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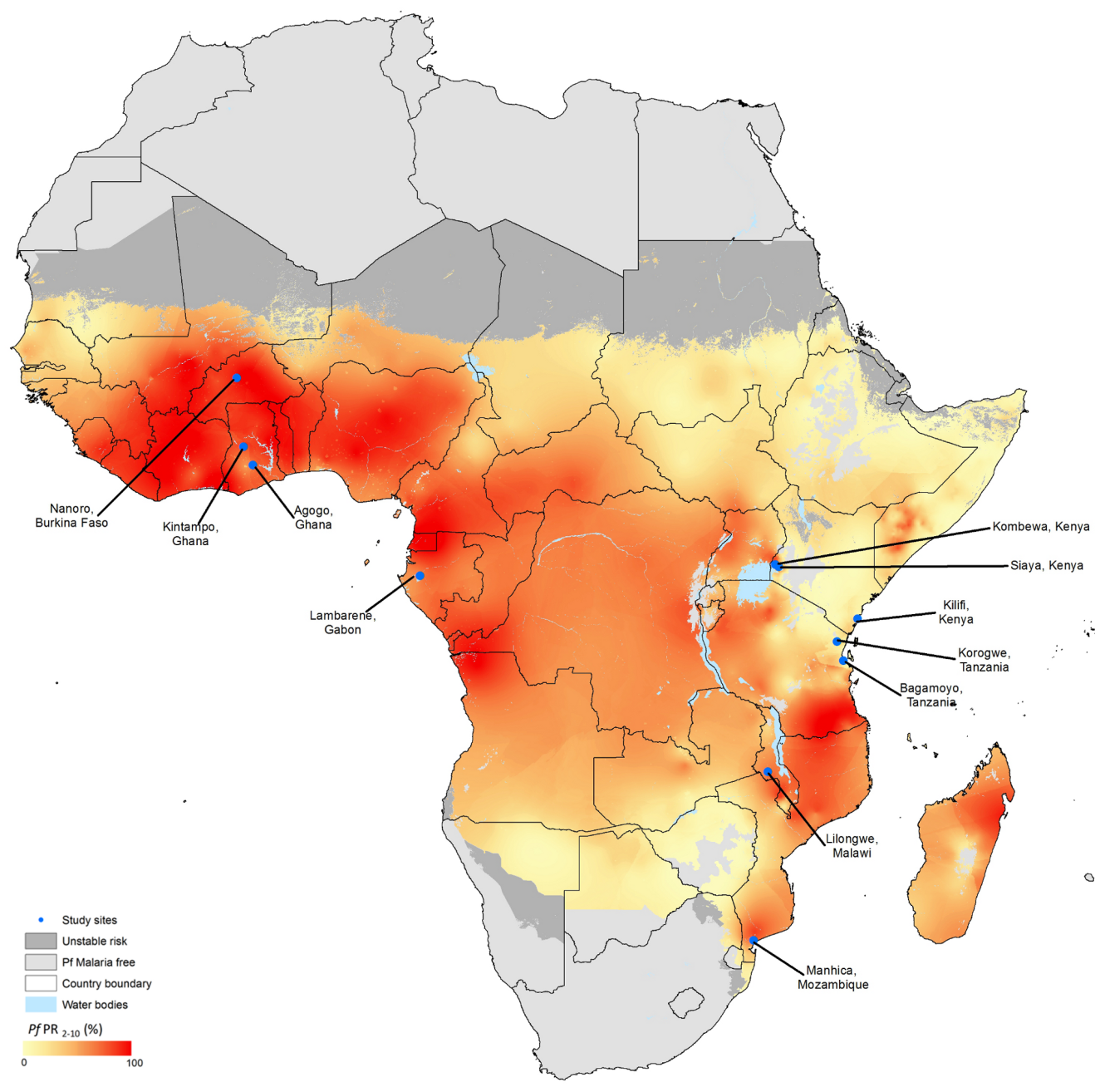
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**SUPPLEMENTARY FIGURES**

Figure S1. Study sites and malaria endemicity.

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Adapted from Hay et al, 2009. The location of each participating study site is shown on this previously published map showing the spatial distribution of *P. falciparum* malaria endemicity. The data are the model-based geostatistical point estimates of the annual mean *P. falciparum* parasite rate age-standardized for 2-10 years for 2007 within the stable spatial limits of *P. falciparum* malaria transmission, displayed as a continuum of yellow to red from 0%–100% (see map legend). The rest of the land area was defined as unstable risk (medium grey areas) or no risk (light grey). Nanoro, Burkina Faso has highly seasonal malaria transmission.

Figure S2. Baseline characteristics in each study site (intention-to-treat population).

|  |  |
| --- | --- |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **Mean age at first vaccination (months)** | **Mean age at first vaccination (weeks)** |
|  |  |
| **Mean age at the time of booster dose (M20) (months)** | **Men age at time of booster dose (M20) (weeks)** |
|  |  |
| **Gender (% male)** | **Gender (% male)** |
|  |  |
|  |  |
| *Figure continues on next page* |  |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **Mean height-for-age Z-score at first vaccination** | **Mean height-for-age Z-score at first vaccination** |
|  |  |
| **Mean height-for-age Z-score at the time of booster dose (M20)** | **Mean height-for-age Z-score at the time of booster dose (M20)** |
|  |  |
| **Mean weight-for-age Z-score at first vaccination** | **Mean weight-for-age Z-score at first vaccination** |
|  |  |
|  |  |
| *Figure continues on next page* |  |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **Mean weight-for-age Z-score at the time of booster dose (M20)** | **Mean weight-for-age Z-score at the time of booster dose (M20)** |
|  |  |
| **Mean distance from outpatient facility (km)** | **Mean distance from outpatient facility (km)** |
|  |  |
| **Mean distance from inpatient facility (km)** | **Mean distance from inpatient facility (km)** |
|  |  |
|  |  |
| *Figure continues on next page* |  |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **Mean haemoglobin at first vaccination (g/dL)** | **Mean haemoglobin at first vaccination (g/dL)** |
|  |  |
| **Mean haemoglobin at the time of booster dose (M20) (g/dL)** | **Mean haemoglobin at the time of booster dose (M20) (g/dL)** |
|  |  |
| **Prevalence of moderate anaemia at first vaccination (%)** | **Prevalence of moderate anaemia at first vaccination (%)** |
|  |  |
|  |  |
| *Figure continues on next page* |  |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **Prevalence of moderate anaemia at the time of booster dose (M20) (%)** | **Prevalence of moderate anaemia at the time of booster dose (M20) (%)** |
|  |  |

Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre(i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

M20 = Month 20.

Moderate anaemia = a documented haemoglobin concentration < 8·0 g per decilitre identified at a cross sectional survey.

Figure S3. Malaria control measures in place at each study site (intention-to-treat population).

|  |  |
| --- | --- |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **IPTi coverage (%)** | **IPTi coverage (%)** |
|  |  |
| **ITN coverage at Month 14 (%)** | **ITN coverage at Month 14 (%)** |
|  |  |
|  |  |
| **ITN coverage at Month 31 (%)** | **ITN coverage at Month 31 (%)** |
|  |  |
| *Figure continues on next page* |  |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **ITN coverage at study end (%)** | **ITN coverage at study end (%)** |
|  |  |
| **IRS use from M0 to M14 (%)** | **IRS use from M0 to M14 (%)** |
|  |  |
|  |  |
| **IRS use from M20 to M31 (%)** | **IRS use from M20 to M31 (%)** |
|  |  |
| *Figure continues on next page* |  |
| **A. Children enrolled in the 5-17 months age category** | **B. Infants enrolled in the 6-12 weeks age category** |
| **Percentage of malaria drug treatments that were ACTs (%)** | **Percentage of malaria drug treatments that were ACTs (%)** |
|  |  |
|  |  |

Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre(i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

M20 = Month 20.

IPTi = intermittent preventive treatment of malaria in infants: percentage of subjects with at least one application from study start until end of follow-up period.

ITN = insecticide treated bed-net with or without holes.

IRS = indoor residual spraying.

ACT = artemisinin-based combination therapy.

Figure S4. Cumulative incidence of clinical malaria from booster dose until Month 32 among children in the 5-17 months age category (intention-to-treat population).



The graph shows the cumulative incidence of first or only episode of clinical malaria (primary case definition) over the 12 months period following the booster dose (i.e. until Month 32).

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

Figure S5. Vaccine efficacy over time (clinical malaria primary case definition) in the 5-17 months age category (per-protocol population).

|  |  |
| --- | --- |
| **A. VE over time in the R3C group : all episodes of clinical malaria primary case definition (model=group\*(log(time))) (M2.5-SE)** | **B. VE over time post booster dose in the R3R group : all episodes of clinical malaria primary case definition (model=group\*(time)) (M21-SE)** |
|  |  |

Cox regression models including all episodes of clinical malaria (Andersen-Gill) with time-varying covariates (time, log(time), sqrt(time), time²..). The best model fit was selected based on AIC and SBC and plotted VE over time using the selected model.

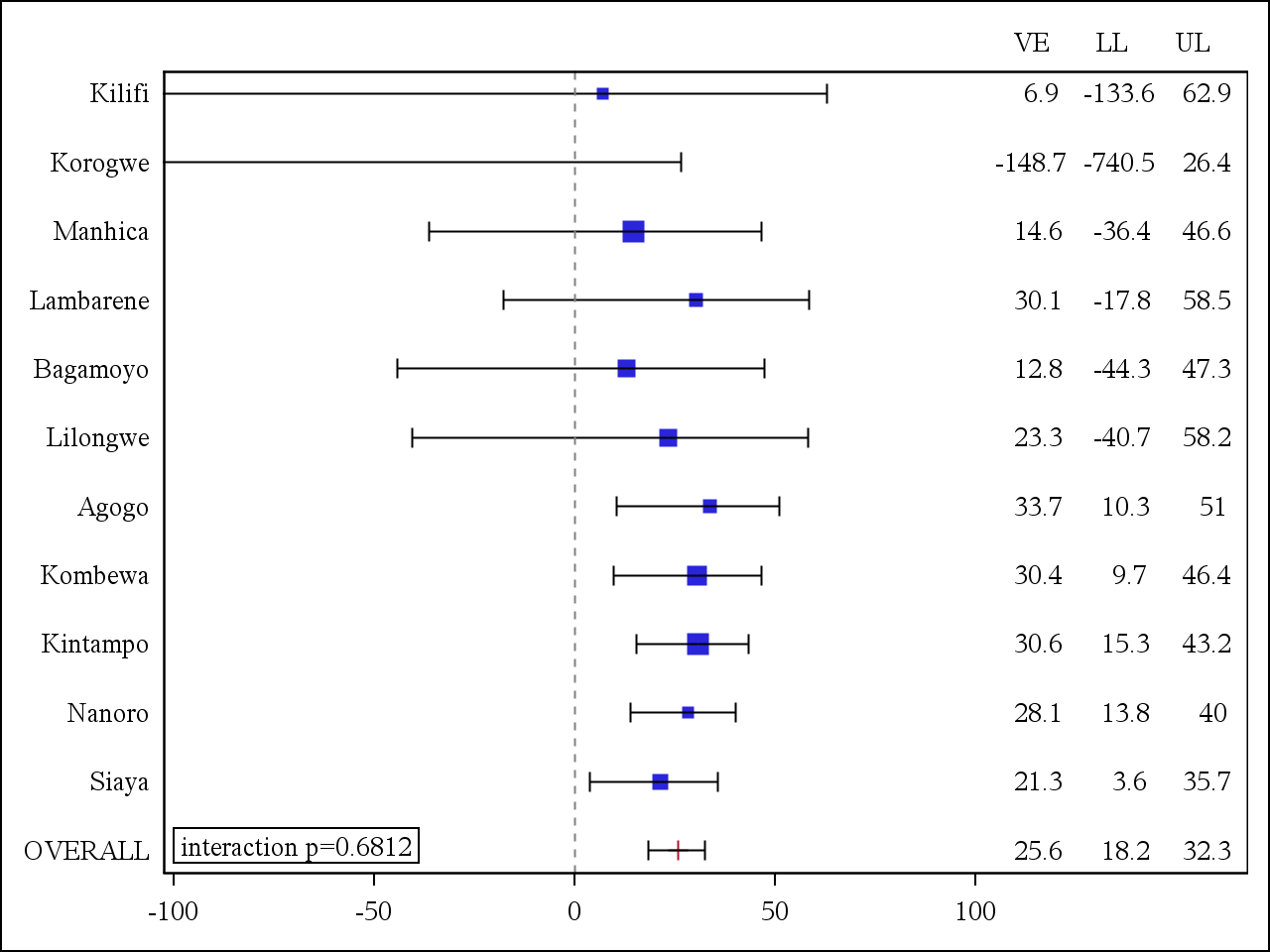
R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

M2·5-SE = follow-up from 14 days post dose-3 (Month 2·5) to study end (end of extension phase).

M21-SE = follow-up from day of booster dose to study end (end of extension phase).

Figure S6. Incremental vaccine efficacy of a booster dose against clinical malaria by study site among children in the 5-17 months age category (intention-to-treat population).



Incremental vaccine efficacy of a booster dose against all episodes of clinical (primary case definition) (M21-M32).

The size of each blue square reflects the relative number of subjects enrolled at each study site; the horizontal bars show the lower limit and upper limit of the 95% confidence interval. Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre(i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.

M21-M32 = follow-up from day of booster dose to 32 months post dose-1 (Month 32).

VE = vaccine efficacy against all episodes of clinical malaria meeting the primary case definition unadjusted for covariates.

LL = lower limit of the 95% confidence interval.

UL = upper limit of the 95% confidence interval.

Figure S7. Markers of severe malaria in children and young infants by vaccination group (intention-to-treat population).

|  |  |
| --- | --- |
| **A. Distribution of markers of severe malaria in the 5-17 months age category (M0-SE)** | **B. Distribution of number of markers of severe malaria in the 5-17 months age category (M0-SE)** |
|  |  |
| **C. Distribution of markers of severe malaria in the 6-12 weeks age category(M0-SE)** | **D. Distribution of number of markers of severe malaria in the 6-12 weeks age category (M0-SE)** |
|  |  |

Analysis of episodes of severe malaria meeting the secondary case definition.

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2, two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin concentration of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

Error bars represent 95% confidence interval.

% of episodes = proportion of the total number of severe malaria cases per group.

Anaemia= haemoglobin < 5·0 g/dL.

Prostration = in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.

Respiratory distress = lower chest wall indrawing or abnormally deep breathing.

Seizures = two or more seizures occurring in the total time period including 24 hours prior to admission time in the emergency room and during hospitalization.

Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness)

Hypoglycaemia = glucose < 2·2 mmol/L.

Acidosis = base excess ≤ -10·0 mmol/L.

Lactaemia = lactate ≥ 5·0 mmol/L.

Figure S8. Cumulative incidence of clinical malaria from booster dose until Month 32 among infants in the 6-12 weeks age category (intention-to-treat population).



The graph shows the cumulative incidence of first or only episode of clinical malaria primary case definition over the 12 months period following the booster dose (i.e. until Month 32).

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

Figure S9. Vaccine efficacy over time (clinical malaria primary case definition) in the 6-12 weeks age category (per-protocol population).

|  |  |
| --- | --- |
| **A. VE over time in the R3C group : all episodes of clinical malaria primary case definition (model=group\*(log(time))) (M2.5-SE)** | **B. VE over time post booster dose in the R3R group : all episodes of clinical malaria primary case definition (model=group\*(SQRT(time))) (M21-SE)** |
|  |  |

Cox regression models including all episodes of clinical malaria (Andersen-Gill) with time-varying covariates (time, log(time), sqrt(time), time²..). The best model fit was selected based on AIC and SBC and plotted VE over time using the selected model.

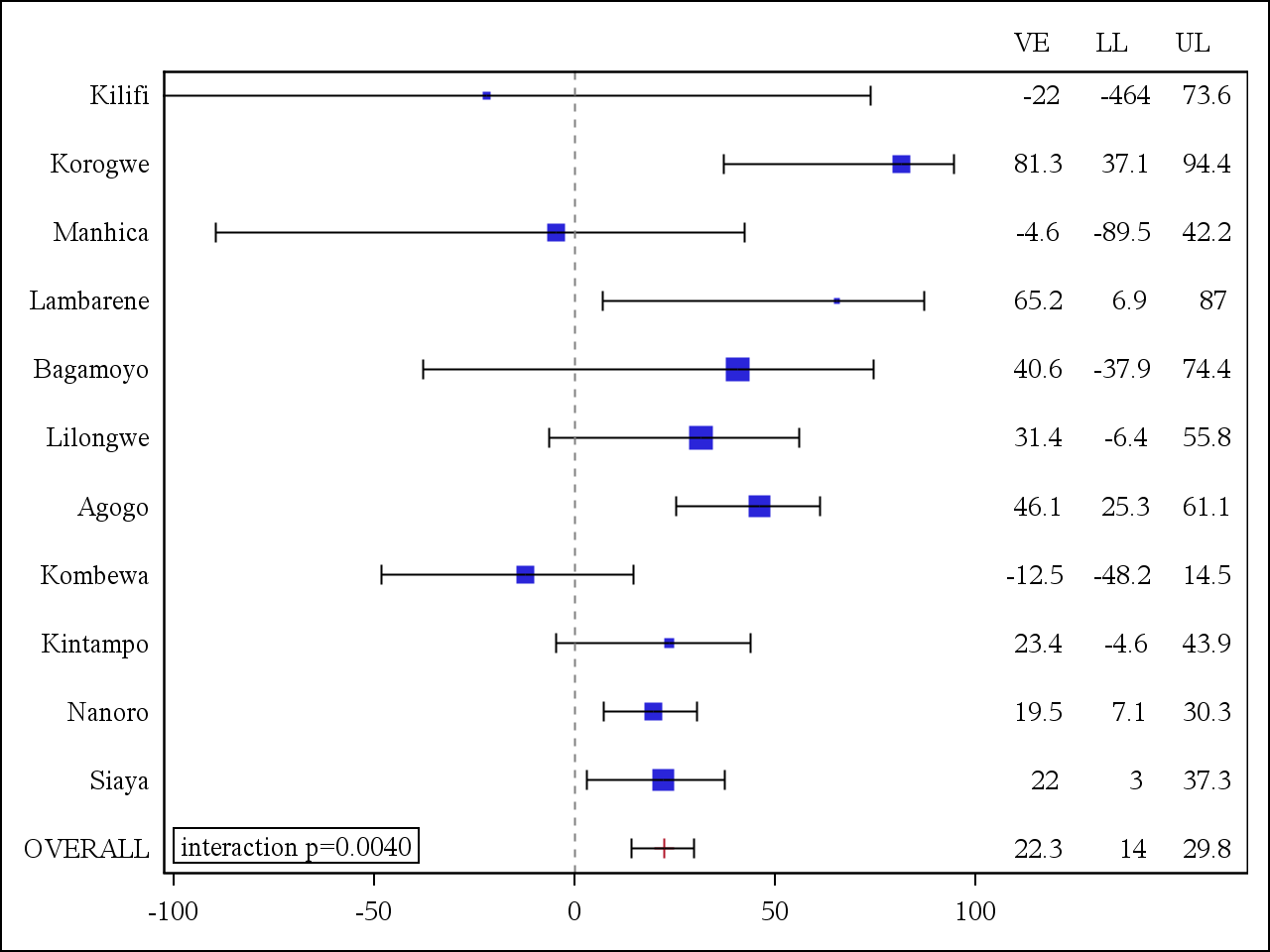
R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

M2·5-SE = follow-up from 14 days post dose-3 (Month 2·5) to study end (end of extension phase).

M21-SE = follow-up from day of booster dose to study end (end of extension phase).

Figure S10. Incremental vaccine efficacy of a booster dose against clinical malaria by study site among infants in the 6-12 weeks age category (intention-to-treat).



Incremental vaccine efficacy of a booster dose against all episodes of clinical (primary case definition) (M21-M32).

The size of each blue square reflects the relative number of subjects enrolled at each study site; the horizontal bars show the lower limit and upper limit of the 95% confidence interval. Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria, defined as a measured or reported fever within previous 24h and parasite density >0 parasites per cubic millimetre(i.e. clinical malaria secondary case definition), measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up.

M21-M32 = follow-up from day of booster dose to 32 months post dose-1 (Month 32).

VE = vaccine efficacy against all episodes of clinical malaria meeting the primary case definition unadjusted for covariates.

LL = lower limit of the 95% confidence interval.

UL = upper limit of the 95% confidence interval.

Figure S11. Vaccine efficacy by tertile of anti-CS antibody concentration among children in the 5-17 months age category (per-protocol population for efficacy).

|  |  |
| --- | --- |
| **A. Anti-CS geometric mean titres at one month post dose-3 in the R3C group** | **B. Vaccine efficacy against clinical malaria per anti-CS tertile over 30 months post dose-3 in the R3C group (M2·5-M32)** |
|  |  |
|  | Tertile 3 vs. tertile 1: 3·6% (-25·6;26·0) reduction in malaria episodes (p=0·7865) |
| **C. Anti-CS geometric mean titres at one month post booster dose in the R3R group** | **D. Vaccine efficacy against clinical malaria per anti-CS tertile over 12 months post booster dose in the R3R group (M21-M32)** |
|  |  |
|  | Tertile 3 vs. tertile 1: 23·2% (-4·1;43·3) reduction in malaria episodes (p=0·0888) |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

Error bars represent 95% confidence interval.

