Protocol

Impact of Malaria in Pregnancy on Infants Study Group

Version 2.0

April 2021

WorldWide Antimalarial Resistance Network (WWARN)

WWARN Logo (new version)

**Suggested citation:** Protocol for a systematic review and individual participant data meta-analysis of the relationship between maternal malaria infection during pregnancy and infant outcomes.

Version History

|  |  |  |
| --- | --- | --- |
| Version number | Revision(s) & reason for amendment | Release date |
| v1.0 |  | 11.11.2019 |
| V2.0 | Adding Dr. Holger Unger. Adding MTCT as outcome |  |
|  |  |  |

WorldWide Antimalarial Resistance Network (WWARN)

[www.wwarn.org](http://www.wwarn.org)

**Table of Contents**

[Administrative information 1](#_Toc25674273)

[1. Protocol for a systematic review and individual participant data meta-analysis of the relationship between maternal malaria infection during pregnancy and infant outcomes 1](#_Toc25674274)

[2. Systematic review protocol Prospero registration number 1](#_Toc25674275)

[3. Authors for the Impact of Malaria in Pregnancy on Infants Study Group 1](#_Toc25674276)

[4. Amendments 3](#_Toc25674277)

[5. Support 3](#_Toc25674278)

[Introduction 3](#_Toc25674279)

[6. Background 3](#_Toc25674280)

[7. Objectives 4](#_Toc25674281)

[Methods 6](#_Toc25674282)

[8. Eligibility criteria 6](#_Toc25674283)

[9. Information sources 6](#_Toc25674284)

[10. Search strategy 6](#_Toc25674285)

[11. Study records 6](#_Toc25674286)

[12. Data items 8](#_Toc25674287)

[13. Exposures and outcome definitions and prioritization 10](#_Toc25674288)

[14. Risk of bias in individual studies 12](#_Toc25674289)

[15. Data synthesis 13](#_Toc25674290)

[16. Meta-bias 15](#_Toc25674291)

[17. Confidence in cumulative evidence 15](#_Toc25674292)

[18. Ethics and dissemination 15](#_Toc25674293)

[19. References 15](#_Toc25674294)

[Supplement 1: Variables of interest 19](#_Toc25674295)

# Administrative information

## Protocol for a systematic review and individual participant data meta-analysis of the relationship between maternal malaria infection during pregnancy and infant outcomes

## Systematic review protocol Prospero registration number

CRD42020162260 (URL: https://www.crd.york.ac.uk/PROSPERO/display\_record.php?RecordID=162260)

## Authors for the Impact of Malaria in Pregnancy on Infants Study Group (Core group)

van Eijk AM,1\* Holger Unger, 1 Eleanor Ochodo,2 Hill J,1 Stepniewska K,3 Khairalla C,1 Kakuru A,4 Jagannathan P,5 Mayor A,6 Ter Kuile FO1

**Affiliations**:

1 Liverpool School of Tropical Medicine, Liverpool, United Kingdom

2 Kenya Medical Research Institute, Kisumu, Kenya

3 Worldwide Antimalarial Resistance Network (WWARN) and Centre for Tropical Medicine, Oxord, United Kingdom

4 Infectious Diseases Researcy Collaboration, Kampala, Uganda

5 Stanford University, San Francisco, CA, USA

6 CRESIB Barcelona Centre for International Health Research, Barcelona, Spain

**Corresponding author**:

Annemieke (AM) van Eijk

Department of Clinical Sciences,

Liverpool School of Tropical Medicine,

Pembroke Place, Liverpool, UK

[anna.vaneijk@lstmed.ac.uk](mailto:anna.vaneijk@lstmed.ac.uk) or amvaneijk@gmail.com

