4 (658·5–916·0)	..	..
Girls						
Vaccinated	46	46	7538·3	610·2 (446·8–813·9)	0·82 (0·57–1·19); p=0·30	0·83 (0·57–1·21); p=0·34
Unvaccinated	69	69	9282·5	743·3 (578·4–940·7)	..	..
Boys						
Vaccinated	44	44	7838·5	561·3 (407·9–753·6)	0·69 (0·48–1·00); p=0·048	0·70 (0·49–1·02); p=0·062
Unvaccinated	78	78	9578·7	814·3 (643·7–1016·3)	..	..
Death, due to malaria, at-risk 12 months						
Vaccinated	15	15	15 376·8	97·5 (54·6–160·9)	0·63 (0·34–1·18); p=0·16	0·65 (0·35–1·21); p=0·17
Unvaccinated	29	29	18 861·2	153·8 (103·0–220·8)	..	..
Any hospitalisation due to other adverse events						
30 days						
Vaccinated	450	465	3000·0	15 499·8 (14 122·8–16 974·7)	1·70 (1·48–1·95); p<0·001	1·66 (1·45–1·91); p<0·001
Unvaccinated	342	358	3919·8	9133·0 (8211·4–10 129·9)	..	..
12 months						
Vaccinated	1444	1589	14 729·0	10 788·2 (10 264·2–11 332·0)	1·20 (1·12–1·29); p<0·001	1·18 (1·10–1·27); p<0·001
Unvaccinated	1545	1630	18 132·9	8989·2 (8558·0–9436·4)	..	..
Hospitalisation due to anaemia†, at-risk 30 days						
Vaccinated	268	270	3009·0	8973·0 (7934·5–10 109·7)	1·71 (1·43; 2·05); p<0·001	1·67 (1·40; 2·01); p<0·001
Unvaccinated	203	206	3926·6	5246·3 (4554·3–6013·7)	..	..
Hospitalisation due to pneumonia‡, at-risk 30 days						
Vaccinated	134	135	3014·4	4478·4 (3754·9–5300·8)	1·73 (1·33–2·23); p<0·001	1·69 (1·31–2·19); p<0·001
Unvaccinated	101	102	3930·6	2595·0 (2115·9–3150·2)	..	..

Vaccinated children from the exposed clusters and unvaccinated children from the unexposed clusters are shown. IRR=incidence rate ratio. NE=not estimable (due to insufficient number of events). Person-years were calculated as the sum of the follow-up periods at risk of the children (in years). Adjusted IRR was calculated as an estimation of risk ratio using a Poisson or negative binomial regression model with country as a fixed effect and unvaccinated or unexposed as a reference. Only events that had occurrences within the evaluated at-risk period are shown. *Of the six generalised convulsive seizures, three occurred after dose 1 and three after dose 3, two cases occurred in the first week and four in the second week of the at-risk period, and five cases presented with a suspected concomitant medical condition (sepsis, bacterial infection, or pneumonia) that could explain the occurrence of seizures; of the three cerebral malaria cases, two occurred after dose 2 and one after dose 3; of the six meningitis cases, two occurred after dose 1, one after dose 2, and three after dose 3 (the latter including the aetiology-confirmed meningitis case); of the 160 deaths, 33 occurred after dose 1, 30 after dose 2, and 97 after dose 3 (follow-up periods after each dose were different: 1 month after dose 1 and dose 2 and 12 months after dose 3). †Anaemia as measured by haemoglobin <11 g/dL (post-hoc analysis). ‡Pneumonia includes all Medical Dictionary for Regulatory Activities preferred terms: pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia chlamydial, pneumonia pneumococcal, and pneumonia viral (post-hoc analysis).

Table 3: **Incidence rates and IRRs of adverse events occurring within the predefined at-risk periods after vaccination (analysis set)**

all-cause mortality were 659·7 (95% CI 561·5–770·3) in vaccinated children versus 724·5 (622·3–838·8) in unvaccinated children in the cluster-design comparison. Country-adjusted IRRs for all-cause mortality were 0·92 (95% CI 0·74–1·13; p=0·43) and 0·76 (0·59–0·99; p=0·045) in the cluster-design and before–after

comparison, respectively. Country-adjusted IRRs were 0·95 (95% CI 0·70–1·28; p=0·72) and 0·83 (0·57–1·21; p=0·34) in girls and 0·89 (0·66–1·20; p=0·44) and 0·70 (0·49–1·02; p=0·062) in boys, in the cluster-design and before–after comparison, respectively (table 3).