Anti-CS = anti-circumsporozoite protein antibodies.

GMT = geometric mean antibody titre.

EU/mL = ELISA unit per millilitre.

M21-M32 = follow-up from day of booster dose to 30 months post dose-3 (Month 32).

M2·5-M32 = follow-up from 14 days post dose-3 (Month 2·5) to 30 months post dose-3 (Month 32).

P-value from negative binomial random effect model.

Figure S12. Vaccine efficacy by tertile of anti-CS antibody concentration among infants in the 6-12 weeks age category (per-protocol population for efficacy).

|  |  |
| --- | --- |
| **A. Anti-CS geometric mean titres at one month post dose-3 in the R3C group** | **B. Vaccine efficacy against clinical malaria per anti-CS tertile over 30 months post dose-3 in the R3C group (M2·5-M32)** |
|  |  |
|  | Tertile 3 vs. tertile 1: 36·9% (17·3;51·8) reduction in malaria episodes (p=0·0009) |
| **C. Anti-CS geometric mean titres at one month post booster dose in the R3R group** | **D. Vaccine efficacy against clinical malaria per anti-CS tertile over 12 months post booster dose in the R3R group (M21-M32)** |
|  |  |
|  | Tertile 3 vs. tertile 1: 34·3% (10·8; 51·6) reduction in malaria episodes (p=0·0072) |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

Error bars represent 95% confidence interval.

Anti-CS = anti-circumsporozoite protein antibodies.

GMT = geometric mean antibody titre.

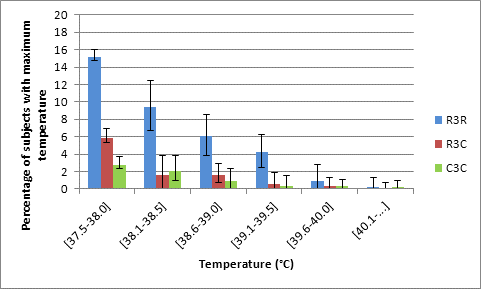
EU/mL = ELISA unit per millilitre.

M21-M32 = follow-up from day of booster dose to 30 months post dose-3 (Month 32).

M2·5-M32 = follow-up from 14 days post dose-3 (Month 2·5) to 30 months post dose-3 (Month 32).

P-value from negative binomial random effect model.

Figure S13. Distribution of maximal temperature within seven days post booster dose among children in the 5-17 months age category (intention-to-treat population).



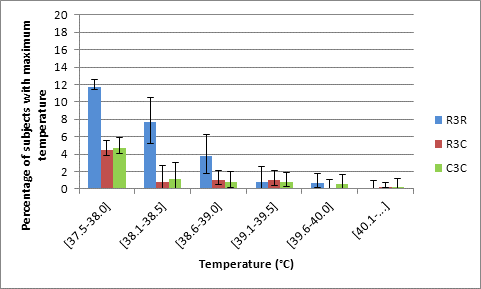
R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

Error bars represent 95% confidence interval.

Figure S14. Distribution of maximal temperature within seven days post booster dose among infants in the 6-12 weeks age category (intention-to-treat population).



R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

Error bars represent 95% confidence interval.

Figure S15. Time-to-onset distribution of meningitis cases post dose-1, dose-2, dose-3 and booster dose for both age categories (intention-to-treat population).

|  |
| --- |
| **A. Children enrolled in the 5-17 months age category** |
|  |
| **B. Infants enrolled in the 6-12 weeks age category** |
|  |

R3R = RTS,S/AS01 primary schedule with booster (Blue bars).

R3C = RTS,S/AS01 primary schedule without booster (Red bars).

C3C = control group (Green bars).

MedDRA Preferred Term = Meningitis, Meningitis haemophilus, Meningitis meningococcal, Meningitis pneumococcal, Meningitis salmonella, Meningitis tuberculous, Meningitis viral.

**SUPPLEMENTARY TABLES**

Table S1a. List of ethic committees and review boards.

|  |  |
| --- | --- |
| **Study centres** | **Ethics review body** |
| Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso | Western Institutional Review Board (WIRB) |
| Comité d’Ethique Institutionnel du Centre Muraz (Institutional Ethics Committee of Muraz Centre) |
| Comite d’Ethique pour la Recherche en Santé (Ethics Committee for Health Research) |
| Albert Schweitzer Hospital, Lambaréné, Gabon | Western Institutional Review Board (WIRB) |
| Comité d’Ethique Régional Indépendant de Lambaréné (CERIL)  (Independent Regional Ethics Committee of Lambaréné) |
|  | Comité National d’Ethique pour la Recherche (National Ethics Committee for Research  The Board) |
| School of Medical Sciences, Kumasi (Agogo), Ghana | Western Institutional Review Board (WIRB) |
| Ghana Health Service (GHS) Ethical Review Committee (ERC)  Research and Development Division |
|  | Committee on Human Research Publication and Ethics (CHRPE) |
| Kintampo Health Research Centre, Kintampo, Ghana | Western Institutional Review Board (WIRB) |
| Kintampo Health Research Centre (KHRC) Institutional Ethics Committee (IEC) |
|  | London School of Hygiene and Tropical Medicine Research Ethics Committee |
|  | Ghana Health Service (GHS) Ethical Review Committee (ERC) Research and Development Division |
| KEMRI - Walter Reed Project, Kombewa, Kenya | Western Institutional Review Board (WIRB) |
| Kenya Medical Research Institute (KEMRI) National Ethics Review Committee |
|  | Walter Reed Army Institute of Research (WRAIR) IRB |
| KEMRI - Wellcome Trust Research Program, Kilifi, Kenya | Western Institutional Review Board (WIRB) |
| Kenya Medical Research Institute (KEMRI) National Ethics Review Committee |
| KEMRI/CDC Research and Public Health Collaboration, Siaya, Kenya | Western Institutional Review Board (WIRB) |
| Kenya Medical Research Institute (KEMRI) National Ethics Review Committee |
| Centres for Disease Control and Prevention (CDC) – IRB |
| University of North Carolina Project, Lilongwe, Malawi | Western Institutional Review Board (WIRB) |
| National Health Sciences Research Committee |
|  | Office of Human Research Ethics |
| Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique | Western Institutional Review Board (WIRB) |
| Comitè Etic Investigació Clinica (Hospital Clinic (Barcelona University) Ethics Committee) |
|  | Comité Nacional de Bioética para a Saúde (National Bioethical Health Committee, Mozambique) |
| Ifakara Health Institute, Bagamoyo, Tanzania | Western Institutional Review Board (WIRB) |
| Tanzanian Medical Research Coordinating Committee (MRCC) operating within the National Institute for Medical Research (NIMR) |
|  | Ethikkommission beider Basel (EKBB)  (Ethics Committee of the local government responsible for the Swiss Tropical and public Health Institute and the University of Basel, Switzerland) |
|  | Ifakara Health Institute IRB |
| National Institute for Medical Research, Korogwe, Tanzania | Western Institutional Review Board (WIRB) |
| London School of Hygiene and Tropical Medicine Research Ethics Committee |
| Tanzania Medical Research Coordinating Committee (MRCC) operating within National Institute for Medical Research (NIMR) |
|  | The Danish National Committee on Biomedical Research Ethics |

Table S1b. Investigational centres and affiliated partners.

|  |  |  |  |
| --- | --- | --- | --- |
| **Country** | **Investigational centres** | **Abbreviated name** | **Affiliated partner** |
| Burkina Faso | Institut de Recherche en Science de la Santé | Nanoro | Prince Leopold Institute of Tropical Medicine, Belgium |
| Gabon | Albert Schweitzer Hospital, Medical Research Unit | Lambaréné | University of Tübingen, Germany |
| Ghana | Kwame Nkrumah University of Science and Technology, School of Medical Sciences, Kumasi | Agogo |  |
| Ghana | Kintampo Health Research Centre | Kintampo | London School of Hygiene and Tropical Medicine, UK |
| Kenya | KEMRI - Wellcome Trust Research Program | Kilifi | University of Oxford, UK |
| Kenya | KEMRI - Walter Reed Project | Kombewa | Walter Reed Army Institute of Research, USA |
| Kenya | KEMRI/CDC Research and Public Health Collaboration | Siaya | US Centres for Disease Control and Prevention, USA |
| Malawi | University of North Carolina Project | Lilongwe | University of North Carolina at Chapel Hill, USA |
| Mozambique | Centro de Investigação em Saúde de Manhiça | Manhiça | Barcelona Centre for International Health Research (CRESIB), Hospital Clinic - Universitat de Barcelona |
| Tanzania | Ifakara Health Institute (IHI), Bagamoyo Branch | Bagamoyo | Swiss Tropical and Public Health Institute, Switzerland |
| Tanzania | National Institute for Medical Research, Korogwe Branch | Korogwe | London School of Hygiene and Tropical Medicine, UK  Centre for Medical Parasitology at University of Copenhagen and Copenhagen University Hospital, Denmark  Kilimanjaro Christian Medical College, Tanzania |

Table S2. Algorithm for the evaluation of a hospital admission as a potential case of severe malaria.

|  |  |
| --- | --- |
| For all acute hospital admissions (except planned admissions for medical investigation/care or elective surgery or trauma admissions), a blood sample was taken for evaluation of: | |
|  | Malaria parasite density |
|  | Blood culture |
|  | Haemoglobin |
|  | Blood glucose, lactate and base excess |
| **Lumbar puncture was indicated by the presence of:** | |
|  | Seizure except simple febrile seizure (defined as a seizure associated with fever, which lasts for 5 minutes or less, generalized as opposed to focal, not followed by transient or persistent neurological abnormalities, occurring in a child ≥ 6 months of age, with full recovery within 1 hour) |
|  | Blantyre Coma Score < 5 (children ≤ 9 months of age < 4 [in association with best motor response of 1])1 |
|  | Prostration in a child < 3 year of age |
|  | Meningism/stiff neck/bulging fontanelle |
|  | Clinician’s judgment |
| **Chest X-ray (CXR) was indicated by the presence of:** | |
|  | Tachypnea (≥ 50 breaths per minute in a child < 1 year and ≥ 40 breaths per minute in a child ≥ 1 year)2 |
|  | Lower chest wall indrawing |
|  | Abnormally deep breathing |
|  | Clinician’s judgment |

1. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989;71:441-59.
2. Berkley JA, Ross A, Mwangi I et al. Prognostic indicators of early and late death in children admitted to district hospital in Kenya: cohort study. *BMJ* 2003;326:361-6.

Table S3. Case definitions of severe malaria.

|  |  |  |
| --- | --- | --- |
| **Primary case definition** | *P. falciparum* > 5000 parasites per mm3 | **AND** one or more marker of disease severity:   * Prostration * Respiratory distress * Blantyre score ≤ 2 * Seizures 2 or more * Hypoglycaemia < 2·2 mmol/L * Acidosis: base excess ≤ -10·0 mmol/L * Lactate ≥ 5·0 mmol/L * Anaemia < 5·0 g/dL   **AND** without diagnosis of a co-morbidity:   * Radiographically proven pneumonia * Meningitis on CSF examination * Positive blood culture * Gastroenteritis with dehydration |
| **Secondary case definition** | *P. falciparum* > 5000 parasites per mm3 | **AND** one or more marker of disease severity without excluding co-morbidity |

Prostration = in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.

Respiratory distress = lower chest wall indrawing or abnormally deep breathing.

Two or more seizures = two or more seizures occurring in the total time period including 24 hours prior to admission time in the emergency room and during hospitalization.

Radiographically proven pneumonia = a consolidation or pleural effusion defined per protocol on a chest x-ray taken within 72 hours of admission.

Meningitis on cerebrospinal fluid (CSF) examination = white blood cells ≥ 50 x106/L or positive culture of compatible organism or latex agglutination test positive for Hib, pneumococcal or meningococcal antigen.

Gastroenteritis with dehydration = history of three or more loose or watery stools in previous 24 hours, an observed watery stool and decreased skin turgor (> 2 seconds for skin to return following skin pinch).

Positive blood culture = defined per protocol on a blood culture taken within 72 hours of admission.

Table S4. Incidence of clinical malaria (secondary case definition) among infants in the 6-12 weeks age category control group during a 12-month follow-up period post dose-3 ordered by increasing malaria incidence.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Control group (C3C)** | | | |
| **All episodes of clinical malaria secondary case definition**  **(per-protocol population for efficacy)** | **N** | **n** | **T (year)** | **n/T** |
| Kilifi | 102 | 3 | 95·9 | 0·03 |
| Korogwe | 183 | 16 | 170·8 | 0·09 |
| Manhiça | 188 | 22 | 175·4 | 0·13 |
| Lambaréné | 62 | 11 | 57·1 | 0·19 |
| Bagamoyo | 244 | 47 | 227·9 | 0·21 |
| Lilongwe | 258 | 149 | 210·6 | 0·71 |
| Agogo | 221 | 298 | 209·9 | 1·42 |
| Kombewa | 196 | 372 | 166·5 | 2·23 |
| Kintampo | 99 | 194 | 84·7 | 2·29 |
| Nanoro | 225 | 605 | 182·2 | 3·32 |
| Siaya | 229 | 749 | 175·3 | 4·27 |
| **Overall** | **2007** | **2466** | **1756·2** | **1·40** |
| **All episodes of clinical malaria secondary case definition (intention-to-treat population)** | **N** | **n** | **T (year)** | **n/T** |
| Kilifi | 105 | 3 | 116·7 | 0·03 |
| Korogwe | 195 | 16 | 220·6 | 0·07 |
| Manhiça | 212 | 27 | 237·2 | 0·11 |
| Lambaréné | 68 | 14 | 71·2 | 0·2 |
| Bagamoyo | 269 | 53 | 296·9 | 0·18 |
| Lilongwe | 279 | 164 | 283·2 | 0·58 |
| Agogo | 230 | 325 | 263·7 | 1·23 |
| Kombewa | 210 | 424 | 213·1 | 1·99 |
| Kintampo | 110 | 227 | 114·6 | 1·98 |
| Nanoro | 228 | 693 | 231·4 | 2·99 |
| Siaya | 273 | 945 | 253·6 | 3·73 |
| **Overall** | **2179** | **2891** | **2302·2** | **1·26** |

The incidence of clinical malaria meeting the secondary case definition in infants in the control group during 12 months of follow-up was used to categorize malaria incidence across study sites. For all tables and figures reported here, study sites are presented from the lowest to the highest incidence of clinical malaria.

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre.

N = number of subjects included in each group.

n = number of episodes included in each group.

T(year) = person years at risk.

n/T = person year rate in each group.

Table S5. Percentage of subjects reporting serious adverse events until the end of the extension phase among children in the 5-17 months age category (intention-to-treat population).