Email addresses from other authors: [eleanor.ochodo@gmail.com](mailto:eleanor.ochodo@gmail.com), [jenny.hill@lstmed.ac.uk](mailto:jenny.hill@lstmed.ac.uk), [kasia.stepniewska@wwarn.org](mailto:kasia.stepniewska@wwarn.org), [abelkakuru@gmail.com](mailto:abelkakuru@gmail.com), [prasj@stanford.edu](mailto:prasj@stanford.edu), [alfredo.mayor@isglobal.org](mailto:agmayor@clinic.ub.es), [feiko.terkuile@lstmed.ac.uk](mailto:feiko.terkuile@lstmed.ac.uk), holger.unger@lstmed.ac.uk

**Guarantor**: Annemieke (AM) van Eijk

**Author contributions**

FtK conceived the review. Ave wrote the first draft of the protocol, with subsequent input from FtK. All other authors made substantial contributions to the conception and further design of this protocol. AvE and HWU will do the literature search, review all abstracts independently, and assess study quality; FtK will serve as the tiebreaker. AvE and HWU will abstract all data independently where applicable. AvE and HWU will review individual patient data for consistency and merge datasets. HWU, AvE, KS and FtK will conduct the analyses with review and interpretation of the data by all others. HWU, Ave and FtK will draft the first report with subsequent input from all others.

**Other collaborators**

Prof Phillippe Guerin, Worldwide Antimalarial Resistance Network (WWARN), Centre for Tropical Medicine and Global Health, and Infectious Diseases Data Observatory, University of Oxord, UK

Caitlin Richmond, Worldwide Antimalarial Resistance Network (WWARN) and Centre for Tropical Medicine and Global Health, University of Oxord, UK

**Names full study group in alphabetical order last name (in progress)**:

*To be added when datasets are received*

**Abbreviations, terms and definitions**

|  |  |
| --- | --- |
| IPD | Individual participant data |
| IPTi | Intermittent preventive treatment in infancy |
| IPTp | Intermittent preventive treatment in pregnancy |
| ITN | Insecticide-treated net |
| LAMP | Loop-mediated isothermal amplification |
| LLINs | Long-lasting insecticide-treated nets |
| LBW | Low birth weight |
| MiP | Malaria in Pregnancy |
| PCR | Polymerase chain reaction |
| RDT | Rapid diagnostic malaria test |
| SP | Sulfadoxine-pyrimethamine |
| WWARN | World Wide Antimalarial Resistance Network |

1. Amendments

Not yet applicable.

## Support

This review is funded by a grant from the Bill and Melinda Gates Foundation Malaria to the WorldWide Antimalarial Resistance Network (WWARN). The funder had no role in the development of the protocol and is not involved in any other aspect of the project, such as the design of the project’s protocol and analysis plan, data collection, and analyses.

# Introduction

## Background

Approximately 31 million pregnant women in malaria-endemic regions in Africa were estimated to be at risk of infection with malaria in 2015.1 Malaria can have devasting effects on the pregnancy and infant. Although the effects of malaria during pregnancy on birth outcomes are known,2,3 the long term impact of maternal malaria exposure during pregnancy on the infant and child development are not clear.

There are multiple reports that exposure in utero to malaria and other infections affects the developments of the fetal immune system (summarised by Harrington et al. 2018)4,5 and may affect the acquisition of malaria in the first year of life. In the early months of life, the prevalence of clinical malaria is low6, as the transfer of maternal malaria antibodies leads to protection of the infant during this period, and foetal haemoglobin may not support the development of the pathology of malaria.7 Placental malaria does not seem to have a consistent effect on the transfer of antimalarial antibodies to the infant but cellular responses to malaria antigens may differ depending on intra-uterine exposure.8-11 Malaria in pregnancy was a risk factor for the acquisition of infant malaria in several studies, but in some studies the higher risk was only detected late in infancy12,13 or an increased risk was only seen after the first year of life for infants of primigravidae,14 or differed by gravidity,14,15 or intra-uterine foetal sensitization to malaria.9 Other studies reported a shorter time to first clinical malaria infection, or higher odds of clinical or any malaria, and for some this was modified by the timing of the exposure during pregnancy or compartment of detected infection.16-19