Ten (<0·1%) of 20 639 vaccinated children from the exposed clusters reported febrile convulsions during hospitalisation, all occurring more than 3 days after vaccination and only one within the risk period of 7 days. In the unexposed clusters, eight (<0·1%) of 22 137 unvaccinated children reported febrile convulsions.

Within 12 months after vaccination, the estimated country-adjusted IRRs for any hospitalisation due to other adverse events were 0·86 (95% CI 0·81–0·91; p<0·001; cluster-design), and 1·18 (1·10–1·27; p<0·001; before–after comparison). Country-adjusted IRRs for hospitalisation due to anaemia and pneumonia tended to be higher in the before–after comparison than in the cluster-design comparison (table 3). Incidence rates and IRRs for hospitalisations by primary system organ class are reported in the appendix (pp 16–17).

Discussion

In the framework of the MVIP, RTS,S/AS01$_E$ was introduced in selected areas in three sub-Saharan African countries through their respective national immunisation programmes. Feasibility and impact were evaluated in the Malaria Vaccine Pilot Evaluation (MVPE), along with an assessment of the safety signals detected in the pivotal phase 3 trial.[9] MVPE data collected approximately 24 months after vaccine introduction in Malawi and Ghana, and around 19 months after introduction in Kenya, showed no evidence[11] of the safety signals that had been observed in the RTS,S/AS01$_E$ phase 3 trial.[4,7] Based on this evidence, WHO recommended in 2021 that RTS,S/AS01$_E$ should be widely implemented in regions with moderate-to-high *Plasmodium falciparum* malaria transmission to prevent malaria in young children.[14]

Our ongoing phase 4 programme is part of a post-approval plan comprising four complementary studies to evaluate the safety, effectiveness, and impact of RTS,S/AS01$_E$ in young children through active participant follow-up. The EPI-MAL-003 study is fully embedded in the MVIP and used broad eligibility criteria for enrolment, leading to a large analysis set of 44 912 children, making it the largest observational study to date on the outcomes of malaria vaccination in real-world settings. The study design includes both active surveillance (based on home visits with continuous monitoring of outpatient and inpatient visits) and enhanced pharmacovigilance procedures and uses comprehensive data collection systems, allowing collection of individual-level data, whereas the MVPE relied mostly on cross-sectional community surveys and sentinel hospital reporting. Additionally, training of medical and non-medical personnel involved was provided throughout the study, improving the identification, reporting, and proper management of suspected adverse events of special interest. Refer to the graphical abstract for a visual representation of the key findings of the study (appendix p 18).

In our study, we observed high vaccine coverage of around 85% for the first three RTS,S/AS01$_E$ doses, which indicates successful integration of the vaccine in the EPI in each country. This coverage is higher than that estimated in the MVPE in the first 18 months after vaccine introduction (up to 66%).[11] However, vaccine uptake was evaluated through household surveys in the MVPE, which could have led to underestimation.

Over the 1-year period after primary vaccination, we found no evidence of an association between vaccine exposure and any prespecified adverse events of special interest or aetiology-confirmed meningitis. All cases of generalised convulsive seizures requiring hospitalisation within the 2-week at-risk period occurred in vaccinated children, but, as no cases were reported during this period among unvaccinated children, the relative risk could not be estimated. Although RTS,S/AS01$_E$ was previously found to be associated with an increased risk of generalised convulsive seizures within 3 days after vaccination,[7] our findings are reassuring. Few cases required hospitalisation, and most convulsions occurred in the second week after vaccination, often involving children with suspected contributing medical conditions. For aetiology-confirmed meningitis within 12 months after vaccination, incidence rates were similar between vaccinated and unvaccinated children for each comparison, indicating no evidence of an increased risk. However, incidence rates for cerebral malaria were higher in vaccinated children than in unvaccinated children in both comparisons, although statistical significance was not reached due to the small number of cases. Incidence rates for all-cause death tended to be lower in vaccinated children versus unvaccinated children, indicating an 8% reduction in mortality in the cluster-design comparison. This finding compares well with the 9% reduction observed from the MVPE data;[11] however, unlike the MVPE estimates, our estimates also included deaths caused by injury. In the temporal comparison, a 24% reduction in mortality was observed after RTS,S/AS01$_E$ implementation. When estimated by sex, a reduction in mortality rates was observed for vaccinated girls and boys, similar to the MVPE findings.[11]

The risk of hospitalisation due to other adverse events occurring within 12 months after vaccination was reduced by 14% in vaccinated children versus unvaccinated children in the cluster-design comparison, in line with the 9% reduction observed for all-cause hospitalisation in the MVPE.[11] However, in the before–after comparisons, the risk was increased by 18%. This discrepancy is hard to interpret, but might be at least partly due to an increased awareness of adverse events among parents and health-care workers due to the MVIP, which could have led parents to seek health advice and medical staff to recommend hospitalisations more

frequently. In the before–after comparison, an increased risk of hospitalisations due to anaemia and pneumonia within 30 days after vaccination was observed. This finding contrasts with previous findings for decreased anaemia and pneumonia risk in RTS,S/AS01$_E$-vaccinated children versus unvaccinated children.[15] No biological mechanism supports a potential causal association between RTS,S/AS01$_E$ vaccination and anaemia or pneumonia. We saw no other evidence of any arising safety concerns.