|  | | **R3R**  **N = 2976** | | | | **R3C**  **N = 2972** | | | | **C3C**  **N = 2974** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Primary System Organ Class** | **Preferred Term** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| **At least one SAE** |  | 720 | 24·2 | 22·7 | 25·8 | 752 | 25·3 | 23·7 | 26·9 | 846 | 28·4 | 26·8 | 30·1 |
| **At least one SAE excluding malaria** |  | 673 | 22·6 | 21·1 | 24·2 | 704 | 23·7 | 22·2 | 25·3 | 784 | 26·4 | 24·8 | 28·0 |
| **Fatalities** |  | 61 | 2·0 | 1·6 | 2·6 | 51 | 1·7 | 1·3 | 2·3 | 46 | 1·5 | 1·1 | 2·1 |
| **At least one related SAE** |  | 8 | 0·3 | 0·1 | 0·5 | 4 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 |
| **All SAEs** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Primary System Organ Class** | **Preferred Term** |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood and lymphatic system disorders | Anaemia | 126 | 4·2 | 3·5 | 5·0 | 150 | 5·0 | 4·3 | 5·9 | 197 | 6·6 | 5·8 | 7·6 |
|  | Disseminated intravascular coagulation | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hypochromic anaemia | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Intravascular haemolysis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Leukaemoid reaction | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Lymphadenitis | 4 | 0·1 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 |
|  | Neutropenia | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Pancytopenia | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| Cardiac disorders | Cardiac failure | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Cardiomyopathy | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Congenital, familial and genetic disorders | Atrial septal defect | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Cerebral palsy | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Choledochal cyst | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Congenital megacolon | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Cryptorchism | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Glucose-6-phosphate dehydrogenase deficiency | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hydrocele | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Phimosis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Sickle cell anaemia | 1 | 0·0 | 0·0 | 0·2 | 4 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 |
|  | Sickle cell anaemia with crisis | 4 | 0·1 | 0·0 | 0·3 | 4 | 0·1 | 0·0 | 0·3 | 6 | 0·2 | 0·1 | 0·4 |
|  | Ventricular septal defect | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
| Ear and labyrinth disorders | Deafness | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hearing impaired | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
| Gastrointestinal disorders | Aphthous stomatitis | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Colitis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Constipation | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Enteritis | 10 | 0·3 | 0·2 | 0·6 | 18 | 0·6 | 0·4 | 1·0 | 15 | 0·5 | 0·3 | 0·8 |
|  | Food poisoning | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Gastritis | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Gastrointestinal haemorrhage | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Gastrointestinal motility disorder | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Gastro-oesophageal reflux disease | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Ileus paralytic | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Intestinal obstruction | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Intestinal perforation | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Intussusception | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Mouth ulceration | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Rectal prolapse | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Stomatitis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Stress ulcer | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Umbilical hernia | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Umbilical hernia, obstructive | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Upper gastrointestinal haemorrhage | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| General disorders and administration site conditions | Death | 3 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Drowning | 3 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Generalised oedema | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hernia | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hypothermia | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Injection site reaction | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Pyrexia | 18 | 0·6 | 0·4 | 1·0 | 10 | 0·3 | 0·2 | 0·6 | 16 | 0·5 | 0·3 | 0·9 |
| Hepatobiliary disorders | Cholecystitis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hepatitis | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Hepatitis acute | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hepatitis toxic | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
| Immune system disorders | Anaphylactic reaction | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Hypersensitivity | 0 | 0·0 | 0·0 | 0·1 | 3 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·1 |
| Infections and infestations | Abscess | 7 | 0·2 | 0·1 | 0·5 | 7 | 0·2 | 0·1 | 0·5 | 5 | 0·2 | 0·1 | 0·4 |
|  | Abscess jaw | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Abscess limb | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 3 | 0·1 | 0·0 | 0·3 |
|  | Acarodermatitis | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Aids dementia complex | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Amoebiasis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Arthritis bacterial | 2 | 0·1 | 0·0 | 0·2 | 7 | 0·2 | 0·1 | 0·5 | 1 | 0·0 | 0·0 | 0·2 |
|  | Ascariasis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Bacteraemia | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Bacterial infection | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Bone tuberculosis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Breast abscess | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Bronchiolitis | 25 | 0·8 | 0·5 | 1·2 | 13 | 0·4 | 0·2 | 0·7 | 18 | 0·6 | 0·4 | 1·0 |
|  | Bronchitis | 13 | 0·4 | 0·2 | 0·7 | 15 | 0·5 | 0·3 | 0·8 | 21 | 0·7 | 0·4 | 1·1 |
|  | Bronchopneumonia | 33 | 1·1 | 0·8 | 1·6 | 35 | 1·2 | 0·8 | 1·6 | 40 | 1·3 | 1·0 | 1·8 |
|  | Bullous impetigo | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Burkholderia cepacia complex sepsis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Burn infection | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Cellulitis | 8 | 0·3 | 0·1 | 0·5 | 7 | 0·2 | 0·1 | 0·5 | 6 | 0·2 | 0·1 | 0·4 |
|  | Cellulitis of male external genital organ | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Cellulitis orbital | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Cellulitis pharyngeal | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Cerebral malaria | 4 | 0·1 | 0·0 | 0·3 | 4 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·1 |
|  | Cholera | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Conjunctivitis | 2 | 0·1 | 0·0 | 0·2 | 4 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·1 |
|  | Conjunctivitis bacterial | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Croup infectious | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Dermatitis infected | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Disseminated tuberculosis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Dysentery | 11 | 0·4 | 0·2 | 0·7 | 13 | 0·4 | 0·2 | 0·7 | 9 | 0·3 | 0·1 | 0·6 |
|  | Eczema infected | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Empyema | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Encephalitis | 4 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Encephalitis viral | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Encephalomyelitis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Enterococcal sepsis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Erysipelas | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Escherichia urinary tract infection | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Furuncle | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Gastroenteritis | 153 | 5·1 | 4·4 | 6·0 | 148 | 5·0 | 4·2 | 5·8 | 177 | 6·0 | 5·1 | 6·9 |
|  | Gastroenteritis *Escherichia coli* | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Gastroenteritis salmonella | 2 | 0·1 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·1 |
|  | Gastroenteritis shigella | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Gastroenteritis viral | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Gastrointestinal candidiasis | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Giardiasis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Gingivitis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Groin abscess | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Haemophilus sepsis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Helminthic infection | 2 | 0·1 | 0·0 | 0·2 | 8 | 0·3 | 0·1 | 0·5 | 6 | 0·2 | 0·1 | 0·4 |
|  | Hepatitis A | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | HIV infection | 22 | 0·7 | 0·5 | 1·1 | 19 | 0·6 | 0·4 | 1·0 | 18 | 0·6 | 0·4 | 1·0 |
|  | HIV infection WHO clinical stage II | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | HIV infection WHO clinical stage IV | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Impetigo | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Infected skin ulcer | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Injection site cellulitis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Klebsiella sepsis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Laryngitis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Lobar pneumonia | 6 | 0·2 | 0·1 | 0·4 | 5 | 0·2 | 0·1 | 0·4 | 7 | 0·2 | 0·1 | 0·5 |
|  | Lower respiratory tract infection | 2 | 0·1 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 | 6 | 0·2 | 0·1 | 0·4 |
|  | Ludwig angina | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Lymph node abscess | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Lymph node tuberculosis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Lymphadenitis bacterial | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Malaria | 294 | 9·9 | 8·8 | 11·0 | 342 | 11·5 | 10·4 | 12·7 | 421 | 14·2 | 12·9 | 15·5 |
|  | Mastoiditis | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Measles | 7 | 0·2 | 0·1 | 0·5 | 2 | 0·1 | 0·0 | 0·2 | 5 | 0·2 | 0·1 | 0·4 |
|  | Meningitis | 5 | 0·2 | 0·1 | 0·4 | 5 | 0·2 | 0·1 | 0·4 | 1 | 0·0 | 0·0 | 0·2 |
|  | Meningitis haemophilus | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Meningitis meningococcal | 3 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Meningitis pneumococcal | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Meningitis tuberculous | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Meningitis viral | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | *Mycobacterium ulcerans* infection | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Nasopharyngitis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Oral candidiasis | 5 | 0·2 | 0·1 | 0·4 | 5 | 0·2 | 0·1 | 0·4 | 4 | 0·1 | 0·0 | 0·3 |
|  | Oropharyngeal candidiasis | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Osteomyelitis | 3 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Otitis externa | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Otitis media | 19 | 0·6 | 0·4 | 1·0 | 10 | 0·3 | 0·2 | 0·6 | 22 | 0·7 | 0·5 | 1·1 |
|  | Otitis media acute | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Otitis media chronic | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Parotitis | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Perineal abscess | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Periorbital cellulitis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Pharyngitis | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Plasmodium ovale infection | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Pneumococcal sepsis | 5 | 0·2 | 0·1 | 0·4 | 4 | 0·1 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·3 |
|  | *Pneumocystis jirovecii* pneumonia | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Pneumonia | 202 | 6·8 | 5·9 | 7·8 | 215 | 7·2 | 6·3 | 8·2 | 223 | 7·5 | 6·6 | 8·5 |
|  | Pneumonia streptococcal | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Postoperative wound infection | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Pseudomonal sepsis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Pulmonary tuberculosis | 7 | 0·2 | 0·1 | 0·5 | 1 | 0·0 | 0·0 | 0·2 | 4 | 0·1 | 0·0 | 0·3 |
|  | Pyelonephritis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Pyoderma | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Pyomyositis | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Rabies | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Respiratory tract infection | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Salmonella sepsis | 36 | 1·2 | 0·8 | 1·7 | 34 | 1·1 | 0·8 | 1·6 | 42 | 1·4 | 1·0 | 1·9 |
|  | Salmonellosis | 1 | 0·0 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·2 |
|  | Schistosomiasis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Sepsis | 33 | 1·1 | 0·8 | 1·6 | 27 | 0·9 | 0·6 | 1·3 | 43 | 1·4 | 1·0 | 1·9 |
|  | Shigella infection | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Skin bacterial infection | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Skin infection | 3 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Staphylococcal sepsis | 3 | 0·1 | 0·0 | 0·3 | 6 | 0·2 | 0·1 | 0·4 | 1 | 0·0 | 0·0 | 0·2 |
|  | Staphylococcal skin infection | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Streptococcal infection | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Streptococcal sepsis | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Subcutaneous abscess | 5 | 0·2 | 0·1 | 0·4 | 4 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·2 |
|  | Taeniasis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Tinea capitis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Tonsillitis | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Toxic shock syndrome | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Tracheobronchitis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Trichiniasis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Tuberculosis | 4 | 0·1 | 0·0 | 0·3 | 5 | 0·2 | 0·1 | 0·4 | 6 | 0·2 | 0·1 | 0·4 |
|  | Typhoid fever | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 |
|  | Upper respiratory tract infection | 29 | 1·0 | 0·7 | 1·4 | 39 | 1·3 | 0·9 | 1·8 | 43 | 1·4 | 1·0 | 1·9 |
|  | Urinary tract infection | 22 | 0·7 | 0·5 | 1·1 | 23 | 0·8 | 0·5 | 1·2 | 28 | 0·9 | 0·6 | 1·4 |
|  | Urinary tract infection bacterial | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Urinary tract infection pseudomonal | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Varicella | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Wound infection | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Wound sepsis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| Injury, poisoning and procedural complications | Accidental exposure to product | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| Accidental poisoning | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Animal bite | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Arthropod sting | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Bronchitis chemical | 3 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Burns first degree | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Burns second degree | 1 | 0·0 | 0·0 | 0·2 | 5 | 0·2 | 0·1 | 0·4 | 2 | 0·1 | 0·0 | 0·2 |
|  | Chemical injury | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Chemical poisoning | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 7 | 0·2 | 0·1 | 0·5 |
|  | Crush injury | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Disinfectant poisoning | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Dislocation of vertebra | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Exposure to toxic agent | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Eye contusion | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Eye injury | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Femur fracture | 3 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Foreign body | 4 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Foreign body aspiration | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Fractured skull depressed | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Head injury | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Herbal toxicity | 2 | 0·1 | 0·0 | 0·2 | 3 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·2 |
|  | Humerus fracture | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Joint injury | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Laceration | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Limb traumatic amputation | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Penis injury | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Petroleum distillate poisoning | 2 | 0·1 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 | 4 | 0·1 | 0·0 | 0·3 |
|  | Pneumonitis chemical | 4 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·2 | 4 | 0·1 | 0·0 | 0·3 |
|  | Poisoning | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Pulmonary contusion | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Road traffic accident | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Sciatic nerve injury | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Skin injury | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Snake bite | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Soft tissue injury | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Thermal burn | 15 | 0·5 | 0·3 | 0·8 | 10 | 0·3 | 0·2 | 0·6 | 15 | 0·5 | 0·3 | 0·8 |
|  | Tibia fracture | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Wound | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Metabolism and nutrition disorders | Dehydration | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Failure to thrive | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Hypoglycaemia | 10 | 0·3 | 0·2 | 0·6 | 10 | 0·3 | 0·2 | 0·6 | 18 | 0·6 | 0·4 | 1·0 |
|  | Hypokalaemia | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hypoproteinaemia | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Kwashiorkor | 11 | 0·4 | 0·2 | 0·7 | 4 | 0·1 | 0·0 | 0·3 | 17 | 0·6 | 0·3 | 0·9 |
|  | Malnutrition | 27 | 0·9 | 0·6 | 1·3 | 27 | 0·9 | 0·6 | 1·3 | 21 | 0·7 | 0·4 | 1·1 |
|  | Marasmus | 6 | 0·2 | 0·1 | 0·4 | 8 | 0·3 | 0·1 | 0·5 | 4 | 0·1 | 0·0 | 0·3 |
|  | Underweight | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Musculoskeletal and connective tissue disorders | Arthritis | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
| Joint effusion | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Myositis | 2 | 0·1 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Torticollis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | Brain neoplasm | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Nervous system disorders | Arachnoid cyst | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Cerebral atrophy | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Convulsion | 57 | 1·9 | 1·5 | 2·5 | 45 | 1·5 | 1·1 | 2·0 | 58 | 2·0 | 1·5 | 2·5 |
|  | Depressed level of consciousness | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Encephalopathy | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Epilepsy | 3 | 0·1 | 0·0 | 0·3 | 10 | 0·3 | 0·2 | 0·6 | 2 | 0·1 | 0·0 | 0·2 |
|  | Febrile convulsion | 159 | 5·3 | 4·6 | 6·2 | 184 | 6·2 | 5·4 | 7·1 | 164 | 5·5 | 4·7 | 6·4 |
|  | Haemorrhage intracranial | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hemiparesis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Hemiplegia | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Hydrocephalus | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Meningism | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Mental retardation | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Paraparesis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Speech disorder developmental | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
| Psychiatric disorders | Neurodevelopmental disorder | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Renal and urinary disorders | Nephrotic syndrome | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
| Reproductive system and breast disorders | Acquired phimosis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| Respiratory, thoracic and mediastinal disorders | Asphyxia | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| Aspiration | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Asthma | 9 | 0·3 | 0·1 | 0·6 | 6 | 0·2 | 0·1 | 0·4 | 8 | 0·3 | 0·1 | 0·5 |
|  | Bronchospasm | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 3 | 0·1 | 0·0 | 0·3 |
|  | Cough | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Epistaxis | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 2 | 0·1 | 0·0 | 0·2 |
|  | Interstitial lung disease | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Pleural effusion | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Pneumonia aspiration | 7 | 0·2 | 0·1 | 0·5 | 1 | 0·0 | 0·0 | 0·2 | 6 | 0·2 | 0·1 | 0·4 |
|  | Pulmonary oedema | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Respiratory acidosis | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Respiratory disorder | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
| Skin and subcutaneous tissue disorders | Dermatitis | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·2 |
|  | Dermatitis allergic | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Erythema multiforme | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Rash | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Rash maculo-papular | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Rash papular | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 |
|  | Skin lesion | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Stevens-Johnson syndrome | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Urticaria | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·2 |
|  | Vitiligo | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
| Social circumstances | Child abuse | 1 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Sexual abuse | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
| Vascular disorders | Haematoma | 2 | 0·1 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 |
|  | Hypovolaemic shock | 0 | 0·0 | 0·0 | 0·1 | 0 | 0·0 | 0·0 | 0·1 | 1 | 0·0 | 0·0 | 0·2 |
|  | Shock | 0 | 0·0 | 0·0 | 0·1 | 3 | 0·1 | 0·0 | 0·3 | 5 | 0·2 | 0·1 | 0·4 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term).

At least one SAE excluding malaria = at least one SAE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.

SAE = serious adverse event.

N = number of subjects with at least one administered dose.

n/% = number/percentage of subjects reporting the SAE at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S6. Percentage of subjects reporting serious adverse events until the end of the extension phase among infants in the 6-12 weeks age category (intention-to-treat population).

|  | | **R3R**  **N = 2180** | | | | **R3C**  **N = 2178** | | | | **C3C**  **N = 2179** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Primary System Organ Class** | **Preferred Term** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| **At least one SAE** |  | 580 | 26·6 | 24·8 | 28·5 | 602 | 27·6 | 25·8 | 29·6 | 619 | 28·4 | 26·5 | 30·4 |
| **At least one SAE excluding malaria** |  | 562 | 25·8 | 24·0 | 27·7 | 582 | 26·7 | 24·9 | 28·6 | 591 | 27·1 | 25·3 | 29·0 |
| **Fatalities** |  | 51 | 2·3 | 1·7 | 3·1 | 55 | 2·5 | 1·9 | 3·3 | 42 | 1·9 | 1·4 | 2·6 |
| **At least one related SAE** |  | 6 | 0·3 | 0·1 | 0·6 | 1 | 0·0 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
| **All SAEs** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Primary System Organ Class** | **Preferred Term** |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood and lymphatic system disorders | Anaemia | 90 | 4·1 | 3·3 | 5·1 | 106 | 4·9 | 4·0 | 5·9 | 116 | 5·3 | 4·4 | 6·4 |
|  | Haemolysis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Haemolytic anaemia | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Lymphadenitis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·3 |
|  | Thrombocytopenia | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Cardiac disorders | Cardiac arrest | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pericardial effusion | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Congenital, familial and genetic disorders | Cerebral palsy | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Congenital megacolon | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Fallot’s tetralogy | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Glucose-6-phosphate dehydrogenase deficiency | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Phimosis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Sickle cell anaemia | 1 | 0·0 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 | 5 | 0·2 | 0·1 | 0·5 |
|  | Sickle cell anaemia with crisis | 1 | 0·0 | 0·0 | 0·3 | 4 | 0·2 | 0·1 | 0·5 | 5 | 0·2 | 0·1 | 0·5 |
|  | Trisomy 21 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Urethral valves | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| Ear and labyrinth disorders | Deafness | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| Eye disorders | Periorbital oedema | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Gastrointestinal disorders | Constipation | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Enteritis | 7 | 0·3 | 0·1 | 0·7 | 10 | 0·5 | 0·2 | 0·8 | 18 | 0·8 | 0·5 | 1·3 |
|  | Food poisoning | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Gastritis | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 4 | 0·2 | 0·1 | 0·5 |
|  | Haematemesis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Inguinal hernia | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
|  | Intestinal obstruction | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Intussusception | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Rectal polyp | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Rectal prolapse | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Stomatitis | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Vomiting | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| General disorders and administration site conditions | Death | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
| Drowning | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Generalised oedema | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Hypothermia | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Injection site reaction | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pyrexia | 15 | 0·7 | 0·4 | 1·1 | 11 | 0·5 | 0·3 | 0·9 | 18 | 0·8 | 0·5 | 1·3 |
| Hepatobiliary disorders | Cholecystitis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Hepatitis | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Hepatitis acute | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| Immune system disorders | Allergy to arthropod sting | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·3 |
|  | Anaphylactic reaction | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Drug hypersensitivity | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Hypersensitivity | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Immune reconstitution inflammatory syndrome | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Infections and infestations | Abscess | 4 | 0·2 | 0·1 | 0·5 | 8 | 0·4 | 0·2 | 0·7 | 5 | 0·2 | 0·1 | 0·5 |
|  | Abscess limb | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Abscess neck | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Amoebiasis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Arthritis bacterial | 3 | 0·1 | 0·0 | 0·4 | 3 | 0·1 | 0·0 | 0·4 | 1 | 0·0 | 0·0 | 0·3 |
|  | Atypical pneumonia | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Bacterial infection | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·3 |
|  | Brain abscess | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Bronchiolitis | 19 | 0·9 | 0·5 | 1·4 | 13 | 0·6 | 0·3 | 1·0 | 24 | 1·1 | 0·7 | 1·6 |
|  | Bronchitis | 6 | 0·3 | 0·1 | 0·6 | 11 | 0·5 | 0·3 | 0·9 | 3 | 0·1 | 0·0 | 0·4 |
|  | Bronchopneumonia | 35 | 1·6 | 1·1 | 2·2 | 19 | 0·9 | 0·5 | 1·4 | 34 | 1·6 | 1·1 | 2·2 |
|  | Bullous impetigo | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Burn infection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Candida infection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Cellulitis | 6 | 0·3 | 0·1 | 0·6 | 4 | 0·2 | 0·1 | 0·5 | 6 | 0·3 | 0·1 | 0·6 |
|  | Central nervous system viral infection | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Cerebral malaria | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Conjunctivitis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Conjunctivitis bacterial | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Dysentery | 4 | 0·2 | 0·1 | 0·5 | 6 | 0·3 | 0·1 | 0·6 | 7 | 0·3 | 0·1 | 0·7 |
|  | Encephalitis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Encephalitis viral | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Enterococcal sepsis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Escherichia sepsis | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Escherichia urinary tract infection | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Exanthema subitum | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Febrile infection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Gastroenteritis | 162 | 7·4 | 6·4 | 8·6 | 171 | 7·9 | 6·8 | 9·1 | 171 | 7·8 | 6·8 | 9·1 |
|  | Gastroenteritis salmonella | 5 | 0·2 | 0·1 | 0·5 | 2 | 0·1 | 0·0 | 0·3 | 4 | 0·2 | 0·1 | 0·5 |
|  | Gastroenteritis shigella | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Giardiasis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Groin abscess | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Haemophilus sepsis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Helminthic infection | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Hepatitis A | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Hepatitis B | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Hepatitis infectious | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | HIV associated nephropathy | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | HIV infection | 20 | 0·9 | 0·6 | 1·4 | 16 | 0·7 | 0·4 | 1·2 | 12 | 0·6 | 0·3 | 1·0 |
|  | HIV infection WHO clinical stage III | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | HIV infection WHO clinical stage IV | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Impetigo | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Infection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Injection site abscess | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Laryngitis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Listeria sepsis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Liver abscess | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Lobar pneumonia | 8 | 0·4 | 0·2 | 0·7 | 9 | 0·4 | 0·2 | 0·8 | 7 | 0·3 | 0·1 | 0·7 |
|  | Lower respiratory tract infection | 0 | 0·0 | 0·0 | 0·2 | 4 | 0·2 | 0·1 | 0·5 | 2 | 0·1 | 0·0 | 0·3 |
|  | Ludwig angina | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Lymph node abscess | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Malaria | 180 | 8·3 | 7·1 | 9·5 | 208 | 9·6 | 8·3 | 10·9 | 233 | 10·7 | 9·4 | 12·1 |
|  | Mastoiditis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Measles | 14 | 0·6 | 0·4 | 1·1 | 10 | 0·5 | 0·2 | 0·8 | 8 | 0·4 | 0·2 | 0·7 |
|  | Meningitis | 2 | 0·1 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 | 3 | 0·1 | 0·0 | 0·4 |
|  | Meningitis haemophilus | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Meningitis pneumococcal | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Meningitis salmonella | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Moraxella infection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Mumps | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Oral candidiasis | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Oropharyngeal candidiasis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Osteomyelitis | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Otitis externa | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Otitis media | 11 | 0·5 | 0·3 | 0·9 | 11 | 0·5 | 0·3 | 0·9 | 7 | 0·3 | 0·1 | 0·7 |
|  | Otitis media acute | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Parotitis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Periorbital cellulitis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Peritonitis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pharyngitis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Pneumococcal bacteraemia | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pneumococcal sepsis | 5 | 0·2 | 0·1 | 0·5 | 4 | 0·2 | 0·1 | 0·5 | 3 | 0·1 | 0·0 | 0·4 |
|  | *Pneumocystis jirovecii* pneumonia | 4 | 0·2 | 0·1 | 0·5 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pneumonia | 217 | 10·0 | 8·7 | 11·3 | 206 | 9·5 | 8·3 | 10·8 | 202 | 9·3 | 8·1 | 10·6 |
|  | Pneumonia pneumococcal | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pneumonia streptococcal | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pneumonia viral | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pulmonary tuberculosis | 6 | 0·3 | 0·1 | 0·6 | 6 | 0·3 | 0·1 | 0·6 | 2 | 0·1 | 0·0 | 0·3 |
|  | Pyomyositis | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Respiratory tract infection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Rubella | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Salmonella bacteraemia | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Salmonella sepsis | 25 | 1·1 | 0·7 | 1·7 | 34 | 1·6 | 1·1 | 2·2 | 37 | 1·7 | 1·2 | 2·3 |
|  | Sepsis | 23 | 1·1 | 0·7 | 1·6 | 15 | 0·7 | 0·4 | 1·1 | 13 | 0·6 | 0·3 | 1·0 |
|  | Septic shock | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Staphylococcal sepsis | 5 | 0·2 | 0·1 | 0·5 | 5 | 0·2 | 0·1 | 0·5 | 2 | 0·1 | 0·0 | 0·3 |
|  | Staphylococcal skin infection | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Streptococcal sepsis | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Subcutaneous abscess | 6 | 0·3 | 0·1 | 0·6 | 1 | 0·0 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
|  | Superinfection | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Tonsillitis | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Tuberculosis | 2 | 0·1 | 0·0 | 0·3 | 4 | 0·2 | 0·1 | 0·5 | 3 | 0·1 | 0·0 | 0·4 |
|  | Typhoid fever | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Upper respiratory tract infection | 19 | 0·9 | 0·5 | 1·4 | 31 | 1·4 | 1·0 | 2·0 | 24 | 1·1 | 0·7 | 1·6 |
|  | Urinary tract infection | 11 | 0·5 | 0·3 | 0·9 | 15 | 0·7 | 0·4 | 1·1 | 22 | 1·0 | 0·6 | 1·5 |
|  | Urosepsis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Vaginal infection | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Varicella | 2 | 0·1 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Viral infection | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Injury, poisoning and procedural complications | Burns first degree | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Burns second degree | 3 | 0·1 | 0·0 | 0·4 | 2 | 0·1 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
|  | Clavicle fracture | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Femur fracture | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Greenstick fracture | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Head injury | 0 | 0·0 | 0·0 | 0·2 | 4 | 0·2 | 0·1 | 0·5 | 0 | 0·0 | 0·0 | 0·2 |
|  | Herbal toxicity | 0 | 0·0 | 0·0 | 0·2 | 2 | 0·1 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
|  | Human bite | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Humerus fracture | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Limb injury | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Petroleum distillate poisoning | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Pneumonitis chemical | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Soft tissue injury | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 |
|  | Thermal burn | 14 | 0·6 | 0·4 | 1·1 | 9 | 0·4 | 0·2 | 0·8 | 11 | 0·5 | 0·3 | 0·9 |
|  | Tibia fracture | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Vaccination failure | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 |
|  | Wrist fracture | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Metabolism and nutrition disorders | Dehydration | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Failure to thrive | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Hyperkalaemia | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Hypoglycaemia | 2 | 0·1 | 0·0 | 0·3 | 3 | 0·1 | 0·0 | 0·4 | 3 | 0·1 | 0·0 | 0·4 |
|  | Hypokalaemia | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Kwashiorkor | 8 | 0·4 | 0·2 | 0·7 | 8 | 0·4 | 0·2 | 0·7 | 4 | 0·2 | 0·1 | 0·5 |
|  | Malnutrition | 20 | 0·9 | 0·6 | 1·4 | 30 | 1·4 | 0·9 | 2·0 | 19 | 0·9 | 0·5 | 1·4 |
|  | Marasmus | 6 | 0·3 | 0·1 | 0·6 | 5 | 0·2 | 0·1 | 0·5 | 7 | 0·3 | 0·1 | 0·7 |
|  | Metabolic acidosis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Musculoskeletal and connective tissue disorders | Arthritis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| Compartment syndrome | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Dactylitis | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Myositis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Osteoarthritis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Rickets | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Torticollis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | Acute promyelocytic leukaemia | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Inflammatory pseudotumour | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Langerhans’ cell histiocytosis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
| Nervous system disorders | Cerebellar ataxia | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Convulsion | 45 | 2·1 | 1·5 | 2·8 | 32 | 1·5 | 1·0 | 2·1 | 32 | 1·5 | 1·0 | 2·1 |
|  | Encephalomalacia | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Encephalopathy | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Epilepsy | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Febrile convulsion | 100 | 4·6 | 3·7 | 5·6 | 90 | 4·1 | 3·3 | 5·1 | 101 | 4·6 | 3·8 | 5·6 |
|  | Hydrocephalus | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Loss of consciousness | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Metabolic encephalopathy | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Monoparesis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Myoclonus | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Paraparesis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Uraemic encephalopathy | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Psychiatric disorders | Neurodevelopmental disorder | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Renal and urinary disorders | Glomerulonephritis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Glomerulonephritis acute | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Hydronephrosis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Nephritis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Renal failure acute | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Renal tubular necrosis | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Urinary retention | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Reproductive system and breast disorders | Acquired phimosis | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Respiratory, thoracic and mediastinal disorders | Apnoeic attack | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
| Asthma | 6 | 0·3 | 0·1 | 0·6 | 3 | 0·1 | 0·0 | 0·4 | 7 | 0·3 | 0·1 | 0·7 |
|  | Bronchial hyperreactivity | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Bronchospasm | 3 | 0·1 | 0·0 | 0·4 | 5 | 0·2 | 0·1 | 0·5 | 5 | 0·2 | 0·1 | 0·5 |
|  | Obstructive airways disorder | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pleural effusion | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Pneumonia aspiration | 2 | 0·1 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 4 | 0·2 | 0·1 | 0·5 |
|  | Pneumonitis | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 1 | 0·0 | 0·0 | 0·3 |
|  | Respiratory arrest | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Skin and subcutaneous tissue disorders | Dermatitis exfoliative | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
|  | Drug eruption | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 |
|  | Urticaria | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 | 0 | 0·0 | 0·0 | 0·2 |
| Vascular disorders | Hypovolaemic shock | 0 | 0·0 | 0·0 | 0·2 | 1 | 0·0 | 0·0 | 0·3 | 0 | 0·0 | 0·0 | 0·2 |
|  | Shock | 1 | 0·0 | 0·0 | 0·3 | 2 | 0·1 | 0·0 | 0·3 | 4 | 0·2 | 0·1 | 0·5 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