It has been argued that it is difficult to disentangle the effect of the environment from the effect of intra-uterine malaria exposure; pregnant women with malaria are more likely to live in an environment with a higher risk of malaria; some studies have taken this into account by including an environmental malaria risk factor in the analytical model.20,21 Some studies reported observing no association between maternal malaria and infant malaria incidence,21-23 or only an association between maternal and infant malaria among small-for-gestational-age infants.24 A recent review noted that evidence of an association between malaria in pregnancy or intermittent preventive treatment and risk of malaria in infancy is limited and of variable quality; however, one trial comparing intermittent preventive treatment with sulfadoxine pyrimethamine vs. dihydroartemisinin-piperaquine (DP) noted gender differences in susceptibility to malaria in infancy, with placental malaria potentially more severe among male infants.25-27

Malaria during pregnancy may also affect the risk of other infections during infancy such as diarrhoea, gastrointestinal and acute respiratory infections,28,29 and all-cause febrile episodes30, by modulating of the foetal immune system or transfer of maternal antibodies.4

Heterogeneity in study results has also been reported for the associations between malaria exposure during pregnancy and infant anaemia or haemoglobin levels, with some studies reporting an association between maternal malaria and infant anaemia or haemoglobin levels, 9 31-36 but not others.37,38 Similarly, the reported associations between maternal malaria and infant growth have been variable.28,39-42

We propose an individual participant data (IPD) meta-analysis to better understand the effects of malaria during pregnancy on infant outcomes. An IPD approach is needed to enable standardisation of outcomes across studies, to be able to adjust for exposures and confounders appropriately, and provide greater scope for subgroup analyses.43

## Objectives

The objectives of the evaluation of the association between maternal malaria and infant and child health outcomes are as follows:

1. Primary Objective:
   * To determine the association between malaria exposure during pregnancy and infant/child malaria infection (28 days-60 months), all-cause and malaria-associated sick-child clinic visits (any species), infant anaemia and infant growth.
2. Secondary objectives:
   * To determine the association between malaria exposure during pregnancy and post-infant (12-59 months) malaria infection, all-cause and malaria-associated clinic visits, anaemia and growth.
   * To determine if these associations differ between subgroups, including by timing of maternal exposure, gravidity, the gender of the newborn, and maternal / child HIV status.
   * To determine among cohorts of HIV-positive women if MTCT transmission is affected by malaria in pregnancy and chemoprevention during pregnancy.
3. Tertiary objectives
   * To determine the association between malaria exposure during pregnancy on early neonatal, neonatal, post-neonatal and infant mortality. If sufficient data is available, we will also explore child mortality after the age of 12 months (12-59 months).
   * To determine the association between malaria exposure during pregnancy and cord anaemia/haemoglobin

**PICOTS Framework**

|  |  |
| --- | --- |
| **Components** | **Characteristics** |
| **Population** | Pregnant women and the infants (>28 days and ≤12 months of age) or children (>12 month and <60 months of age) born out of these pregnancies |
| **Condition** | Known malaria exposure during pregnancy defined as malaria during pregnancy (RDT/BS/PCR/LAMP; trimester of known exposure) or malaria at delivery (peripheral or placental RDT/BS/PCR/LAMP or placental histology). Test results will be explored by type of test and different test results and timing of test result will be explored when combined (composite exposure definion). |
| **Control** | No documented or known malaria exposure during pregnancy |
| **Outcomes** | Infant outcomes (28 days-60 months of age):   1. Clinical malaria (malaria in the presence of a history of fever or documented fever, or detected during a sick-child clinic visit regardless of the presence of fever) 2. Any malaria (clinical or asymptomatic) 3. Mean haemoglobin 4. Infant anaemia (age-appropriate definition if aged <6 months; otherwise hb<11 g/dl) 5. Infant growth (e.g. length, weight, mid-upper arm circumference and corresponding z-scores) 6. All cause sick-child clinic visits 7. Mortality   Where available:   1. The outcomes above during childhood (<60 months of age) 2. Effect of cord haemoglobin on infant outcomes 3. Mother-to child transmission of HIV where applicable and available |
| **Timing** | No time restrictions |
| **Setting** | Cohort study or trial (randomised, quasi-randomised or cluster-randomised) among pregnant women in any malarious area with infant follow-up for at least 28 days. English language. There will be no restriction for continent. |