Our study is not without limitations. First, being done under the MVIP, its design was dependent on the staggered, cluster-randomised, RTS,S/AS01$_E$ implementation in the national EPIs. This restriction affected study site selection and imposed the use of a cluster-randomised design. This design might lead to over-representation or under-representation of certain subgroups in the overall sample. Nevertheless, basic demographic data showed a good overall balance between vaccinated and unvaccinated children. Second, despite investing substantial resources in enhancing pharmacovigilance practices and clinical data collection, safety research in mostly rural areas in sub-Saharan Africa remains challenging. The study period overlapped with the COVID-19 pandemic, which further limited the possibility of home visits. Nevertheless, several measures were put in place to minimise any impact, such as conducting home visits remotely, via telephone contact. We observed no important protocol deviations due to COVID-19 that led to participant elimination from the analysis set. The study assessed events that resulted in hospitalisation, but children might die before reaching a hospital and the use of the verbal autopsy might limit the ascertainment of the exact cause of death, despite use of a standardised tool. Observer bias and differences in preferred term reporting and coding of data across different study sites cannot be excluded, although medical and non-medical personnel were trained to reduce the impact of this. Finally, results of the before–after comparison are sometimes difficult to interpret, despite efforts to standardise data collection over the two studies. Due to the long study durations and the temporal separation of data collection, improvements over time in detecting and reporting adverse events and changes in diagnostic procedures could have occurred; this factor, together with the variable implementation of malaria control measures and potential year-to-year variations in malaria transmission, could have affected the results.

In conclusion, our findings support the favourable safety profile of RTS,S/AS01$_E$ and its continued use in children in national immunisation programmes in sub-Saharan Africa. Over the 1-year follow-up period after primary vaccination, we found no evidence of vaccination being associated with any safety risk, including the signals previously identified in the pivotal phase 3 study.

Contributors

ARO, CC, KM, KPA, LN, LS, MOn, MOr, MS, MD, NAA, BO, POA, FR, SiK, VH, WO, and YGM were involved in the study concept or design. ARO, BO, BOO, DKA, DM, EA, FO, GOO, IO, JNO, JMO, JO, KM, KK, KPA, LN, LOA, MOn, MBK, NAA, NF, OB, PO-O, POA, PM, PDA, RC, RYC, SBEH, SO-A, SeK, PMS, SiK, SKA, TMJ, VS, VKP, WO, and WN were involved in data acquisition. ARO, BO, CC, EA, EAO, FO, JNO, JMO, JO, KM, KK, KPA, LN, LS, MOn, MOr, MD, NAA, NF, OB, POA, PDA, RD, FR, SBEH, SO-A, SeK, PMS, SiK, TMJ, VS, VH, WO, WN, and YGM were involved in data analysis. ARO, BO, BOO, CC, EA, EAO, FO, GOO, JNO, JMO, JO, KM, KK, KPA, LN, LS, MOn, MOr, MS, MD, NAA, NF, OB, PO-O, POA, PDA, RD, RYC, FR, SBEH, SO-A, SeK, PMS, SiK, VS, VH, WO, WN, and YGM were involved in data interpretation. BO, KM, KPA, LN, MOn, MS, POA, VH, and VS were members of the core writing team. All authors had full access to the clinical study report, individual listings, and any additional analyses that were done. All authors had final responsibility for the decision to submit for publication. MOn and VH had access to and verified all the data used in the study.

Declaration of interests

CC, LS, MS, MD, RD, FR, VH, and YGM are or were employees of GSK when the study was designed, initiated, or conducted. MOr was a contractor for GSK when the study was designed, initiated, or conducted. CC, MS, MD, FR, VH, and YGM also hold financial equities in GSK. KM reports funding to his institution through a clinical trial agreement from GSK for the conduct of the study. NF reports funding to his institution from GSK in the form of a contract. All other authors declare no competing interests.

Data sharing

GSK makes available anonymised individual participant data and associated documents from interventional clinical studies that evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data, and for clinical studies not listed, please submit an enquiry via the website.

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