At least one SAE = at least one SAE experienced (regardless of the MedDRA Preferred Term).

At least one SAE excluding malaria = at least one SAE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.

SAE = serious adverse event.

N = number of subjects with at least one administered dose.

n/% = number/percentage of subjects reporting the SAE at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S7. Overall vaccine efficacy against clinical and severe malaria among children in the 5-17 months age category (per-protocol population for efficacy).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy against clinical malaria (primary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | | |
|  | | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M2·5-SE | | 2306 | 6597 | 7355·8 | 0·9 | 2336 | 8352 | 7352·4 | 1·14 | 26·2 | 20·8 | 31·2 | <0·0001 |
|  | M2·5-M32 | | 2306 | 4104 | 5093·3 | 0.8 | 2336 | 5813 | 5053·1 | 1·15 | 33·9 | 28·9 | 38·.6 | <0·0001 |
|  | M2·5-M20\* | | 4557 | 4257 | 6186·0 | 0·69 | 2328 | 3639 | 3100·4 | 1·17 | 45·7 | 41·7 | 49·5 | <0·0001 |
|  | M21-M32 | | 2057 | 1872 | 1956·1 | 0·96 | 2050 | 2135 | 1945·5 | 1·1 | 13·5 | 5·4 | 20·9 | 0·0015 |
|  | M33-SE | | 1838 | 2493 | 2266·4 | 1·1 | 1864 | 2539 | 2303·2 | 1·1 | 0·1 | -9·9 | 9·1 | 0·9843 |
|  | M21-SE | | 2057 | 4365 | 4218·6 | 1·03 | 2050 | 4674 | 4244·9 | 1·1 | 8·2 | 0·4 | 15·3 | 0·0389 |
| **Efficacy against severe malaria (primary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | | |
|  | | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M2·5-SE | | 2306 | 141 | 0·06 | | 2336 | 135 | 0·06 | | -5·8 | -35·0 | 17·0 | 0·6640 |
|  | M2·5-M32 | | 2306 | 116 | 0·05 | | 2336 | 120 | 0·05 | | 2·1 | -27·5 | 24·8 | 0·8938 |
|  | M2·5-M20\* | | 4557 | 120 | 0·03 | | 2328 | 95 | 0·04 | | 35·5 | 14·6 | 51·1 | 0·0016 |
|  | M21-M32 | | 2057 | 48 | 0·02 | | 2051 | 32 | 0·02 | | -49·6 | -142 | 6·3 | 0·0898 |
|  | M33-SE | | 1838 | 29 | 0·02 | | 1864 | 16 | 0·01 | | -83·8 | -262 | 3·4 | 0·0512 |
|  | M21-SE | | 2057 | 73 | 0·04 | | 2051 | 48 | 0·02 | | -51·6 | -123 | -3·9 | 0·0264 |
| **Efficacy against clinical malaria (primary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | | |
|  | | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M2·5-SE | | 2276 | 5691 | 7247·4 | 0·79 | 2336 | 8352 | 7352·4 | 1·14 | 39·0 | 34·3 | 43·3 | <0·0001 |
|  | M2·5-M32 | | 2276 | 3438 | 5019·2 | 0·68 | 2336 | 5813 | 5053·1 | 1·15 | 46·1 | 41·8 | 50·1 | <0·0001 |
|  | M2·5-M20\* | | 4557 | 4257 | 6186·0 | 0·69 | 2328 | 3639 | 3100·4 | 1·17 | 45·7 | 41·7 | 49·5 | <0·0001 |
|  | M21-M32 | | 2017 | 1384 | 1933·4 | 0·72 | 2050 | 2135 | 1945·5 | 1·1 | 38·5 | 32·2 | 44·1 | <0·0001 |
|  | M33-SE | | 1784 | 2254 | 2231·3 | 1·01 | 1864 | 2539 | 2303·2 | 1·1 | 14·6 | 5·8 | 22·6 | 0·0017 |
|  | M21-SE | | 2017 | 3637 | 4161·6 | 0·87 | 2050 | 4674 | 4244·9 | 1·1 | 27·6 | 21·2 | 33·5 | <0·0001 |
| **Efficacy against severe malaria (primary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | | |
|  | | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M2·5-SE | | 2276 | 94 | 0·04 | | 2336 | 135 | 0·06 | | 28·5 | 6·3 | 45·7 | 0·0100 |
|  | M2·5-M32 | | 2276 | 79 | 0·03 | | 2336 | 120 | 0·05 | | 32·4 | 9·5 | 49·8 | 0·0058 |
|  | M25-M20\* | | 4557 | 120 | 0·03 | | 2328 | 95 | 0·04 | | 35·5 | 14·6 | 51·1 | 0·0016 |
|  | M21-M32 | | 2017 | 34 | 0·02 | | 2051 | 32 | 0·02 | | -8·0 | -80·8 | 35·3 | 0·8045 |
|  | M33-SE | | 1784 | 20 | 0·01 | | 1864 | 16 | 0·01 | | -30·6 | -170 | 35·7 | 0·5036 |
|  | M21-SE | | 2017 | 52 | 0·03 | | 2051 | 48 | 0·02 | | -10·2 | -66·6 | 27·0 | 0·6857 |
| **Incremental efficacy against clinical malaria (primary case definition) of a booster dose** | | | | | | | | | | | | | | |
|  | | **R3R** | | | | | **R3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | **N** | | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M21-SE | 2017 | | 3637 | 4161·6 | 0·87 | 2057 | 4365 | 4218·6 | 1·03 | 21·3 | 14·2 | 27·8 | <0·0001 |
|  | M21-M32 | 2017 | | 1384 | 1933·4 | 0·72 | 2057 | 1872 | 1956·1 | 0·96 | 29·0 | 21·6 | 35·6 | <0·0001 |

\*Data from previous analysis (comparing R3R+R3C versus C3C).

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

n (clinical malaria) = number of episodes meeting the case definition.

n (severe malaria) = number of subjects reporting at least one event in each group.

T = person years at risk.

n/T = incidence rate.

Proportion affected = proportion of subjects reporting at least one event.

VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

M2·5-SE = follow-up from 14 days post dose-3 (Month 2·5) to study end (end of extension phase).

M2·5-M32 = follow-up from 14 days post dose-3 (Month 2·5) to 30 months post dose-3 (Month 32).

M2·5-M20 = follow-up from 14 days post dose-3 (Month 2·5) to 18 months post dose-3 (Month 20).

M21-M32 = follow-up from day of booster dose to 30 months post dose-3 (Month 32).

M33-SE = follow-up from start of extension phase to study end (end of extension phase).

M21-SE = follow-up from day of booster dose to study end (end of extension phase).

SE = study end (the median follow-up in the 5-17 months age category was 48 months post dose-1).

Clinical malaria primary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37·5°C and *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria.

Severe malaria primary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

For clinical malaria: p-value from negative binomial regression.

For severe malaria: p-value from two-sided Fisher exact test.

Table S8. Overall vaccine efficacy against clinical and severe malaria secondary case definition among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy against clinical malaria (secondary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | |
|  | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M0-SE | 2972 | 11627 | 9876·3 | 1·18 | 2974 | 15029 | 9786·5 | 1·54 | 30·0 | 25·5 | 34·3 | <0·0001 |
|  | M0-M32 | 2972 | 7325 | 7079·7 | 1·03 | 2974 | 10341 | 6950·9 | 1·49 | 35·7 | 31·3 | 39·7 | <0·0001 |
| **Efficacy against severe malaria (secondary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | |
|  | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M0-SE | 2972 | 186 | 0·06 | | 2974 | 204 | 0·07 | | 8·8 | -11·8 | 25·6 | 0·3732 |
|  | M0-M32 | 2972 | 162 | 0·05 | | 2974 | 183 | 0·06 | | 11·4 | -10·0 | 28·7 | 0·2672 |
| **Efficacy against clinical malaria (secondary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | |
|  | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M0-SE | 2976 | 10629 | 9803·4 | 1.08 | 2974 | 15029 | 9786·5 | 1·5 | 35·5 | 31·2 | 39·5 | <0·0001 |
|  | M0-M32 | 2976 | 6615 | 7001·6 | 0.94 | 2974 | 10341 | 6950·9 | 1·5 | 41·6 | 37·6 | 45·4 | <0·0001 |
| **Efficacy against severe malaria (secondary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | |
|  | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M0-SE | 2976 | 141 | 0·05 | | 2974 | 204 | 0·07 | | 30·9 | 14·0 | 44·7 | 0·0005 |
|  | M0-M32 | 2976 | 121 | 0·04 | | 2974 | 183 | 0·06 | | 33·9 | 16·4 | 47·9 | 0·0003 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

n (clinical malaria) = number of episodes meeting the case definition.

n (severe malaria) = number of subjects reporting at least one event in each group.

T = person years at risk.

n/T = incidence rate.

Proportion affected = proportion of subjects reporting at least one event.

VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase).

M0-M32 = follow-up from day of dose-1 (Month 0) to 32 months post dose-1 (Month 32).

SE = study end (the median follow-up in the 5-17 months age category was 48 months post dose-1).

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37.5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

For clinical malaria: p-value from negative binomial regression.

For severe malaria: p-value from two-sided Fisher exact test.

Table S9. Vaccine efficacy against clinical malaria by age (5-11 months and 12-17 months) among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy against clinical malaria (primary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | |
|  | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria (M0-M32) | 5-11 months | 1676 | 2551 | 4052·7 | 0·63 | 1700 | 3557 | 4056·5 | 0·88 | 35·8 | 25·9 | 44·3 | <0·0001 |
|  | 12-17 months | 1296 | 2160 | 3127·2 | 0·69 | 1274 | 3211 | 3032·0 | 1·06 | 39·2 | 29·6 | 47·5 | <0·0001 |
|  | Overall | 2972 | 4711 | 7180.0 | 0·66 | 2974 | 6768 | 7088·5 | 0·95 | 35·2 | 30·5 | 39·5 | <0·0001 |
| **Efficacy against clinical malaria (primary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | |
|  | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria (M0-M32) | 5-11 months | 1678 | 2181 | 3976·7 | 0·55 | 1700 | 3557 | 4056·5 | 0·88 | 42·8 | 34·2 | 50·3 | <0·0001 |
|  | 12-17 months | 1298 | 1897 | 3123·1 | 0·61 | 1274 | 3211 | 3032·0 | 1·06 | 46·5 | 38.0 | 53·9 | <0·0001 |
|  | Overall | 2976 | 4078 | 7099·7 | 0·57 | 2974 | 6768 | 7088·5 | 0·95 | 43·9 | 39·7 | 47·8 | <0·0001 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

n = number of episodes meeting the case definition.

T = person years at risk.

n/T = incidence rate.

VE = vaccine efficacy (negative binomial model for clinical malaria).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

M0-M32 = follow-up from day of dose-1 (Month 0) to 32 months post dose-1 (Month 32).

Clinical malaria primary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37.5°C and *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria.

For clinical malaria: p-value from negative binomial regression.

Table S10. Outcome of all cases of severe malaria (secondary case definition) recorded among children in the 5-17 months age category (intention-to-treat population).

| **Time period** | **Outcome** | **R3R+R3C** | | **R3R** | | **R3C** | | **C3C** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **N** | **n** | **N** | **n** | **N** | **n** | **N** | **n** |
| M0-M20 | Died | 205 | 6 | - | - | - | - | 158 | 2 |
| M0-M20 | Survived with sequelae | 205 | 0 | - | - | - | - | 158 | 0 |
| M0-M20 | Survived without sequelae | 205 | 199 | - | - | - | - | 158 | 156 |
| M21-SE | Died | - | - | 76 | 3 | 103 | 6 | 76 | 2 |
| M21-SE | Survived with sequelae | - | - | 76 | 1 | 103 | 0 | 76 | 0 |
| M21-SE | Survived without sequelae | - | - | 76 | 72 | 103 | 97 | 76 | 74 |

R3R+R3C = RTS,S/AS01 primary schedule (combined R3R + R3C groups analysed over the period before the administration of the booster dose at Month 20).

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of cases of severe malaria secondary case definition.

n = number of cases of severe malaria secondary case definition of each outcome.

M0-M20 = follow-up from day of dose-1 (Month 0) to 20 months post dose-1 (Month 20).

M21-SE = follow-up from day of booster dose to study end (end of extension phase).

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

Table S11. Outcome of all cases severe malaria (secondary case definition) recorded among infants in the 6-12 weeks age category (intention-to-treat population).

| **Time period** | **Outcome** | **R3R+R3C** | | **R3R** | | **R3C** | | **C3C** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **N** | **n** | **N** | **n** | **N** | **n** | **N** | **n** |
| M0-M20 | Died | 148 | 1 | - | - | - | - | 86 | 2 |
| M0-M20 | Survived with sequelae | 148 | 0 | - | - | - | - | 86 | 0 |
| M0-M20 | Survived without sequelae | 148 | 147 | - | - | - | - | 86 | 84 |
| M21-SE | Died | - | - | 53 | 3 | 63 | 2 | 68 | 0 |
| M21-SE | Survived with sequelae | - | - | 53 | 0 | 63 | 0 | 68 | 1 |
| M21-SE | Survived without sequelae | - | - | 53 | 50 | 63 | 61 | 68 | 67 |

R3R+R3C = RTS,S/AS01 primary schedule (combined R3R + R3C groups analysed over the period before the administration of the booster dose at Month 20).

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of cases of severe malaria secondary case definition.

n = number of cases of severe malaria secondary case definition of each outcome.

M0-M20 = follow-up from day of dose-1 (Month 0) to 20 months post dose-1 (Month 20).

M21-SE = follow-up from day of booster dose to study end (end of extension phase).

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

Table S12. Overall vaccine efficacy against incident severe malaria anaemia, malaria hospitalization and fatal malaria until the end of the extension phase (M0-SE) among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy of a primary schedule without booster (R3C)** | | | | | | | | | | | |
|  | | **R3C** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Incident severe malaria anaemia | Case definition 1 | 2972 | 34 | 0·01 | 2974 | 44 | 0·01 | 22·7 | -23.8 | 52·1 | 0·3050 |
| Case definition 2 | 2972 | 43 | 0·01 | 2974 | 54 | 0·02 | 20·3 | -21·2 | 47·9 | 0·3060 |
| Malaria hospitalization | Case definition 1 | 2972 | 286 | 0·1 | 2974 | 347 | 0·12 | 17·5 | 3·3 | 29·7 | 0·0116 |
|  | Case definition 2 | 2972 | 324 | 0·11 | 2974 | 400 | 0·13 | 18·9 | 5·9 | 30·2 | 0·0029 |
| Fatal malaria | Primary case definition | 2972 | 2 | 0 | 2974 | 1 | 0 | -100·1 | -12E3 | 89·6 | 0·6248 |
|  | Secondary case definition | 2972 | 8 | 0 | 2974 | 4 | 0 | -100·1 | -808 | 46·4 | 0·2662 |
|  | ICD10 code | 2972 | 17 | 0·01 | 2974 | 12 | 0 | -41·8 | -225 | 36·2 | 0·3603 |
| **Efficacy of a primary schedule with booster (R3R)** | | | | | | | | | | | |
|  | | **R3R** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Incident severe malaria anaemia | Case definition 1 | 2976 | 23 | 0·01 | 2974 | 44 | 0·01 | 47·8 | 11·6 | 69·9 | 0·0099 |
| Case definition 2 | 2976 | 28 | 0·01 | 2974 | 54 | 0·02 | 48·2 | 16·7 | 68·4 | 0·0038 |
| Malaria hospitalization | Case definition 1 | 2976 | 227 | 0·08 | 2974 | 347 | 0·12 | 34·6 | 22·5 | 44·9 | <0·0001 |
|  | Case definition 2 | 2976 | 272 | 0·09 | 2974 | 400 | 0·13 | 32·0 | 20·5 | 42·0 | <0·0001 |
| Fatal malaria | Primary case definition | 2976 | 1 | 0 | 2974 | 1 | 0 | 0·1 | -7744 | 98·7 | 1·0000 |
|  | Secondary case definition | 2976 | 7 | 0 | 2974 | 4 | 0 | -74·9 | -715 | 55·5 | 0·5484 |
|  | ICD10 code | 2976 | 13 | 0 | 2974 | 12 | 0 | -8·3 | -160 | 54·5 | 1·0000 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects included in each group (without missing values).

n = number of subjects reporting at least one event in each group.

Proportion affected = proportion of subjects reporting at least one event.

VE (%) = vaccine efficacy (conditional method).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

P-value = two-sided Fisher exact test.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase). The median follow-up in the 5-17 months age category was 48 months post dose-1.

Incident severe malaria anaemia case definition 1 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 5000 parasites per cubic millimetre.

Incident severe malaria anaemia case definition 2 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 0 parasites per cubic millimetre.

Malaria hospitalization case definition 1 = a medical hospitalization with confirmed *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre.

Malaria hospitalization case definition 2 = a hospitalization which, in the judgment of the principal investigator, *P. falciparum* infection was the sole or a major contributing factor to the presentation.

Fatal malaria primary definition = a case of severe malaria meeting the primary case definition of severe malaria with a fatal outcome.

Fatal malaria secondary case definition = a case of severe malaria meeting the secondary case definition of severe malaria with a fatal outcome.

Fatal malaria (ICD10 code) = a fatal case associated with International Classification Disease (ICD10) code B50, B53, B54.