# Methods

## Eligibility criteria

***Inclusion criteria***

**Studies with:**

* Cohort studies and randomized and non-randomized trials with information about maternal malaria exposure defined as malaria during pregnancy and/or at the time of delivery, collected at a single or multiple time points, systematically for all participants, independent of symptoms or complaints
* Information on one or more infant outcomes at one or more follow up visits (at a single or multiple time points) from 28 days <60 months of age

***Exclusion criteria***

* Studies with infant follow-up less than 28 days
* Treatment studies for pregnant women, whereby women needed to be malaria-positive at the time of enrolment
* Studies with information on maternal clinical malaria at unscheduled visits only during pregnancy (either history or using a malaria test) and no systematic maternal blood taking of all participants at one or more time points during pregnancy
* Studies with information on cord malaria only and not on maternal blood malaria

## Information sources

The main information source will be the Malaria in Pregnancy Library,44 which is updated every four months and including data from over 20 databases, including PubMed, Google Scholar, the Global Health database, and Web of Science, and includes 'grey literature' (e.g. reports), theses, and conference abstracts. We will also contact experts in this field for the inclusion of unpublished material.

## Search strategy

The search terms for the Malaria in Pregnancy Library will include “infant\* OR child\*” and “cohort OR trial OR follow”; specifications of malaria or pregnancy are not required since these are the primary criteria for inclusion in the Malaria in Pregnancy Library. These search criteria will provide a low-specificity, high sensitivity search allowing us to evaluate each cohort study or trial for potential eligibility.

## Study records

***Data management of study records***

We will import all citations into excel and Endnote. Duplicates will be removed, and the last date of the search documented. The search will be repeated after each update of the Malaria in Pregnancy Library among the new entries of the library; results of the first search and the updates will be compiled into a Stata dataset, that will be used for the flow chart. IPD data from investigators will be transformed into Stata v16, curated and saved in a single database.

***Selection process***

Two independent reviewers will screen the full-text article if available to check if the study is eligible in the first screen. The second screen will compare the studies selected by either one of these reviewers. In the second screen, the two reviewers will screen abstracts and full texts and agree on final study eligibility. The final number of studies to be obtained will be agreed upon with any disagreements on citations being resolved by consensus or by contacting a third reviewer who will serve as the tiebreaker. Studies considered eligible after full-text review by the two independent reviewers will be included in the final set of studies for inclusion. A log of all studies excluded and reasons for exclusion after the 1st and 2nd screen will be kept to account for any differences in inferences made. Studies with only an abstract available will not *a-priori* be excluded; an attempt to contact the authors to obtain more information will be made where the abstract does not provide enough information for inclusion. Data from reports from studies with multiple publications will be combined in one record entry, to avoid duplication of individual data. For articles retrieved in languages other than English, the content will be verified for inclusion using a colleague who masters that language.

For all studies, quality assessment will be conducted by two persons using spreadsheets using an adaptation of the Newcastle-Ottawa scale for cohort studies; disagreements will be resolved through discussion among study group members and by contacting the investigators. The data extractors will not be blind to the journal titles or the study authors or institutions.

***Data collection process***

For the IPD analyses, the principal investigators (PI) of potential studies will be approached and invited to share their data with WWARN. They will be provided with an excel spreadsheet containing the variables of interest (supplement 1). They will be requested to compile either a custom made dataset or make the full dataset available; the data will need to be uploaded online to WWARN by the study or a WWarn agreement need to be signed by the PIs or a representative for the reviewers to do it. Each study PI will be approached up to three times unless a representative of the study immediately expresses no interest or if the data is unavailable. The outcomes of the search and the requests for data will be recorded in a database and illustrated in a flow chart. From the studies where we cannot obtain the individual data, an attempt will be made to use data extracted from the published material as part of aggregated data in the two-stage models using the ‘ad’ option from ‘ipdmetan’ command where possible and appropriate.