Table S13. Overall vaccine efficacy against serious illnesses until the end of the extension phase (M0-SE) among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy of a primary schedule without booster (R3C)** | | | | | | | | | | | |
|  | | **R3C** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Bacteraemia | Case definition 1 | 2972 | 60 | 0·02 | 2974 | 77 | 0·03 | 22·0 | -10·7 | 45·3 | 0·1664 |
|  | Case definition 2 (Salmonella sepsis) | 2972 | 35 | 0·01 | 2974 | 52 | 0·02 | 32·6 | -5·4 | 57·4 | 0·0834 |
| Pneumonia | Primary case definition | 2972 | 100 | 0·03 | 2974 | 127 | 0·04 | 21·2 | -3·2 | 40·0 | 0·0783 |
|  | Secondary case definition 1 | 2972 | 17 | 0·01 | 2974 | 22 | 0·01 | 22·7 | -52·5 | 61·4 | 0·5210 |
| All-cause hospitalization | Primary case definition | 2972 | 682 | 0·23 | 2974 | 771 | 0·26 | 11·5 | 1·7 | 20·3 | 0·0079 |
| All-cause mortality | Case definition 1 | 2972 | 51 | 0·02 | 2974 | 46 | 0·02 | -10·9 | -69·0 | 27·0 | 0·6107 |
|  | Case definition 2 | 2972 | 46 | 0·02 | 2974 | 41 | 0·01 | -12·3 | -75·4 | 27·9 | 0·5915 |
| Blood transfusions | - | 2972 | 91 | 0·03 | 2974 | 109 | 0·04 | 16·5 | -11·4 | 37·5 | 0·2213 |
| **Efficacy of a primary schedule with booster (R3R)** | | | | | | | | | | | |
|  | | **R3R** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Bacteraemia | Case definition 1 | 2976 | 70 | 0·02 | 2974 | 77 | 0·03 | 9·2 | -27·2 | 35·2 | 0·5602 |
|  | Case definition 2 (Salmonella sepsis) | 2976 | 41 | 0·01 | 2974 | 52 | 0·02 | 21·2 | -21·0 | 49·0 | 0·2526 |
| Pneumonia | Primary case definition | 2976 | 125 | 0·04 | 2974 | 127 | 0·04 | 1·6 | -26·9 | 23·8 | 0·8978 |
|  | Secondary case definition 1 | 2976 | 32 | 0·01 | 2974 | 22 | 0·01 | -45·4 | -163 | 18·1 | 0·2182 |
| All-cause hospitalization | Primary case definition | 2976 | 644 | 0·22 | 2974 | 771 | 0·26 | 16·5 | 7·2 | 24·9 | 0·0001 |
| All-cause mortality | Case definition 1 | 2976 | 61 | 0·02 | 2974 | 46 | 0·02 | -32·5 | -98·7 | 11·1 | 0·1717 |
|  | Case definition 2 | 2976 | 54 | 0·02 | 2974 | 41 | 0·01 | -31·6 | -103 | 13·9 | 0·2144 |
| Blood transfusions | - | 2976 | 78 | 0·03 | 2974 | 109 | 0·04 | 28·5 | 3·5 | 47·2 | 0·0213 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects included in each group (without missing values).

n = number of subjects reporting at least one event in each group.

Proportion affected = proportion of subjects reporting at least one event.

VE(%) = vaccine efficacy (conditional method).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

P-value = two-sided Fisher exact test.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase). The median follow-up in the 5-17 months age category was 48 months post dose-1.

Bacteraemia case definition 1 = a child with a positive blood culture taken within 72 hours of admission.

Bacteraemia case definition 2 (Salmonella sepsis) = a child with a positive salmonella blood culture taken within 72 hours of admission.

Pneumonia primary case definition = cough or difficulty breathing (on history) and tachypnea (≥ 50 breaths per minute < 1 year, ≥ 40 breaths per minute ≥ 1year) and lower chest wall indrawing.

Pneumonia secondary case definition 1 = a case of pneumonia meeting the primary case definition of pneumonia with chest x-ray consolidation or pleural effusion on x-ray taken within 72 h of admission.

All-cause hospitalization primary case definition = a medical hospitalization of any cause, excluding planned admissions for medical investigation/care or elective surgery and trauma.

All-cause mortality case definition 1 = a fatality of any cause, including mortality in the community and in hospital.

All-cause mortality case definition 2 = a fatality of medical cause, including mortality in the community and in hospital and excluding trauma, which may be diagnosed by verbal autopsy.

Blood transfusion = a child with inpatient admission with documented blood transfusion.

Table S14. Vaccine efficacy against prevalent parasitaemia until the end of the extension phase among children in the 5-17 months age category (intention-to-treat population)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy of a primary schedule without booster (R3C)** | | | | | | | | | | | | | | | | |
| **Intention-to-treat population** | **Month 32** | | | | **Month 44** | | | | **SE early** | | | | **SE late** | | | |
| **Site** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** |
| Kilifi | 100 | -132 | 100 | 0·1159 |  |  |  |  |  |  |  |  |  |  |  |  |
| Korogwe |  |  |  |  |  |  |  |  | 100 | -3833 | 100 | 1·0000 |  |  |  |  |
| Manhiça | -42·2 | -397 | 56·7 | 0·5920 | 61·1 | -62·2 | 93·3 | 0·2177 |  |  |  |  | -23·2 | -259 | 56·2 | 0·8082 |
| Lambaréné | 8·9 | -83·0 | 55·2 | 0·8623 | 13·6 | -161 | 72·6 | 0·7936 | 14·3 | -214 | 78·5 | 1·0000 | 59·7 | -68·0 | 93·1 | 0·2059 |
| Bagamoyo | 59·8 | -76·1 | 93·3 | 0·2094 |  |  |  |  |  |  |  |  |  |  |  | . |
| Lilongwe | -36·8 | -447 | 62·6 | 0·7714 | 100 | -5037 | 100 | 1·0000 |  |  |  |  | 100 | -5157 | 100 | 1·0000 |
| Agogo | 53·6 | 9·7 | 77·3 | 0·0103 | 49·7 | -17·9 | 80·1 | 0·1062 |  |  |  |  | -22·2 | -170 | 44·1 | 0·5724 |
| Kombewa | 8·8 | -46·8 | 43·6 | 0·7099 | -28·3 | -92·5 | 14·3 | 0·1652 | 33·3 | -68·4 | 74·2 | 0·3275 | 11·5 | -41·1 | 44·9 | 0·6124 |
| Kintampo | 32·9 | 1·8 | 54·5 | 0·0169 | 29·0 | -14·2 | 56·4 | 0·0927 | 22·0 | -32·1 | 53·9 | 0·2811 | 5·9 | -42·7 | 38·2 | 0·8096 |
| Nanoro | 44·6 | 8·8 | 67·0 | 0·0059 | 46·2 | 3·3 | 70·9 | 0·0126 | 39·6 | -10·4 | 68·2 | 0·0143 | 37·7 | 5·1 | 59·6 | 0·0029 |
| Siaya | 15·3 | -24·8 | 42·7 | 0·3198 | 7·7 | -31·4 | 35·1 | 0·5706 | 16·4 | -147 | 74·6 | 0·7442 | 5·7 | -38·1 | 35·6 | 0·7305 |
| **Overall** | **28·3** | **14·1** | **40·3** | **0·0001** | **15·5** | **-2·6** | **30·5** | **0·0573** | **28·1** | **1·3** | **47·8** | **0·0274** | **14·7** | **-3·0** | **29·5** | **0·0631** |
| **Efficacy of a primary schedule with booster (R3R)** | | | | | | | | | | | | | | | | |
| **Intention-to-treat population** | **Month 32** | | | | **Month 44** | | | | **SE early** | | | | **SE late** | | | |
| **Site** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** |
| Kilifi | 100 | -138 | 100 | 0·1203 |  |  |  |  |  |  |  |  |  |  |  |  |
| Korogwe |  |  |  |  |  |  |  |  | 3·3 | -7492 | 98·8 | 1·0000 |  |  |  |  |
| Manhiça | -24·4 | -348 | 64·2 | 0·7820 | 26·6 | -141 | 79·0 | 0·5944 |  |  |  |  | -4·0 | -210 | 64·4 | 1·0000 |
| Lambaréné | 37·2 | -34·9 | 72·0 | 0·1978 | 22·5 | -158 | 79·6 | 0·7733 | 0·0 | -234 | 70·1 | 1·0000 | 82·6 | -29·6 | 99·6 | 0·0753 |
| Bagamoyo | 71·8 | -48·2 | 97·1 | 0·1044 |  |  |  | . |  |  |  |  |  |  |  | . |
| Lilongwe | 18·9 | -277 | 83·9 | 1·0000 | 100 | -4381 | 100 | 1·0000 |  |  |  |  | 100 | -4462 | 100 | 1·0000 |
| Agogo | 59·3 | 18·2 | 81·0 | 0·0049 | 44·4 | -26·9 | 77·1 | 0·1652 |  |  |  |  | -4·3 | -136 | 53·9 | 1·0000 |
| Kombewa | 21·1 | -28·9 | 52·2 | 0·3106 | -10·3 | -67·0 | 27·1 | 0·6408 | 65·3 | -5·9 | 90·4 | 0·0295 | -8·9 | -68·6 | 29·5 | 0·7183 |
| Kintampo | 19·8 | -15·5 | 44·4 | 0·1878 | 31·9 | -11·0 | 58·9 | 0·0653 | 30·2 | -19·7 | 59·5 | 0·1187 | 16·9 | -28·1 | 46·5 | 0·3260 |
| Nanoro | 54·2 | 22·6 | 73·7 | 0·0007 | 37·8 | -9·9 | 65·6 | 0·0623 | 44·9 | 3·8 | 69·1 | 0·0028 | 41·6 | 9·8 | 62·8 | 0·0010 |
| Siaya | 31·6 | -2·8 | 54·9 | 0·0309 | 15·3 | -21·4 | 41·0 | 0·2521 | 40·3 | -102 | 86·1 | 0·3136 | 3·1 | -41·0 | 33·4 | 0·9096 |
| **Overall** | **34·8** | **21·4** | **46·0** | **<0·0001** | **19·3** | **1·7** | **33·9** | **0·0187** | **29·9** | **3·9** | **49·2** | **0·0179** | **16·1** | **-1·4** | **30·6** | **0·0436** |

VE (%) = vaccine efficacy (conditional method).

LL = lower limit of the 95% confidence interval.

UL = upper limit of the 95% confidence interval.

P-value = two-sided Fisher exact test.

Month 32 = cross sectional survey at 32 months post dose-1.

Month 44 = cross sectional survey at 44 months post dose-1.

SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 5-17 months: 14 months post Month 32).

SE late = study end in subjects having done Month 32 visit ≤ 30 June 2012 (median follow-up in 5-17 months: 17 months post Month 32).

Table S15. Anthropometric findings in children in the 5-17 months age category (intention-to-treat population).

|  |  |  | **R3R** | | **R3C** | | **C3C** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study timepoint** | **Characteristics** | **Parameters** | **N** | **Value** | **N** | **Value** | **N** | **Value** |
| Month 32 | Height [cm] | N | 2363 | 2351 | 2382 | 2367 | 2392 | 2377 |
|  |  | Missing | 2363 | 12 | 2382 | 15 | 2392 | 15 |
|  |  | Mean | 2363 | 94·7 | 2382 | 94·5 | 2392 | 94·4 |
|  |  | SD | 2363 | 4·6 | 2382 | 4·8 | 2392 | 4·7 |
|  |  | Minimum | 2363 | 72·0 | 2382 | 79·0 | 2392 | 79·0 |
|  |  | Maximum | 2363 | 112·0 | 2382 | 110·0 | 2392 | 109·0 |
|  | Height for age Z-score | N | 2363 | 2351 | 2382 | 2367 | 2392 | 2377 |
|  |  | Missing | 2363 | 12 | 2382 | 15 | 2392 | 15 |
|  |  | Mean | 2363 | -1·3 | 2382 | -1·4 | 2392 | -1·4 |
|  |  | SD | 2363 | 1·0 | 2382 | 1·0 | 2392 | 1·0 |
|  |  | Minimum | 2363 | -7·0 | 2382 | -5·1 | 2392 | -5·2 |
|  |  | Maximum | 2363 | 2·1 | 2382 | 2·8 | 2392 | 2·3 |
|  | Weight for age Z-score | N | 2363 | 2361 | 2382 | 2381 | 2392 | 2383 |
|  |  | Missing | 2363 | 2 | 2382 | 1 | 2392 | 9 |
|  |  | Mean | 2363 | -0·9 | 2382 | -1·0 | 2392 | -1·0 |
|  |  | SD | 2363 | 0·9 | 2382 | 0·9 | 2392 | 0·9 |
|  |  | Minimum | 2363 | -5·4 | 2382 | -4·2 | 2392 | -4·3 |
|  |  | Maximum | 2363 | 2·5 | 2382 | 1·7 | 2392 | 1·6 |
|  | Mid upper arm circumference Z-score | N | 2363 | 2361 | 2382 | 2379 | 2392 | 2390 |
|  | Missing | 2363 | 2 | 2382 | 3 | 2392 | 2 |
|  |  | Mean | 2363 | -0·4 | 2382 | -0·4 | 2392 | -0·4 |
|  |  | SD | 2363 | 0·9 | 2382 | 0·9 | 2392 | 0·8 |
|  |  | Minimum | 2363 | -5·3 | 2382 | -4·1 | 2392 | -3·4 |
|  |  | Maximum | 2363 | 2·7 | 2382 | 3·5 | 2392 | 2·2 |
| Month 44 | Height [cm] | N | 1275 | 1270 | 1289 | 1287 | 1307 | 1300 |
|  |  | Missing | 1275 | 5 | 1289 | 2 | 1307 | 7 |
|  |  | Mean | 1275 | 101·9 | 1289 | 101·6 | 1307 | 101·6 |
|  |  | SD | 1275 | 4·8 | 1289 | 4·7 | 1307 | 4·8 |
|  |  | Minimum | 1275 | 82·0 | 1289 | 85·0 | 1307 | 85·0 |
|  |  | Maximum | 1275 | 116·0 | 1289 | 116·0 | 1307 | 118·0 |
|  | Height for age Z-score | N | 1275 | 1270 | 1289 | 1287 | 1307 | 1300 |
|  |  | Missing | 1275 | 5 | 1289 | 2 | 1307 | 7 |
|  |  | Mean | 1275 | -1·1 | 1289 | -1·2 | 1307 | -1·2 |
|  |  | SD | 1275 | 1·0 | 1289 | 0·9 | 1307 | 1·0 |
|  |  | Minimum | 1275 | -5·3 | 1289 | -5·2 | 1307 | -4·6 |
|  |  | Maximum | 1275 | 1·9 | 1289 | 1·9 | 1307 | 1·9 |
|  | Weight for age Z-score | N | 1275 | 1274 | 1289 | 1288 | 1307 | 1306 |
|  |  | Missing | 1275 | 1 | 1289 | 1 | 1307 | 1 |
|  |  | Mean | 1275 | -0·9 | 1289 | -1·0 | 1307 | -0·9 |
|  |  | SD | 1275 | 0·9 | 1289 | 0·9 | 1307 | 0·8 |
|  |  | Minimum | 1275 | -3·8 | 1289 | -4·0 | 1307 | -4·2 |
|  |  | Maximum | 1275 | 1·6 | 1289 | 1·7 | 1307 | 2·0 |
|  | Mid upper arm circumference Z-score | N | 1275 | 1218 | 1289 | 1246 | 1307 | 1242 |
|  | Missing | 1275 | 57 | 1289 | 43 | 1307 | 65 |
|  |  | Mean | 1275 | -0·7 | 1289 | -0·7 | 1307 | -0·6 |
|  |  | SD | 1275 | 0·8 | 1289 | 0·9 | 1307 | 0·8 |
|  |  | Minimum | 1275 | -3·0 | 1289 | -3·3 | 1307 | -3·9 |
|  |  | Maximum | 1275 | 1·9 | 1289 | 2·2 | 1307 | 2·0 |
| SE early | Height [cm] | N | 774 | 769 | 755 | 748 | 768 | 765 |
|  |  | Missing | 774 | 5 | 755 | 7 | 768 | 3 |
|  |  | Mean | 774 | 102·1 | 755 | 102·0 | 768 | 102·0 |
|  |  | SD | 774 | 5·4 | 755 | 5·6 | 768 | 5·4 |
|  |  | Minimum | 774 | 83·0 | 755 | 87·0 | 768 | 84·0 |
|  |  | Maximum | 774 | 118·0 | 755 | 119·0 | 768 | 120·0 |
|  | Height for age Z-score | N | 774 | 769 | 755 | 748 | 768 | 765 |
|  |  | Missing | 774 | 5 | 755 | 7 | 768 | 3 |
|  |  | Mean | 774 | -1·3 | 755 | -1·3 | 768 | -1·3 |
|  |  | SD | 774 | 1·0 | 755 | 1·0 | 768 | 1·0 |
|  |  | Minimum | 774 | -5·5 | 755 | -4·0 | 768 | -5·0 |
|  |  | Maximum | 774 | 1·9 | 755 | 1·4 | 768 | 2·0 |
|  | Weight for age Z-score | N | 774 | 774 | 755 | 755 | 768 | 768 |
|  |  | Missing | 774 | 0 | 755 | 0 | 768 | 0 |
|  |  | Mean | 774 | -1·0 | 755 | -1·0 | 768 | -1·0 |
|  |  | SD | 774 | 0·8 | 755 | 0·8 | 768 | 0·8 |
|  |  | Minimum | 774 | -3·7 | 755 | -3·5 | 768 | -3·7 |
|  |  | Maximum | 774 | 2·0 | 755 | 2·1 | 768 | 1·1 |
|  | Mid upper arm circumference Z-score | N | 774 | 602 | 755 | 597 | 768 | 622 |
|  | Missing | 774 | 172 | 755 | 158 | 768 | 146 |
|  |  | Mean | 774 | -0·8 | 755 | -0·8 | 768 | -0·8 |
|  |  | SD | 774 | 0·9 | 755 | 0·9 | 768 | 0·8 |
|  |  | Minimum | 774 | -3·5 | 755 | -3·6 | 768 | -3·3 |
|  |  | Maximum | 774 | 2·3 | 755 | 2·0 | 768 | 1·5 |
| SE late | Height [cm] | N | 1290 | 1275 | 1283 | 1270 | 1317 | 1305 |
|  |  | Missing | 1290 | 15 | 1283 | 13 | 1317 | 12 |
|  |  | Mean | 1290 | 105·5 | 1283 | 105·3 | 1317 | 105·0 |
|  |  | SD | 1290 | 4·8 | 1283 | 4·9 | 1317 | 5·3 |
|  |  | Minimum | 1290 | 87·0 | 1283 | 88·0 | 1317 | 41·0 |
|  |  | Maximum | 1290 | 121·0 | 1283 | 121·0 | 1317 | 123·0 |
|  | Height for age Z-score | N | 1290 | 1275 | 1283 | 1270 | 1317 | 1305 |
|  |  | Missing | 1290 | 15 | 1283 | 13 | 1317 | 12 |
|  |  | Mean | 1290 | -1·0 | 1283 | -1·1 | 1317 | -1·1 |
|  |  | SD | 1290 | 0·9 | 1283 | 0·9 | 1317 | 1·0 |
|  |  | Minimum | 1290 | -4·7 | 1283 | -5·0 | 1317 | -14·9 |
|  |  | Maximum | 1290 | 2·0 | 1283 | 2·0 | 1317 | 2·1 |
|  | Weight for age Z-score | N | 1290 | 1287 | 1283 | 1281 | 1317 | 1313 |
|  |  | Missing | 1290 | 3 | 1283 | 2 | 1317 | 4 |
|  |  | Mean | 1290 | -0·9 | 1283 | -1·0 | 1317 | -1·0 |
|  |  | SD | 1290 | 0·9 | 1283 | 0·9 | 1317 | 0·8 |
|  |  | Minimum | 1290 | -4·1 | 1283 | -4·3 | 1317 | -3·8 |
|  |  | Maximum | 1290 | 1·9 | 1283 | 1·6 | 1317 | 1·6 |
|  | Mid upper arm circumference Z-score | N | 1290 | 507 | 1283 | 548 | 1317 | 566 |
|  | Missing | 1290 | 783 | 1283 | 735 | 1317 | 751 |
|  |  | Mean | 1290 | -0·7 | 1283 | -0·8 | 1317 | -0·7 |
|  |  | SD | 1290 | 0·8 | 1283 | 0·9 | 1317 | 0·8 |
|  |  | Minimum | 1290 | -3·4 | 1283 | -3·6 | 1317 | -3·0 |
|  |  | Maximum | 1290 | 1·8 | 1283 | 2·1 | 1317 | 1·8 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

SD = standard deviation.

Month 32 = cross sectional survey at 32 months post dose-1.

Month 44 = cross sectional survey at 44 months post dose-1.

SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 5-17 months: 14 months post Month 32).

SE late = study end in subjects having done Month 32 visit ≤ 30 June 2012 (median follow-up in 5-17 months: 17 months post Month 32).

Table S16. Cumulative cases of clinical and severe malaria averted in each site and overall among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Clinical malaria**  **(secondary case definition)** | | **Severe malaria**  **(secondary case definition)** | |
| **Time period** | **Site** | **Primary schedule without booster (R3C)** | **Primary schedule with booster (R3R)** | **Primary schedule without booster (R3C)** | **Primary schedule with booster (R3R)** |
| M0-M21 | Kilifi | 35 | 35 | 0 | 0 |
|  | Korogwe | 129 | 129 | 8 | 8 |
|  | Manhiça | 116 | 116 | 13 | 13 |
|  | Lambaréné | 305 | 305 | 25 | 25 |
|  | Bagamoyo | 335 | 335 | 28 | 28 |
|  | Lilongwe | 389 | 389 | -3 | -3 |
|  | Agogo | 1518 | 1518 | 13 | 13 |
|  | Kombewa | 1682 | 1682 | 38 | 38 |
|  | Kintampo | 1867 | 1867 | 20 | 20 |
|  | Nanoro | 2399 | 2399 | 7 | 7 |
|  | Siaya | 3105 | 3105 | 50 | 50 |
|  | **Overall** | 963 | 963 | 19 | 19 |
| M0-M32 | Kilifi | 132 | 172 | 12 | 6 |
|  | Korogwe | 151 | 126 | 15 | 11 |
|  | Manhiça | 234 | 294 | 19 | 22 |
|  | Lambaréné | 381 | 395 | 39 | 51 |
|  | Bagamoyo | 424 | 538 | 28 | 28 |
|  | Lilongwe | 533 | 604 | -12 | 1 |
|  | Agogo | 1779 | 2221 | 13 | 12 |
|  | Kombewa | 1875 | 2451 | 30 | 34 |
|  | Kintampo | 2474 | 3042 | -31 | 11 |
|  | Nanoro | 2983 | 3750 | 11 | 1 |
|  | Siaya | 3847 | 4656 | 4 | 32 |
|  | **Overall** | 1221 | 1475 | 12 | 20 |
| M0-SE | Kilifi | 250 | 303 | 12 | 6 |
|  | Korogwe | 215 | 205 | 23 | 19 |
|  | Manhiça | 341 | 236 | 24 | 27 |
|  | Lambaréné | 498 | 472 | 54 | 57 |
|  | Bagamoyo | 477 | 607 | 37 | 37 |
|  | Lilongwe | 532 | 685 | -17 | 6 |
|  | Agogo | 2060 | 2722 | 8 | 25 |
|  | Kombewa | 1937 | 2510 | 4 | 17 |
|  | Kintampo | 2663 | 3892 | -42 | -15 |
|  | Nanoro | 2897 | 4217 | -8 | -6 |
|  | Siaya | 4443 | 6565 | 3 | 37 |
|  | **Overall** | 1363 | 1774 | 8 | 19 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase). For the 5-17 months age category SE= up to 48 months post dose-1.

Table S17. Overall vaccine efficacy against clinical and severe malaria among children in the 6-12 weeks age category (per-protocol population for efficacy).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy against clinical malaria (primary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | | |
|  | | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M2·5-SE | | 2005 | 5072 | 5322·9 | 0·95 | 2007 | 5666 | 5264·6 | 1·08 | 18·2 | 11·4 | 24·5 | <0·0001 |
|  | M2·5-M32 | | 2005 | 3856 | 4396·8 | 0·88 | 2007 | 4479 | 4343·8 | 1·03 | 20·4 | 13·5 | 26·8 | <0·0001 |
|  | M2·5-M20\* | | 3996 | 3848 | 5396·8 | 0·71 | 2007 | 2464 | 2674·0 | 0·92 | 26·6 | 20·3 | 32·4 | <0·0001 |
|  | M21-M32 | | 1788 | 1942 | 1687·0 | 1·15 | 1762 | 2012 | 1671·0 | 1·2 | 8·5 | -0·6 | 16·7 | 0·0652 |
|  | M33-SE | | 1548 | 1216 | 926·4 | 1·31 | 1546 | 1187 | 921·9 | 1·29 | 3·9 | -7·6 | 14·1 | 0·4905 |
|  | M21-SE | | 1788 | 3158 | 2613·1 | 1·21 | 1762 | 3199 | 2591·8 | 1·23 | 8·1 | -0·4 | 15·9 | 0·0622 |
| **Efficacy against severe malaria (primary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | | |
|  | | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M2·5-SE | | 2005 | 89 | 0·04 | | 2007 | 102 | 0·05 | | 12·7 | -17·2 | 35·0 | 0·3737 |
|  | M2·5-M32 | | 2005 | 79 | 0·04 | | 2007 | 89 | 0·04 | | 11·1 | -21·7 | 35·2 | 0·4782 |
|  | M2·5-M20\* | | 3996 | 100 | 0·03 | | 2007 | 59 | 0·03 | | 14·9 | -19·5 | 38·9 | 0·3486 |
|  | M21-M32 | | 1788 | 35 | 0·02 | | 1762 | 38 | 0·02 | | 9·2 | -47·6 | 44·3 | 0·7234 |
|  | M33-SE | | 1548 | 13 | 0·01 | | 1546 | 14 | 0·01 | | 7·3 | -113 | 59·9 | 0·8498 |
|  | M21-SE | | 1788 | 46 | 0·03 | | 1762 | 51 | 0·03 | | 11·1 | -35·1 | 41·7 | 0·6071 |
| **Efficacy against clinical malaria (primary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | | |
|  | | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M2·5-SE | | 1985 | 4532 | 5245·2 | 0·86 | 2007 | 5666 | 5264·6 | 1·08 | 26·7 | 20·5 | 32·4 | <0·0001 |
|  | M2·5-M32 | | 1985 | 3466 | 4339·5 | 0·8 | 2007 | 4479 | 4343·8 | 1·03 | 28·4 | 22·1 | 34·2 | <0·0001 |
|  | M2·5-M20\* | | 3996 | 3848 | 5396·8 | 0·71 | 2007 | 2464 | 2674·0 | 0·92 | 26·6 | 20·3 | 32·4 | <0·0001 |
|  | M21-M32 | | 1743 | 1520 | 1662·3 | 0·91 | 1762 | 2012 | 1671·0 | 1·2 | 30·3 | 23·0 | 37·0 | <0·0001 |
|  | M33-SE | | 1516 | 1069 | 907·4 | 1·18 | 1546 | 1187 | 921·9 | 1·29 | 12·4 | 1·9 | 21·7 | 0·0217 |
|  | M21-SE | | 1743 | 2586 | 2568·0 | 1·01 | 1762 | 3199 | 2591·8 | 1·23 | 25·9 | 18·8 | 32·4 | <0·0001 |
| **Efficacy against severe malaria (primary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | | |
|  | | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M2·5-SE | | 1985 | 80 | 0·04 | | 2007 | 102 | 0·05 | | 20·7 | -7·3 | 41·6 | 0·1289 |
|  | M2·5-M32 | | 1985 | 73 | 0·04 | | 2007 | 89 | 0·04 | | 17·1 | -14·3 | 40·0 | 0·2300 |
|  | M2·5-M20\* | | 3996 | 100 | 0·03 | | 2007 | 59 | 0·03 | | 14·9 | -19·5 | 38·9 | 0·3486 |
|  | M21-M32 | | 1743 | 23 | 0·01 | | 1762 | 38 | 0·02 | | 38·8 | -5·4 | 65·2 | 0·0700 |
|  | M33-SE | | 1516 | 11 | 0·01 | | 1546 | 14 | 0·01 | | 19·9 | -90·0 | 67·1 | 0·6892 |
|  | M21-SE | | 1743 | 33 | 0·02 | | 1762 | 51 | 0·03 | | 34·6 | -3·3 | 59·1 | 0·0602 |
| **Incremental efficacy against clinical malaria (primary case definition) of a booster dose** | | | | | | | | | | | | | | |
|  | | **R3R** | | | | | **R3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Per-protocol population for efficacy** | | **N** | | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M21-SE | 1743 | | 2586 | 2568·0 | 1·01 | 1788 | 3158 | 2613·1 | 1·21 | 19·5 | 11·5 | 26·8 | <0·0001 |
|  | M21-M32 | 1743 | | 1520 | 1662·3 | 0·91 | 1788 | 1942 | 1687·0 | 1·15 | 24·0 | 15·7 | 31·5 | <0·0001 |

\*Data from previous analysis (comparing R3R+R3C versus C3C).

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

n (clinical malaria) = number of episodes meeting the case definition.

n (severe malaria) = number of subjects reporting at least one event in each group.

T = person years at risk.

n/T = incidence rate.

Proportion affected = proportion of subjects reporting at least one event.

VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

M2·5-M20 = follow-up from 14 days post dose-3 (Month 2·5) to 18 months post dose-3 (Month 20).

M21-M32 = follow-up from day of booster dose to 30 months post dose-3 (Month 32).

M33-SE = follow-up from start of extension phase to study end (end of extension phase).

M2·5-SE = follow-up from 14 days post dose-3 (Month 2·5) to study end (end of extension phase).

M21-SE = follow-up from day of booster dose to study end (end of extension phase).

SE = study end (the median follow-up in the 6-12 weeks was 38 months post dose-1).

Clinical malaria primary case definition = illness in a child brought to a study facility with a measured temperature of ≥ 37·5°C and *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria.

Severe malaria primary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

For clinical malaria: p-value from negative binomial regression.

For severe malaria: p-value from two-sided Fisher exact test.

Table S18. Overall vaccine efficacy against clinical and severe malaria secondary case definition among infants in the 6-12 weeks age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy against clinical malaria (secondary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | |
|  | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M0-SE | 2178 | 8146 | 6071·3 | 1·34 | 2179 | 9146 | 6031·9 | 1·52 | 18·1 | 11·8 | 23·9 | <0·0001 |
|  | M0-M32 | 2178 | 6315 | 5109·2 | 1·24 | 2179 | 7327 | 5068·7 | 1·45 | 19·6 | 13·3 | 25·5 | <0·0001 |
| **Efficacy against severe malaria (secondary case definition) of a primary schedule without booster (R3C)** | | | | | | | | | | | | | |
|  | | **R3C** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M0-SE | 2178 | 110 | 0·05 | | 2179 | 129 | 0·06 | | 14·7 | -10·9 | 34·5 | 0·2310 |
|  | M0-M32 | 2178 | 97 | 0·04 | | 2179 | 112 | 0·05 | | 13·4 | -14·7 | 34·7 | 0·3210 |
| **Efficacy against clinical malaria (secondary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | |
|  | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **T (year)** | **n/T** | **N** | **n** | **T (year)** | **n/T** | **(%)** | **95% CI** | | **p-value** |
| Clinical malaria | M0-SE | 2180 | 7420 | 6063·1 | 1·22 | 2179 | 9146 | 6031·9 | 1·52 | 27·1 | 21·4 | 32·4 | <0·0001 |
|  | M0-M32 | 2180 | 5757 | 5099·6 | 1·13 | 2179 | 7327 | 5068·7 | 1·45 | 28·3 | 22·6 | 33·6 | <0·0001 |
| **Efficacy against severe malaria (secondary case definition) of a primary schedule with booster (R3R)** | | | | | | | | | | | | | |
|  | | **R3R** | | | | **C3C** | | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | | **N** | **n** | **Proportion affected** | | **(%)** | **95% CI** | | **p-value** |
| Severe malaria | M0-SE | 2180 | 108 | 0·05 | | 2179 | 129 | 0·06 | | 16·3 | -8·9 | 35·8 | 0·1614 |
|  | M0-M32 | 2180 | 99 | 0·05 | | 2179 | 112 | 0·05 | | 11·6 | -16·8 | 33·3 | 0·3600 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

n (clinical malaria) = number of episodes meeting the case definition.

n (severe malaria) = number of subjects reporting at least one event in each group.

T = person years at risk.

n/T = incidence rate.

Proportion affected = proportion of subjects reporting at least one event.

VE = vaccine efficacy (negative binomial model for clinical malaria; 1-relative risk for severe malaria).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase).

M0-M32 = follow-up from day of dose-1 (Month 0) to 32 months post dose-1 (Month 32).

SE = study end (the median follow-up in the 6-12 weeks was 38 months post dose-1).

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37.5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

For clinical malaria: p-value from negative binomial regression.

For severe malaria: p-value from two-sided Fisher exact test.

Table S19. Overall vaccine efficacy against incident severe malaria anaemia, malaria hospitalization and fatal malaria until the end of the extension phase (M0-SE) among infants in the 6-12 weeks age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy of a primary schedule without booster (R3C)** | | | | | | | | | | | |
|  | | **R3C** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Incident severe malaria anaemia | Case definition 1 | 2178 | 31 | 0·01 | 2179 | 35 | 0·02 | 11·4 | -47·9 | 47·2 | 0·7101 |
| Case definition 2 | 2178 | 39 | 0·02 | 2179 | 40 | 0·02 | 2·5 | -55·6 | 38·9 | 1·0000 |
| Malaria hospitalization | Case definition 1 | 2178 | 167 | 0·08 | 2179 | 188 | 0·09 | 11·1 | -10·1 | 28·3 | 0·2680 |
|  | Case definition 2 | 2178 | 199 | 0·09 | 2179 | 222 | 0·10 | 10·3 | -9·1 | 26·3 | 0·2593 |
| Fatal malaria | Primary case definition | 2178 | 0 | 0 | 2179 | 0 | 0 |  |  |  |  |
|  | Secondary case definition | 2178 | 2 | 0 | 2179 | 2 | 0 | 0·0 | -1280 | 92·7 | 1·0000 |
|  | ICD10 code | 2178 | 12 | 0·01 | 2179 | 6 | 0 | -100·1 | -550 | 30·5 | 0·1661 |
| **Efficacy of a primary schedule with booster (R3R)** | | | | | | | | | | | |
|  | | **R3R** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Incident severe malaria anaemia | Case definition 1 | 2180 | 24 | 0·01 | 2179 | 35 | 0·02 | 31·5 | -18·5 | 61·0 | 0·1522 |
| Case definition 2 | 2180 | 27 | 0·01 | 2179 | 40 | 0·02 | 32·5 | -12·7 | 60·2 | 0·1114 |
| Malaria hospitalization | Case definition 1 | 2180 | 142 | 0·07 | 2179 | 188 | 0·09 | 24·5 | 5·6 | 39·7 | 0·0084 |
|  | Case definition 2 | 2180 | 175 | 0·08 | 2179 | 222 | 0·1 | 21·2 | 3·5 | 35·7 | 0·0134 |
| Fatal malaria | Primary case definition | 2180 | 0 | 0 | 2179 | 0 | 0 |  |  |  |  |
|  | Secondary case definition | 2180 | 4 | 0 | 2179 | 2 | 0 | -99·9 | -2110 | 71·3 | 0·6873 |
|  | ICD10 code | 2180 | 8 | 0 | 2179 | 6 | 0 | -33·3 | -366 | 59·4 | 0·7902 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects included in each group (without missing values).

n = number of subjects reporting at least one event in each group.

Proportion affected = proportion of subjects reporting at least one event.

VE (%) = vaccine efficacy (conditional method).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

P-value = two-sided Fisher exact test.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase). The median follow-up in the 6-12 weeks age category was 38 months post dose-1.

Incident severe malaria anaemia case definition 1 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 5000 parasites per cubic millimetre.

Incident severe malaria anaemia case definition 2 = a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a *P. falciparum* parasitaemia at a density of > 0 parasites per cubic millimetre.

Malaria hospitalization case definition 1 = a medical hospitalization with confirmed *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre.

Malaria hospitalization case definition 2 = a hospitalization which, in the judgment of the principal investigator, *P. falciparum* infection was the sole or a major contributing factor to the presentation.

Fatal malaria primary definition = a case of severe malaria meeting the primary case definition of severe malaria with a fatal outcome.

Fatal malaria secondary case definition = a case of severe malaria meeting the secondary case definition of severe malaria with a fatal outcome.

Fatal malaria (ICD10 code) = a fatal case associated with International Classification Disease (ICD10) code B50, B53, B54.

Table S20. Overall vaccine efficacy against serious illnesses until the end of the extension phase (M0-SE) among infants in the 6-12 weeks age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy of a primary schedule without booster (R3C)** | | | | | | | | | | | |
|  | | **R3C** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Bacteraemia | Case definition 1 | 2178 | 56 | 0·03 | 2179 | 52 | 0·02 | -7·7 | -60·3 | 27·5 | 0·6982 |
|  | Case definition 2 (Salmonella sepsis) | 2178 | 36 | 0·02 | 2179 | 34 | 0·02 | -5·9 | -74·5 | 35·6 | 0·8111 |
| Pneumonia | Primary case definition | 2178 | 124 | 0·06 | 2179 | 137 | 0·06 | 9·4 | -16·3 | 29·6 | 0·4437 |
|  | Secondary case definition 1 | 2178 | 37 | 0·02 | 2179 | 30 | 0·01 | -23·4 | -107 | 25·8 | 0·3924 |
| All-cause hospitalization | Primary case definition | 2178 | 549 | 0·25 | 2179 | 567 | 0·26 | 3·1 | -9·1 | 14·0 | 0·5552 |
| All-cause mortality | Case definition 1 | 2178 | 54 | 0·02 | 2179 | 42 | 0·02 | -28·6 | -97·3 | 15·6 | 0·2177 |
|  | Case definition 2 | 2178 | 51 | 0·02 | 2179 | 40 | 0·02 | -27·6 | -98·0 | 17·3 | 0·2463 |
| Blood transfusions | - | 2178 | 75 | 0·03 | 2179 | 88 | 0·04 | 14·7 | -17·4 | 38·2 | 0·3381 |
| **Efficacy of a primary schedule with booster (R3R)** | | | | | | | | | | | |
|  | | **R3R** | | | **C3C** | | | **Point estimate of VE unadjusted for covariates** | | | |
| **Intention-to-treat population** | | **N** | **n** | **Proportion affected** | **N** | **n** | **Proportion affected** | **(%)** | **95% CI** | | **p-value** |
| Bacteraemia | Case definition 1 | 2180 | 53 | 0·02 | 2179 | 52 | 0·02 | -1·9 | -52·3 | 31·8 | 1·0000 |
|  | Case definition 2 (Salmonella sepsis) | 2180 | 27 | 0·01 | 2179 | 34 | 0·02 | 20·6 | -35·5 | 53·9 | 0·3707 |
| Pneumonia | Primary case definition | 2180 | 135 | 0·06 | 2179 | 137 | 0·06 | 1·5 | -25·8 | 22·9 | 0·9005 |
|  | Secondary case definition 1 | 2180 | 36 | 0·02 | 2179 | 30 | 0·01 | -19·9 | -102 | 28·2 | 0·5355 |
| All-cause hospitalization | Primary case definition | 2180 | 528 | 0·24 | 2179 | 567 | 0·26 | 6·9 | -5·0 | 17·5 | 0·1733 |
| All-cause mortality | Case definition 1 | 2180 | 51 | 0·02 | 2179 | 42 | 0·02 | -21·4 | -87·2 | 20·9 | 0·4018 |
|  | Case definition 2 | 2180 | 49 | 0·02 | 2179 | 40 | 0·02 | -22·4 | -90·8 | 21·0 | 0·3917 |
| Blood transfusions | - | 2180 | 73 | 0·03 | 2179 | 88 | 0·04 | 17·1 | -14·4 | 40·0 | 0·2296 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects included in each group (without missing values).

n = number of subjects reporting at least one event in each group.

Proportion affected = proportion of subjects reporting at least one event.

VE(%) = vaccine efficacy (conditional method).

95% CI = lower (LL) and upper (UL) confidence limits of 95% confidence interval.

P-value = two-sided Fisher exact test.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase). The median follow-up in the 6-12 weeks age category was 38 months post dose-1.

Bacteraemia case definition 1 = a child with a positive blood culture taken within 72 hours of admission.

Bacteraemia case definition 2 (Salmonella sepsis) = a child with a positive salmonella blood culture taken within 72 hours of admission.

Pneumonia primary case definition = cough or difficulty breathing (on history) and tachypnea (≥ 50 breaths per minute < 1 year, ≥ 40 breaths per minute ≥ 1year) and lower chest wall indrawing.

Pneumonia secondary case definition 1 = a case of pneumonia meeting the primary case definition of pneumonia with chest x-ray consolidation or pleural effusion on x-ray taken within 72 h of admission.

All-cause hospitalization primary case definition = a medical hospitalization of any cause, excluding planned admissions for medical investigation/care or elective surgery and trauma.

All-cause mortality case definition 1 = a fatality of any cause, including mortality in the community and in hospital.

All-cause mortality case definition 2 = a fatality of medical cause, including mortality in the community and in hospital and excluding trauma, which may be diagnosed by verbal autopsy.

Blood transfusion = a child with inpatient admission with documented blood transfusion.