## Data items

***Variables of interest***

In addition to exposure and outcome variables, we will collect data on co-variates known to be associated with the exposure and outcome variable of interest, based on the literature or known confounders of infant malaria, anaemia and growth; an assessment of the need for inclusion and likelihood of availability will be made by the study groups members. Among pregnant women, malaria is more common among primi- or secundigravidae, women infected with HIV and women of young age (<20 years).45 Location (rural vs semi-rural vs urban) will be requested. Interventions that are known to impact on malaria exposure risk during pregnancy or infancy, such as the use of insecticide-treated nets (ITNs) or indoor residual spraying, intermittent preventive treatment, chemoprophylaxis, or intermittent screening and treatment during pregnancy or infancy will be recorded.3,46-48 Other data elements to be captured are birth weight and gestational age at delivery, both likely to be determinants of infant morbidity and growth. Other known risk factors for infant anaemia will be requested where available, such as maternal and infant HIV status, and use of haematinic supplementation.49,50

***Variable list***

Maternal variables requested include (see supplement 1) participant identification number, visit date, location/site, residence (urban or rural), SES status, gravidity, age, gestational age at enrolment and delivery (and method of assessment), malaria test results by microscopy, PCR, RDT or LAMP, including species and count (microscopy), IRS, ITN use, IPTp, IST or chemoprophylaxis use, recent antimalarial treatment, iron and folate supplementation, number of scheduled vs unscheduled ANC/OPD visits (i.e. normal vs sick-visits), a history of fever or documented fever, haemoglobin and treatment arm if in a trial, birth outcome. Additional maternal variables include HIV-status at the time of the pregnancy, smoking, and maternal nutritional status (height, weight, mid-upper arm circumference), where available.

Infant/child variables include date of birth, APGAR score, birth weight, sex, gestational age assessment by ultrasound in pregnancy or by other means at delivery and cord haemoglobin. Subsequent follow-up data will include date of visit, scheduled or unscheduled visit, infant age, fever history, body temperature, malaria test results (type and results), haemoglobin (test type and result), infant anthropometry where available (weight, height, MUAC or other), infant HIV-status where known, use of malaria prevention (ITN, IRS, IPTi, etc), and recent antimalarial treatment, any trial arm that may be applicable, and infant mortality, if available.

***External study-level data***

External data will be added to this file, such as GPS location from Google Earth (<https://www.google.com/earth/>), country-level HIV-prevalence data among women aged 15-49 years (<http://aidsinfo.unaids.org>) and SP-molecular markers in the region (from <http://www.wwarn.org/dhfr-dhps-surveyor/#0> or local sources), matched by location and time. Using the GPS coordinates, the *Plasmodium falciparum* parasite rate in 2-10 year olds as an indicator of malaria transmission intensity and ITN coverage51 will be obtained from the Malaria Atlas Project (<https://map.ox.ac.uk>) for the study date for studies after 1995; the Malaria Atlas Project has data from 2000 onwards, and we would extrapolate the 2000 data to the years 1995-1999. For studies before 1995, we would look for ad-hoc solutions, e.g. if there are studies available among children 2-10 years in the same area that would provide useful information. For studies with no information on ITN use or use of IPTp at the time of delivery, we will obtain an estimate using national surveys (demographic and health surveys, malaria indicator surveys or multiple indicator cluster surveys) closest in time for the administrative region (<https://dhsprogram.com>, <http://www.malariasurveys.org>, <http://mics.unicef.org>). The season during pregnancy and infant follow-up will be defined using publicly available rainfall data per site based on GPS coordinates.