Table S21. Vaccine efficacy against prevalent parasitaemia until the end of the extension phase among infants in the 6-12 weeks age category (intention-to-treat population).

| **Efficacy of a primary schedule without booster (R3C)** | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Intention-to-treat population** | **Month 32** | | | | **SE early** | | | |
| **Site** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** |
| Kilifi | 100 | -4254 | 100 | 1·0000 |  |  |  |  |
| Korogwe | 100 | -3496 | 100 | 0·4798 |  |  |  |  |
| Manhiça\* |  |  |  |  | 19·1 | -276 | 83·9 | 1·0000 |
| Lambaréné | -127·3 | -1205 | 43·3 | 0·2281 | -533·3 | -29E3 | 23·2 | 0·0528 |
| Bagamoyo | -25·6 | -420 | 68·1 | 0·7671 |  |  |  |  |
| Lilongwe | -217·6 | -1017 | -9·7 | 0·0209 | -483·7 | -5320 | -27·4 | 0·0098 |
| Agogo | 21·2 | -51·5 | 59·7 | 0·5146 | -17·6 | -155 | 45·6 | 0·7087 |
| Kombewa | 7·4 | -53·1 | 43·9 | 0·7861 | 6·8 | -57·1 | 44·7 | 0·7804 |
| Kintampo | 2·3 | -132 | 59·2 | 1·0000 | -39·6 | -159 | 23·5 | 0·1818 |
| Nanoro | -16·7 | -87·4 | 27·0 | 0·5256 | 7·4 | -32·0 | 35·1 | 0·5902 |
| Siaya | 23·3 | -17·4 | 50·2 | 0·1549 | 18·6 | -21·2 | 45·4 | 0·2527 |
| **Overall** | **-4·2** | **-29·1** | **15·8** | **0·6954** | **-7·1** | **-30·5** | **12·1** | **0·4601** |
| **Efficacy of a primary schedule with booster (R3R)** | | | | | | | | |
| **Intention-to-treat population** | **Month 32** | | | | **SE early** | | | |
| **Site** | **VE (%)** | **LL** | **UL** | **p-value** | **VE (%)** | **LL** | **UL** | **p-value** |
| Kilifi | 100 | -4466 | 100 | 1·0000 |  |  |  |  |
| Korogwe | 11·0 | -6888 | 98·9 | 1·0000 |  |  |  |  |
| Manhiça\* |  |  |  |  | -78·0 | -576 | 46·4 | 0·4048 |
| Lambaréné | 45·4 | -377 | 95·4 | 0·6560 | -100·0 | -12E3 | 89·6 | 1·0000 |
| Bagamoyo | 14·3 | -298 | 83·0 | 1·0000 |  |  |  |  |
| Lilongwe | -159·5 | -840 | 14·9 | 0·0820 | -171·7 | -2754 | 55·5 | 0·2675 |
| Agogo | 20·8 | -50·8 | 59·0 | 0·5196 | 10·1 | -103 | 60·6 | 0·8455 |
| Kombewa | 5·0 | -57·6 | 42·7 | 0·8911 | 13·2 | -47·6 | 49·0 | 0·5721 |
| Kintampo | 3·2 | -127 | 58·7 | 1·0000 | 33·8 | -34·8 | 68·2 | 0·1959 |
| Nanoro | 38·4 | -8·4 | 65·8 | 0·0612 | 28·9 | -5·0 | 52·2 | 0·0315 |
| Siaya | 4·2 | -43·2 | 35·9 | 0·8197 | 29·6 | -6·4 | 53·8 | 0·0471 |
| **Overall** | **5·3** | **-17·9** | **23·9** | **0·6071** | **18·2** | **-1·0** | **33·8** | **0·0451** |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

VE (%) = vaccine efficacy (conditional method).

LL = lower limit of the 95% confidence interval.

UL = upper limit of the 95% confidence interval.

P-value = two-sided Fisher exact test.

Month 32 = cross sectional survey at 32 months post dose-1.

SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 6-12 weeks: 7 months post Month 32).

\* In Manhiça, for the cross sectional visit performed at Month 32, parasite prevalence was detected in three subjects in R3C, six subjects in R3R and zero subject in C3C. Because there was no parasite prevalence in the control group the VE cannot be calculated.

Table S22. Anthropometric findings in infants in the 6-12 weeks age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **R3R** | | **R3C** | | **C3C** | |
| **Study timepoint** | **Characteristics** | **Parameters** | **N** | **Value** | **N** | **Value** | **N** | **Value** |
| Month 32 | Height [cm] | N | 1726 | 1709 | 1731 | 1716 | 1725 | 1709 |
|  |  | Missing | 1726 | 17 | 1731 | 15 | 1725 | 16 |
|  |  | Mean | 1726 | 88·5 | 1731 | 88·6 | 1725 | 88·5 |
|  |  | SD | 1726 | 4·0 | 1731 | 4·0 | 1725 | 4·1 |
|  |  | Minimum | 1726 | 69·0 | 1731 | 75·0 | 1725 | 70·0 |
|  |  | Maximum | 1726 | 105·0 | 1731 | 101·0 | 1725 | 102·0 |
|  | Height for age Z-score | N | 1726 | 1709 | 1731 | 1716 | 1725 | 1709 |
|  |  | Missing | 1726 | 17 | 1731 | 15 | 1725 | 16 |
|  |  | Mean | 1726 | -1·5 | 1731 | -1·4 | 1725 | -1·5 |
|  |  | SD | 1726 | 1·1 | 1731 | 1·1 | 1725 | 1·1 |
|  |  | Minimum | 1726 | -7·1 | 1731 | -5·2 | 1725 | -6·3 |
|  |  | Maximum | 1726 | 2·6 | 1731 | 2·0 | 1725 | 2·4 |
|  | Weight for age Z-score | N | 1726 | 1725 | 1731 | 1731 | 1725 | 1724 |
|  |  | Missing | 1726 | 1 | 1731 | 0 | 1725 | 1 |
|  |  | Mean | 1726 | -0·9 | 1731 | -0·9 | 1725 | -0·9 |
|  |  | SD | 1726 | 1·0 | 1731 | 1·0 | 1725 | 1·0 |
|  |  | Minimum | 1726 | -5·0 | 1731 | -4·5 | 1725 | -4·6 |
|  |  | Maximum | 1726 | 2·2 | 1731 | 3·0 | 1725 | 1·9 |
|  | Mid upper arm circumference Z-score | N | 1726 | 1726 | 1731 | 1731 | 1725 | 1725 |
|  | Missing | 1726 | 0 | 1731 | 0 | 1725 | 0 |
|  |  | Mean | 1726 | -0·4 | 1731 | -0·3 | 1725 | -0·4 |
|  |  | SD | 1726 | 0·9 | 1731 | 1·0 | 1725 | 1·0 |
|  |  | Minimum | 1726 | -3·9 | 1731 | -3·4 | 1725 | -3·8 |
|  |  | Maximum | 1726 | 2·9 | 1731 | 4·3 | 1725 | 2·9 |
| SE early | Height [cm] | N | 1555 | 1507 | 1533 | 1493 | 1549 | 1500 |
|  |  | Missing | 1555 | 48 | 1533 | 40 | 1549 | 49 |
|  |  | Mean | 1555 | 93·3 | 1533 | 93·4 | 1549 | 93·2 |
|  |  | SD | 1555 | 4·6 | 1533 | 4·6 | 1549 | 4·6 |
|  |  | Minimum | 1555 | 70·0 | 1533 | 78·0 | 1549 | 72·0 |
|  |  | Maximum | 1555 | 109·0 | 1533 | 111·0 | 1549 | 109·0 |
|  | Height for age Z-score | N | 1555 | 1507 | 1533 | 1493 | 1549 | 1500 |
|  |  | Missing | 1555 | 48 | 1533 | 40 | 1549 | 49 |
|  |  | Mean | 1555 | -1·4 | 1533 | -1·4 | 1549 | -1·4 |
|  |  | SD | 1555 | 1·0 | 1533 | 1·0 | 1549 | 1·0 |
|  |  | Minimum | 1555 | -7·5 | 1533 | -5·2 | 1549 | -6·2 |
|  |  | Maximum | 1555 | 2·1 | 1533 | 2·5 | 1549 | 2·2 |
|  | Weight for age Z-score | N | 1555 | 1552 | 1533 | 1531 | 1549 | 1547 |
|  |  | Missing | 1555 | 3 | 1533 | 2 | 1549 | 2 |
|  |  | Mean | 1555 | -0·9 | 1533 | -0·9 | 1549 | -0·9 |
|  |  | SD | 1555 | 0·9 | 1533 | 0·9 | 1549 | 0·9 |
|  |  | Minimum | 1555 | -4·9 | 1533 | -4·5 | 1549 | -4·7 |
|  |  | Maximum | 1555 | 2·1 | 1533 | 2·5 | 1549 | 1·7 |
|  | Mid upper arm circumference Z-score | N | 1555 | 1555 | 1533 | 1533 | 1549 | 1548 |
|  | Missing | 1555 | 0 | 1533 | 0 | 1549 | 1 |
|  |  | Mean | 1555 | -0·5 | 1533 | -0·4 | 1549 | -0·5 |
|  |  | SD | 1555 | 0·9 | 1533 | 0·9 | 1549 | 0·9 |
|  |  | Minimum | 1555 | -3·2 | 1533 | -3·5 | 1549 | -3·5 |
|  |  | Maximum | 1555 | 2·6 | 1533 | 3·7 | 1549 | 2·5 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects.

SD = standard deviation.

Month 32 = cross sectional survey at 32 months post dose-1.

SE early = study end in subjects having done Month 32 visit > 30 June 2012 (median follow-up in 6-12 weeks: 7 months post Month 32).

Table S23. Cumulative cases of clinical and severe malaria averted in each site and overall in infants in the 6-12 weeks age category (intention-to-treat population).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Clinical malaria**  **(secondary case definition)** | | **Severe malaria**  **(secondary case definition)** | |
| **Time period** | **Site** | **Primary schedule without booster (R3C)** | **Primary schedule with booster (R3R)** | **Primary schedule without booster (R3C)** | **Primary schedule with booster (R3R)** |
| M0-M21 | Kilifi | -9 | -9 | 0 | 0 |
|  | Korogwe | 70 | 70 | -3 | -3 |
|  | Manhiça | 146 | 146 | -10 | -10 |
|  | Lambaréné | 9 | 9 | -25 | -25 |
|  | Bagamoyo | 142 | 142 | 21 | 21 |
|  | Lilongwe | 421 | 421 | -8 | -8 |
|  | Agogo | 443 | 443 | -13 | -13 |
|  | Kombewa | 970 | 970 | 36 | 36 |
|  | Kintampo | 263 | 263 | 2 | 2 |
|  | Nanoro | 993 | 993 | 21 | 21 |
|  | Siaya | 1814 | 1814 | 12 | 12 |
|  | **Overall** | 518 | 518 | 5 | 5 |
| M0-M32 | Kilifi | 4 | -25 | -11 | -12 |
|  | Korogwe | 68 | 177 | -3 | 3 |
|  | Manhiça | 193 | 214 | -11 | -28 |
|  | Lambaréné | -50 | 314 | 1 | 0 |
|  | Bagamoyo | 173 | 211 | 25 | 25 |
|  | Lilongwe | 479 | 679 | 7 | 3 |
|  | Agogo | 570 | 915 | -17 | -18 |
|  | Kombewa | 1095 | 1105 | 74 | 39 |
|  | Kintampo | 36 | 781 | -43 | -20 |
|  | Nanoro | 1101 | 2165 | 10 | 26 |
|  | Siaya | 1853 | 2921 | -1 | 49 |
|  | **Overall** | 526 | 873 | 5 | 9 |
| M0-SE | Kilifi | 27 | -30 | -11 | -12 |
|  | Korogwe | 114 | 190 | -9 | 3 |
|  | Manhiça | 218 | 179 | 17 | 0 |
|  | Lambaréné | -140 | 268 | -31 | 0 |
|  | Bagamoyo | 277 | 309 | 40 | 40 |
|  | Lilongwe | 493 | 772 | 3 | 3 |
|  | Agogo | 585 | 1077 | -17 | -12 |
|  | Kombewa | 1144 | 1404 | 59 | 51 |
|  | Kintampo | -172 | 726 | -43 | -62 |
|  | Nanoro | 1367 | 2428 | 10 | 19 |
|  | Siaya | 2178 | 3406 | 13 | 56 |
|  | **Overall** | 558 | 983 | 8 | 12 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

Clinical malaria secondary case definition = illness in a child brought to a study facility with a measured temperature of ≥37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia at a density of > 0 parasites per cubic millimetre. This definition was used for this analysis as, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.

Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤ 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

M0-SE = follow-up from day of dose-1 (Month 0) to study end (end of extension phase). For the 6-12 weeks, SE= up to 39 months post dose-1.

Table S24. Seropositivity rates and geometric means titres for anti-CS antibodies at Month 20, Month 32, Month 44 and study end in children in the 5-17 months age category (per-protocol population for immunogenicity).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Seropositivity (≥ 0·5 EU/mL)** | | | | **GMT** | | |  | |
| **Group** | **Timing** |  |  | | **95% CI** | |  | **95% CI** | |  | |
|  |  | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** | **Min** | **Max** |
| R3R | PIII(M20) | 442 | 440 | 99·5 | 98·4 | 99·9 | 34·4 | 30·7 | 38·6 | <0·5 | 666·7 |
|  | PIV(M21) | 426 | 425 | 99·8 | 98·7 | 100 | 318·2 | 295·1 | 343·0 | <0·5 | 2733·0 |
|  | PIV(M32) | 414 | 414 | 100 | 99·1 | 100 | 52·4 | 47·8 | 57·6 | 2·2 | 444·0 |
|  | PIV(M44) | 103 | 103 | 100 | 96·5 | 100 | 33·0 | 26·9 | 40·3 | 1·8 | 308·7 |
|  | SE | 104 | 104 | 100 | 96·5 | 100 | 25·4 | 20·6 | 31·2 | 1·1 | 220·8 |
| R3C | PIII(M20) | 438 | 434 | 99·1 | 97·7 | 99·8 | 35·4 | 31·7 | 39·5 | <0·5 | 863·4 |
|  | PIV(M21) | 425 | 421 | 99·1 | 97·6 | 99·7 | 34·2 | 30·5 | 38·3 | <0·5 | 715·0 |
|  | PIV(M32) | 408 | 404 | 99·0 | 97·5 | 99·7 | 19·3 | 17·2 | 21·8 | <0·5 | 447·9 |
|  | PIV(M44) | 101 | 99 | 98·0 | 93·0 | 99·8 | 16·8 | 13·5 | 21·0 | <0·5 | 201·6 |
|  | SE | 99 | 97 | 98·0 | 92·9 | 99·8 | 14·4 | 11·4 | 18·1 | <0·5 | 150·2 |
| C3C | PIII(M20) | 426 | 34 | 8·0 | 5·6 | 11·0 | 0·3 | 0·3 | 0·3 | <0·5 | 51·6 |
|  | PIV(M21) | 409 | 34 | 8·3 | 5·8 | 11·4 | 0·3 | 0·3 | 0·3 | <0·5 | 403·9 |
|  | PIV(M32) | 393 | 46 | 11·7 | 8·7 | 15·3 | 0·3 | 0·3 | 0·3 | <0·5 | 21·6 |
|  | PIV(M44) | 86 | 15 | 17·4 | 10·1 | 27·1 | 0·3 | 0·3 | 0·4 | <0·5 | 5·2 |
|  | SE | 98 | 10 | 10·2 | 5·0 | 18·0 | 0·3 | 0·3 | 0·4 | <0·5 | 7·1 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

Anti-CS = anti-circumsporozoite protein antibodies.

GMT = geometric mean antibody titre calculated on all subjects.

EU/mL = ELISA unit per millilitre.

N = number of subjects with available results.

n/% = number/percentage of subjects with titre equal to or above specified value.

95% CI = 95% confidence interval; LL = lower limit, UL = upper limit.

Min/Max = minimum/maximum.

PIII(M20) = 18 months post dose-3.

PIV(M21) = 1 month post booster dose.

PIV(M32) = 12 months post booster dose.

PIV(M44) = 24 months post booster dose.

SE = Study end.

Table S25. Seropositivity rates and geometric means titres for anti-CS antibodies at Month 20, Month 32 and study end in infants in the 6-12 weeks age category (per-protocol population for immunogenicity).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Seropositivity (≥ 0·5 EU/mL)** | | | | **GMT** | | |  | |
| **Group** | **Timing** |  |  | | **95% CI** | |  | **95% CI** | |  | |
|  |  | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** | **Min** | **Max** |
| R3R | PIII(M20) | 530 | 491 | 92·6 | 90·1 | 94·7 | 5·9 | 5·2 | 6·7 | <0·5 | 205·1 |
|  | PIV(M21) | 503 | 501 | 99·6 | 98·6 | 100 | 169·9 | 153·8 | 187·7 | <0·5 | 3454·6 |
|  | PIV(M32) | 478 | 465 | 97·3 | 95·4 | 98·5 | 15·9 | 13·8 | 18·3 | <0·5 | 268·3 |
|  | SE | 101 | 95 | 94·1 | 87·5 | 97·8 | 8·9 | 6·5 | 12·3 | <0·5 | 139·0 |
| R3C | PIII(M20) | 569 | 529 | 93·0 | 90·6 | 94·9 | 6·6 | 5·8 | 7·5 | <0·5 | 169·3 |
|  | PIV(M21) | 544 | 501 | 92·1 | 89·5 | 94·2 | 6·2 | 5·4 | 7·0 | <0·5 | 325·7 |
|  | PIV(M32) | 515 | 466 | 90·5 | 87·6 | 92·9 | 3·7 | 3·3 | 4·2 | <0·5 | 128·7 |
|  | SE | 103 | 94 | 91·3 | 84·1 | 95·9 | 2·6 | 2·0 | 3·4 | <0·5 | 68·5 |
| C3C | PIII(M20) | 554 | 56 | 10·1 | 7·7 | 12·9 | 0·3 | 0·3 | 0·3 | <0·5 | 97·1 |
|  | PIV(M21) | 519 | 47 | 9·1 | 6·7 | 11·9 | 0·3 | 0·3 | 0·3 | <0·5 | 481·0 |
|  | PIV(M32) | 501 | 67 | 13·4 | 10·5 | 16·7 | 0·3 | 0·3 | 0·3 | <0·5 | 16·7 |
|  | SE | 131 | 20 | 15·3 | 9·6 | 22·6 | 0·3 | 0·3 | 0·4 | <0·5 | 8·6 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

Anti-CS = anti-circumsporozoite protein antibodies.

GMT = geometric mean antibody titre calculated on all subjects.

EU/mL = ELISA unit per millilitre.

N = number of subjects with available results.

n/% = number/percentage of subjects with titre equal to or above specified value.

95% CI = 95% confidence interval; LL = lower limit, UL = upper limit.

Min/Max = minimum/maximum.

PIII(M20) = 18 months post dose-3.

PIV(M21) = 1 month post booster dose.

PIV(M32) = 12 months post booster dose.

PIV(M44) = 24 months post booster dose.

SE = study end.

Table S26. Incidence of solicited local and general symptoms within seven days post booster dose among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Local symptoms** | | | | | | | | | | | | | | | | |
|  |  | **R3R**  **(**RTS,S/AS01) | | | | | **R3C**  **(**Menjugate) | | | | | **C3C**  **(**Menjugate) | | | | |
|  |  |  | | | **95% CI** | |  | | | **95% CI** | |  | | | **95% CI** | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Pain | All | 641 | 109 | 17·0 | 14·2 | 20·1 | 639 | 45 | 7·0 | 5·2 | 9·3 | 633 | 41 | 6·5 | 4·7 | 8·7 |
|  | Grade 3 | 641 | 0 | 0·0 | 0·0 | 0·6 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
| Redness | All | 641 | 15 | 2·3 | 1·3 | 3·8 | 639 | 13 | 2·0 | 1·1 | 3·5 | 633 | 8 | 1·3 | 0·5 | 2·5 |
|  | >20 mm | 641 | 3 | 0·5 | 0·1 | 1·4 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
| Swelling | All | 641 | 42 | 6·6 | 4·8 | 8·8 | 639 | 35 | 5·5 | 3·8 | 7·5 | 633 | 30 | 4·7 | 3·2 | 6·7 |
|  | >20 mm | 641 | 9 | 1·4 | 0·6 | 2·6 | 639 | 1 | 0·2 | 0·0 | 0·9 | 633 | 0 | 0·0 | 0·0 | 0·6 |
| **General symptoms** | | | | | | | | | | | | | | | | |
|  |  | **R3R** | | | | | **R3C** | | | | | **C3C** | | | | |
|  |  |  | | | **95% CI** | |  | | | **95% CI** | |  | | | **95% CI** | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Drowsiness | All | 641 | 55 | 8·6 | 6·5 | 11·0 | 639 | 22 | 3·4 | 2·2 | 5·2 | 633 | 21 | 3·3 | 2·1 | 5·0 |
|  | Grade 3 | 641 | 1 | 0·2 | 0·0 | 0·9 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
|  | Related | 641 | 34 | 5·3 | 3·7 | 7·3 | 639 | 10 | 1·6 | 0·8 | 2·9 | 633 | 13 | 2·1 | 1·1 | 3·5 |
|  | Grade 3 Related | 641 | 0 | 0·0 | 0·0 | 0·6 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
| Irritability | All | 641 | 63 | 9·8 | 7·6 | 12·4 | 639 | 25 | 3·9 | 2·5 | 5·7 | 633 | 18 | 2·8 | 1·7 | 4·5 |
|  | Grade 3 | 641 | 1 | 0·2 | 0·0 | 0·9 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
|  | Related | 641 | 40 | 6·2 | 4·5 | 8·4 | 639 | 12 | 1·9 | 1·0 | 3·3 | 633 | 8 | 1·3 | 0·5 | 2·5 |
|  | Grade 3 Related | 641 | 1 | 0·2 | 0·0 | 0·9 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
| Loss of appetite | All | 641 | 66 | 10·3 | 8·1 | 12·9 | 639 | 27 | 4·2 | 2·8 | 6·1 | 633 | 21 | 3·3 | 2·1 | 5·0 |
|  | Grade 3 | 641 | 1 | 0·2 | 0·0 | 0·9 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
|  | Related | 641 | 39 | 6·1 | 4·4 | 8·2 | 639 | 14 | 2·2 | 1·2 | 3·6 | 633 | 13 | 2·1 | 1·1 | 3·5 |
|  | Grade 3 Related | 641 | 1 | 0·2 | 0·0 | 0·9 | 639 | 0 | 0·0 | 0·0 | 0·6 | 633 | 0 | 0·0 | 0·0 | 0·6 |
| Temperature (axillary) | All (≥37·5°C) | 641 | 233 | 36·3 | 32·6 | 40·2 | 639 | 70 | 11·0 | 8·6 | 13·6 | 633 | 45 | 7·1 | 5·2 | 9·4 |
| >39·0°C | 641 | 34 | 5·3 | 3·7 | 7·3 | 639 | 6 | 0·9 | 0·3 | 2·0 | 633 | 5 | 0·8 | 0·3 | 1·8 |
|  | Related | 641 | 151 | 23·6 | 20·3 | 27·0 | 639 | 29 | 4·5 | 3·1 | 6·5 | 633 | 16 | 2·5 | 1·5 | 4·1 |
|  | >39·0°C Related | 641 | 24 | 3·7 | 2·4 | 5·5 | 639 | 1 | 0·2 | 0·0 | 0·9 | 633 | 0 | 0·0 | 0·0 | 0·6 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects with the administered dose.

n/% = number/percentage of subjects reporting the symptom at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Fever was defined as an axillary temperature ≥37·5°C and grade 3 fever as an axillary temperature >39·0°C.