***Data curation and standardisation***

Data will be fully anonymised. Raw data will be curated in a standardised format using the WWARN procedures ( [https://www.wwarn.org/sites/default/files/attachments/documents/ClinicalDMSAP.pdf](https://protect-eu.mimecast.com/s/m5ASCOPjDUGwyvhENHo3?domain=wwarn.org)), so the data can be combined in a pooled data set.

***IPD integrity***

We will use standard checks to identify missing data, assess data validity and consistency. We will verify the amount of missing data, check the order of dates and assess data validity and consistency. If there are queries, we will approach the study authors for clarification.

## Exposures and outcome definitions and prioritization

The exposures of interest and outcomes are defined in table 1.

| **Type** | **Category** | **Definition** |
| --- | --- | --- |
| ***Exposure*** |  |  |
| Malaria in pregnancy | Malaria | Placental malaria or peripheral maternal malaria at the time of delivery detected by any test (RDT, microscopy, PCR, LAMP, histology), or peripheral maternal malaria detected at any time during pregnancy by any test (RDT, microscopy, PCR, LAMP). Test results will be explored by type of test and different test results and timing of test result will be explored when combined (composite exposure definion). |
| ***Primary outcome*** |  |  |
| Clinical malaria | Malaria | Malaria in the infant detected by any test (RDT, microscopy, PCR) with documented fever or a history of recent fever in the last 24h or 48h (depending on the study definitions in the source study), or detected during a sick-child clinic visit regardless of the presence of fever. |
| ***Secondary outcomes*** | |  |
| Malaria infection | Malaria | Malaria detected by any test (RDT, microscopy, PCR), clinical or asymptomatic |
| Patent malaria | Malaria | Malaria infections detected by microscopy or RDT |
| Sub-patent malaria | Malaria | Malaria infections detected by PCR but not by microscopy or RDT |
| Sub-microscopic malaria | Malaria | Malaria infections which are detected by PCR but not by microscopy |
| Asymptomatic malaria | Malaria | Any malaria infection that is not defined as clinical malaria |
| All-cause sick child clinic visits | Morbidity | Any unscheduled visit to a clinic or equivalent of a sick child visit; i.e. clinics visits that exclude otherwise healthy children coming for scheduled vaccination clinic visits or scheduled follow-up visits. |
| Infant haemoglobin | Hb/anaemia | Haemoglobin in g/dL at any time from birth onwards |
| Any anaemia | Hb/anaemia | Hb <11 g/dl if 6 months or older, age-appropriate definition if aged <6 months (a haemoglobin concentration more than two standard deviations below the mean of similarly aged infants from a reference population not exposed to malaria in the United States52) |
| Moderate-to-severe anaemia | Hb/anaemia | Haemoglobin <8 g/dl or <7 g/dl for infants aged > 5 months. A haemoglobin concentration more than three standard deviations below the mean of similarly aged infants from a reference population not exposed to malaria in the United States52 |
| Weight for age (WAZ), length/height-for-age (LAZ / HAZ), weight-for length/height (WLZ / WFH), MUAC and head circumference | Infant growth | Weight and height gain defined as the age and sex standardized weight-for-age (WAZ), length- or height-for-age (LAZ/HAZ), weight-for length or height (WLZ/WHZ), arm (MUAC) and head circumference-for-age Z scores of the WHO Child Growth Standards (WHO Multicentre Growth Reference Study Group)53 |
| Underweight | Infant growth | Low weight for age: Moderate: Z-score <2SD from reference population; Severe: Z-score <3SD from WHO reference population |
| Stunted | Infant growth | Low length/height for age: Moderate: Z-score <2SD from reference population; Severe: Z-score <3SD from WHO reference population |
| Wasted | Infant growth | Low weight for length/height: Moderate: Z-score <2SD from reference population; Severe: Z-score <3SD from WHO reference population |
| MUAC | Infant growth | Low arm-circumference: Moderate: Z-score <2SD from reference population; Severe: Z-score <3SD from WHO reference population |
| Head circumference | Infant growth | Low head-circumference: Moderate: Z-score <2SD from reference population; Severe: Z-score <3SD from WHO reference population |
| ***Exploratory outcomes*** | |  |
| Early neonatal mortality | Mortality | Neonatal death during the first 7 days |
| Neonatal mortality | Mortality | Neonatal death during the first 28 days of life |
| Post-neonatal mortality | Mortality | Death during the first year excluding the first 28 days of life |
| Infant mortality | Mortality | Death of a child during the first year of life |
| Post-infant mortality | Mortality | Death of a child after the first year of life |
| Under-five mortality | Mortality | Death of a child during the first five years of life |
| Cord haemoglobin | Hb/anaemia | Haemoglobin in gr/dL measured in the cord blood |
| Fetal anaemia | Hb/anaemia | Cord blood Hb <12.5 g /dL |
| Cord blood malaria infection | Malaria | Malaria detected by any test measured in the cord blood |
| Neuro-cognitive development | development | Any neurocognitive test that may have been conducted during the follow up (e.g scales for evaluation of cognitive or motor function such as Mullen Scales of Early Learning) |