Table S27. Incidence of solicited local and general symptoms within seven days post booster dose among infants in the 6-12 weeks age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Local symptoms** | | | | | | | | | | | | | | | | |
|  |  | **R3R**  **(**RTS,S/AS01) | | | | | **R3C**  **(**Menjugate) | | | | | **C3C**  **(**Menjugate) | | | | |
|  |  |  | | | **95 % CI** | |  | | | **95 % CI** | |  | | | **95 % CI** | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Pain | All | 608 | 59 | 9·7 | 7·5 | 12·3 | 625 | 29 | 4·6 | 3·1 | 6·6 | 621 | 25 | 4·0 | 2·6 | 5·9 |
|  | Grade 3 | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
| Redness | All | 608 | 9 | 1·5 | 0·7 | 2·8 | 625 | 12 | 1·9 | 1·0 | 3·3 | 621 | 9 | 1·4 | 0·7 | 2·7 |
|  | >20 mm | 608 | 1 | 0·2 | 0·0 | 0·9 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
| Swelling | All | 608 | 45 | 7·4 | 5·4 | 9·8 | 625 | 28 | 4·5 | 3·0 | 6·4 | 621 | 43 | 6·9 | 5·1 | 9·2 |
|  | >20 mm | 608 | 5 | 0·8 | 0·3 | 1·9 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 2 | 0·3 | 0·0 | 1·2 |
| **General symptoms** | | | | | | | | | | | | | | | | |
|  |  | **R3R** | | | | | **R3C** | | | | | **C3C** | | | | |
|  |  |  | | | **95% CI** | |  | | | **95% CI** | |  | | | **95% CI** | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Drowsiness | All | 608 | 33 | 5·4 | 3·8 | 7·5 | 625 | 19 | 3·0 | 1·8 | 4·7 | 621 | 15 | 2·4 | 1·4 | 4·0 |
|  | Grade 3 | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
|  | Related | 608 | 19 | 3·1 | 1·9 | 4·8 | 625 | 6 | 1·0 | 0·4 | 2·1 | 621 | 5 | 0·8 | 0·3 | 1·9 |
|  | Grade 3 Related | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
| Irritability | All | 608 | 46 | 7·6 | 5·6 | 10·0 | 625 | 23 | 3·7 | 2·3 | 5·5 | 621 | 23 | 3·7 | 2·4 | 5·5 |
|  | Grade 3 | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
|  | Related | 608 | 27 | 4·4 | 2·9 | 6·4 | 625 | 10 | 1·6 | 0·8 | 2·9 | 621 | 6 | 1·0 | 0·4 | 2·1 |
|  | Grade 3 Related | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
| Loss of appetite | All | 608 | 45 | 7·4 | 5·4 | 9·8 | 625 | 27 | 4·3 | 2·9 | 6·2 | 621 | 18 | 2·9 | 1·7 | 4·5 |
|  | Grade 3 | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
|  | Related | 608 | 26 | 4·3 | 2·8 | 6·2 | 625 | 8 | 1·3 | 0·6 | 2·5 | 621 | 6 | 1·0 | 0·4 | 2·1 |
|  | Grade 3 Related | 608 | 0 | 0·0 | 0·0 | 0·6 | 625 | 0 | 0·0 | 0·0 | 0·6 | 621 | 0 | 0·0 | 0·0 | 0·6 |
| Temperature (axillary) | All (≥37·5°C) | 608 | 152 | 25·0 | 21·6 | 28·6 | 625 | 52 | 8·3 | 6·3 | 10·8 | 621 | 58 | 9·3 | 7·2 | 11·9 |
| >39·0°C | 608 | 9 | 1·5 | 0·7 | 2·8 | 625 | 7 | 1·1 | 0·5 | 2·3 | 621 | 10 | 1·6 | 0·8 | 2·9 |
| Related | 608 | 80 | 13·2 | 10·6 | 16·1 | 625 | 15 | 2·4 | 1·3 | 3·9 | 621 | 18 | 2·9 | 1·7 | 4·5 |
|  | >39·0°C Related | 608 | 5 | 0·8 | 0·3 | 1·9 | 625 | 1 | 0·2 | 0·0 | 0·9 | 621 | 3 | 0·5 | 0·1 | 1·4 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of subjects with the administered dose.

n/% = number/percentage of subjects reporting the symptom at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Fever was defined as an axillary temperature ≥37·5°C and grade 3 fever as an axillary temperature >39·0°C.

Table S28. Incidence of seizures within seven days post booster dose in both age categories (intention-to-treat population).

| **5-17 months age category** | | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **R3R**  **N = 2447** | | | | **R3C**  **N = 2472** | | | | **C3C**  **N = 2473** | | | |
|  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Characteristics** | **Categories** | **n** | **n/1000** | **LL** | **UL** | **n** | **n/1000** | **LL** | **UL** | **n** | **n/1000** | **LL** | **UL** |
| Generalized convulsive seizure | Level 1 to 3 | 6 | 2·5 | 0·9 | 5·3 | 3 | 1·2 | 0·3 | 3·5 | 1 | 0·4 | 0·0 | 2·3 |
| Convulsive seizure | Level 1 to 5 | 8 | 3·3 | 1·4 | 6·4 | 4 | 1·6 | 0·4 | 4·1 | 1 | 0·4 | 0·0 | 2·3 |
| Diagnostic certainty level | Level 1 | 1 | 0·4 | 0·0 | 2·3 | 1 | 0·4 | 0·0 | 2·3 | 0 | - | 0·0 | 1·5 |
|  | Level 2 | 5 | 2·0 | 0·7 | 4·8 | 2 | 0·8 | 0·1 | 2·9 | 1 | 0·4 | 0·0 | 2·3 |
|  | Level 3 | 0 | 0·0 | 0·0 | 1·5 | 0 | 0·0 | 0·0 | 1·5 | 0 | 0·0 | 0·0 | 1·5 |
|  | Level 4 | 1 | 0·4 | 0·0 | 2·3 | 0 | - | 0.0 | 1·5 | 0 | - | 0·0 | 1·5 |
|  | Level 5 | 1 | 0·4 | 0·0 | 2·3 | 1 | 0·4 | 0·0 | 2·3 | 0 | - | 0·0 | 1·5 |
| **6-12 weeks age category** | | | | | | | | | | | | | |
|  | | **R3R**  **N = 1825** | | | | **R3C**  **N = 1837** | | | | **C3C**  **N = 1827** | | | |
|  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Characteristics** | **Categories** | **n** | **n/1000** | **LL** | **UL** | **n** | **n/1000** | **LL** | **UL** | **n** | **n/1000** | **LL** | **UL** |
| Generalized convulsive seizure | Level 1 to 3 | 4 | 2·2 | 0·6 | 5·6 | 0 | - | 0·0 | 2·0 | 1 | 0·5 | 0·0 | 3·0 |
| Convulsive seizure | Level 1 to 5 | 4 | 2·2 | 0·6 | 5·6 | 0 | - | 0·0 | 2·0 | 1 | 0·5 | 0·0 | 3·0 |
| Diagnostic certainty level | Level 1 | 1 | 0·5 | 0·0 | 3·0 | 0 | - | 0·0 | 2·0 | 0 | - | 0·0 | 2·0 |
|  | Level 2 | 3 | 1·6 | 0·3 | 4·8 | 0 | - | 0·0 | 2·0 | 1 | 0·5 | 0·0 | 3·0 |
|  | Level 3 | 0 | 0·0 | 0·0 | 2·0 | 0 | 0·0 | 0·0 | 2·0 | 0 | 0·0 | 0·0 | 2·0 |
|  | Level 4 | 0 | 0·0 | 0·0 | 2·0 | 0 | 0·0 | 0·0 | 2·0 | 0 | 0·0 | 0·0 | 2·0 |
|  | Level 5 | 0 | 0·0 | 0·0 | 2·0 | 0 | 0·0 | 0·0 | 2·0 | 0 | 0·0 | 0·0 | 2·0 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

N = number of doses.

n = number of doses in a given category.

n/1000 = n / number of doses with available results x 1000.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Level 1 = witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations.

Level 2 = history of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations.

Level 3 = history of unconsciousness AND other generalized motor manifestations.

Level 4 = reported generalized convulsive seizure with insufficient evidence to meet the case definition.

Level 5 = not a case of generalized convulsive seizure.

Table S29. Percentage of subjects reporting unsolicited adverse events within 30 days post booster dose with an incidence greater or equal to 5% among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **R3R**  **N = 641** | | | | **R3C**  **N = 639** | | | | **C3C**  **N = 633** | | | |
|  | |  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Primary System Organ Class** | **Preferred Term** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one AE |  | 232 | 36·2 | 32·5 | 40·0 | 205 | 32·1 | 28·5 | 35·9 | 215 | 34·0 | 30·3 | 37·8 |
| At least one AE excluding malaria |  | 211 | 32·9 | 29·3 | 36·7 | 180 | 28·2 | 24·7 | 31·8 | 181 | 28·6 | 25·1 | 32·3 |
| General disorders and administration site conditions | Pyrexia | 44 | 6·9 | 5·0 | 9·1 | 10 | 1·6 | 0·8 | 2·9 | 7 | 1·1 | 0·4 | 2·3 |
| Infections and infestations | Malaria | 49 | 7·6 | 5·7 | 10·0 | 53 | 8·3 | 6·3 | 10·7 | 84 | 13·3 | 10·7 | 16·2 |
|  | Upper respiratory tract infection | 61 | 9·5 | 7·4 | 12·1 | 55 | 8·6 | 6·5 | 11·1 | 55 | 8·7 | 6·6 | 11·2 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).

At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.

N = number of subjects with booster dose administered.

n/% = number/percentage of subjects reporting the AE at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S30. Percentage of subjects reporting unsolicited adverse events within 30 days post each vaccination with an incidence greater or equal to 5% among children in the 5-17 months age category (intention-to-treat population).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **R3R**  **N = 740** | | | | **R3C**  **N = 739** | | | | **C3C**  **N = 721** | | | |
|  | |  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Primary System Organ Class** | **Preferred Term** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one AE |  | 646 | 87·3 | 84·7 | 89·6 | 653 | 88·4 | 85·8 | 90·6 | 637 | 88·3 | 85·8 | 90·6 |
| At least one AE excluding malaria |  | 634 | 85·7 | 82·9 | 88·1 | 645 | 87·3 | 84·7 | 89·6 | 621 | 86·1 | 83·4 | 88·6 |
| Blood and lymphatic system disorders | Anaemia | 32 | 4·3 | 3·0 | 6·1 | 28 | 3·8 | 2·5 | 5·4 | 36 | 5·0 | 3·5 | 6·8 |
| Gastrointestinal disorders | Diarrhoea | 87 | 11·8 | 9·5 | 14·3 | 109 | 14·7 | 12·3 | 17·5 | 92 | 12·8 | 10·4 | 15·4 |
|  | Enteritis | 66 | 8·9 | 7·0 | 11·2 | 72 | 9·7 | 7·7 | 12·1 | 65 | 9·0 | 7·0 | 11·3 |
| General disorders and administration site conditions | Pyrexia | 151 | 20·4 | 17·6 | 23·5 | 117 | 15·8 | 13·3 | 18·7 | 75 | 10·4 | 8·3 | 12·9 |
| Infections and infestations | Bronchitis | 38 | 5·1 | 3·7 | 7·0 | 46 | 6·2 | 4·6 | 8·2 | 37 | 5·1 | 3·6 | 7·0 |
|  | Conjunctivitis | 66 | 8·9 | 7·0 | 11·2 | 61 | 8·3 | 6·4 | 10·5 | 74 | 10·3 | 8·1 | 12·7 |
|  | Gastroenteritis | 203 | 27·4 | 24·2 | 30·8 | 190 | 25·7 | 22·6 | 29·0 | 179 | 24·8 | 21·7 | 28·1 |
|  | Malaria | 163 | 22·0 | 19·1 | 25·2 | 154 | 20·8 | 18·0 | 23·9 | 224 | 31·1 | 27·7 | 34·6 |
|  | Nasopharyngitis | 58 | 7·8 | 6·0 | 10·0 | 61 | 8·3 | 6·4 | 10·5 | 61 | 8·5 | 6·5 | 10·7 |
|  | Pneumonia | 95 | 12·8 | 10·5 | 15·5 | 85 | 11·5 | 9·3 | 14·0 | 78 | 10·8 | 8·6 | 13·3 |
|  | Rhinitis | 70 | 9·5 | 7·4 | 11·8 | 53 | 7·2 | 5·4 | 9·3 | 52 | 7·2 | 5·4 | 9·4 |
|  | Upper respiratory tract infection | 335 | 45·3 | 41·6 | 48·9 | 351 | 47·5 | 43·8 | 51·2 | 345 | 47·9 | 44·1 | 51·6 |
| Respiratory, thoracic and mediastinal disorders | Cough | 57 | 7·7 | 5·9 | 9·9 | 62 | 8·4 | 6·5 | 10·6 | 47 | 6·5 | 4·8 | 8·6 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).

At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.

N = number of subjects with at least one administered dose.

n/% = number/percentage of subjects reporting the AE at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S31. Percentage of subjects reporting unsolicited adverse events within 30 days post booster dose with an incidence greater or equal to 5% among infants in the 6-12 weeks age category (intention-to-treat population).

|  | | **R3R**  **N = 608** | | | | **R3C**  **N = 625** | | | | **C3C**  **N = 621** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Primary System Organ Class** | **Preferred Term** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one AE |  | 231 | 38·0 | 34·1 | 42·0 | 239 | 38·2 | 34·4 | 42·2 | 240 | 38·6 | 34·8 | 42·6 |
| At least one AE excluding malaria |  | 211 | 34·7 | 30·9 | 38·6 | 221 | 35·4 | 31·6 | 39·3 | 222 | 35·7 | 32·0 | 39·7 |
| Infections and infestations | Gastroenteritis | 34 | 5·6 | 3·9 | 7·7 | 29 | 4·6 | 3·1 | 6·6 | 40 | 6·4 | 4·6 | 8·7 |
|  | Malaria | 44 | 7·2 | 5·3 | 9·6 | 56 | 9·0 | 6·8 | 11·5 | 55 | 8·9 | 6·7 | 11·4 |
|  | Upper respiratory tract infection | 87 | 14·3 | 11·6 | 17·3 | 93 | 14·9 | 12·2 | 17·9 | 90 | 14·5 | 11·8 | 17·5 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).

At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.

N = number of subjects with booster dose administered.

n/% = number/percentage of subjects reporting the AE at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S32. Percentage of subjects reporting unsolicited adverse events within 30 days post each vaccination with an incidence greater or equal to 5% among infants in the 6-12 weeks age category (intention-to-treat population).

|  | | **R3R**  **N = 725** | | | | **R3C**  **N = 737** | | | | **C3C**  **N = 738** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | | **95% CI** | |  | | **95% CI** | |  | | **95% CI** | |
| **Primary System Organ Class** | **Preferred Term** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one AE |  | 597 | 82·3 | 79·4 | 85·1 | 618 | 83·9 | 81·0 | 86·4 | 632 | 85·6 | 82·9 | 88·1 |
| At least one AE excluding Malaria |  | 588 | 81·1 | 78·1 | 83·9 | 611 | 82·9 | 80·0 | 85·6 | 630 | 85·4 | 82·6 | 87·8 |
| Gastrointestinal disorders | Enteritis | 86 | 11·9 | 9·6 | 14·4 | 63 | 8·5 | 6·6 | 10·8 | 81 | 11·0 | 8·8 | 13·5 |
| General disorders and administration site conditions | Pyrexia | 131 | 18·1 | 15·3 | 21·1 | 137 | 18·6 | 15·8 | 21·6 | 121 | 16·4 | 13·8 | 19·3 |
| Infections and infestations | Bronchitis | 37 | 5·1 | 3·6 | 7·0 | 32 | 4·3 | 3·0 | 6·1 | 33 | 4·5 | 3·1 | 6·2 |
|  | Conjunctivitis | 72 | 9·9 | 7·9 | 12·3 | 67 | 9·1 | 7·1 | 11·4 | 81 | 11·0 | 8·8 | 13·5 |
|  | Gastroenteritis | 133 | 18·3 | 15·6 | 21·4 | 134 | 18·2 | 15·5 | 21·2 | 155 | 21·0 | 18·1 | 24·1 |
|  | Malaria | 88 | 12·1 | 9·8 | 14·7 | 120 | 16·3 | 13·7 | 19·1 | 114 | 15·4 | 12·9 | 18·3 |
|  | Nasopharyngitis | 51 | 7·0 | 5·3 | 9·1 | 54 | 7·3 | 5·6 | 9·5 | 61 | 8·3 | 6·4 | 10·5 |
|  | Otitis media | 32 | 4·4 | 3·0 | 6·2 | 42 | 5·7 | 4·1 | 7·6 | 41 | 5·6 | 4·0 | 7·5 |
|  | Pneumonia | 53 | 7·3 | 5·5 | 9·5 | 56 | 7·6 | 5·8 | 9·8 | 44 | 6·0 | 4·4 | 7·9 |
|  | Rhinitis | 83 | 11·4 | 9·2 | 14·0 | 83 | 11·3 | 9·1 | 13·8 | 94 | 12·7 | 10·4 | 15·4 |
|  | Upper respiratory tract infection | 326 | 45·0 | 41·3 | 48·7 | 333 | 45·2 | 41·5 | 48·9 | 347 | 47·0 | 43·4 | 50·7 |

R3R = RTS,S/AS01 primary schedule with booster.

R3C = RTS,S/AS01 primary schedule without booster.

C3C = control group.

At least one AE = at least one AE experienced (regardless of the MedDRA Preferred Term).

At least one AE excluding malaria = at least one AE experienced (regardless of the MedDRA Preferred Term), excluding malaria, *P. falciparum* infection, and cerebral malaria.

N = number of subjects with at least one administered dose.

n/% = number/percentage of subjects reporting the AE at least once.

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit.

Table S33. Grading of solicited adverse events

|  |  |  |
| --- | --- | --- |
| **Adverse Event** | **Intensity grade** | **Parameter** |
| Pain at injection site | 0 | Absent |
|  | 1 | Minor reaction to touch |
|  | 2 | Cries/protests on touch |
|  | 3 | Cries when limb is moved/spontaneously painful |
| Swelling at injection site | 0 | Absent |
|  | 1 | <5 mm |
|  | 2 | 5-20 mm |
|  | 3 | >20 mm |
| Redness at injection site | 0 | Absent |
|  | 1 | <5 mm |
|  | 2 | 5-20 mm |
|  | 3 | >20 mm |
| Fever | 0 | <37.5°C |
|  | 1 | 37.5-38°C |
|  | 2 | >38-39°C |
|  | 3 | >39°C |
| Irritability/Fussiness | 0 | Behaviour as usual |
|  | 1 | Crying more than usual/ no effect on normal activity |
|  | 2 | Crying more than usual/ interferes with normal activity |
|  | 3 | Crying that cannot be comforted/ prevents normal activity |
| Drowsiness | 0 | Behaviour as usual |
|  | 1 | Drowsiness easily tolerated |
|  | 2 | Drowsiness that interferes with normal activity |
|  | 3 | Drowsiness that prevents normal activity |
| Loss of appetite | 0 | Appetite as usual |
|  | 1 | Eating less than usual/ no effect on normal activity |
|  | 2 | Eating less than usual/ interferes with normal activity |
|  | 3 | Not eating at all |