## Risk of bias in individual studies

Quality assessment will be conducted by two persons; where disagreement occurs, these two persons will review the study together to come to an agreement. We will consider all studies as cohorts, and assess the following components with potential for bias, using an adaptation of the Newcastle Ottawa scale:54 inclusion criteria described and adequate, exposed and non-exposed from the same population, measurement of important confounders available (maternal age, gravidity, rural versus urban residence, HIV infection, and malaria treatment or prevention), clearly described measurement of malaria microscopy, PCR, RDT, LAMP, birthweight, gestational age, infant anthropometry if applicable, and haemoglobin, availability of exposure and outcomes compared to number enrolled (if <75%, higher risk of bias), and assessment of outcome (independent and blind as lower risk). Large multi-country studies will be evaluated by country. Studies will be defined as a lower risk of bias if all or all-but-one eligible items were determined to be at a lower risk of bias. Additionally, enrolment by treatment arm over time will be checked for trials taking part in the IPD to confirm the randomization procedures. The quality score will be used as a covariate as part of sensitivity analyses. Studies will not *a-priori* be excluded based on their quality score.

## Data synthesis

***Study characteristics***

A flow chart will be developed showing studies identified, excluded and included as per PRISMA guidelines (http://www.prisma-statement.org/Extensions/IndividualPatientData.aspx). For studies included in the IPD meta-analysis, the characteristics will be extracted in a spreadsheet. These include the main publication, study country and location, study period, design, inclusion and exclusion criteria, study arms if trial, type of data available (mother: time point and exposure, infant: time point and outcomes), type of tests results available and methods, and other publication from the same study. The variables available for each study will be listed and summarised.

**Analyses**

The analysis will be conducted in Stata or R. We will compare the outcomes of interest in the infants among mothers with and without the exposures. Exposure will be defined as in Table 1: definitions of exposure and outcomes. For the analyses, different approaches will be used, and these will be prespecified in the analysis plan before the start of the analysis. For studies with only a single time point at infant follow up, we will use prevalence ratios. For studies with multiple infant follow up visits, time to the first event or repeated events over time will be used.

For models with binary outcomes (malaria, anaemia, fever), statistical models which will be considered include Cox regression (with shared frailty) for time to event (or parametric survival models if proportional hazards assumption is not met), xtlogit, xtreg, xtgee and melogit. For incidence rate ratio we will use Poisson models (or negative binomial models when appropriate) or Hazard ratio models for repeated events. For models for continuous outcomes, xtreg, xtgee, and mixed models will be considered and fractional polynomial regression models will be explored to study non-linear changes over time. We may explore patterns, e.g. for growth and haemoglobin using fractional polynomials and growth curves. We will use a one-stage approach, using univariate and multivariate analysis when adjusted for covariates. We will evaluate the standard deviation of the random effect as the measure of heterogeneity in mixed-level models.

***Adjusted analysis***

The co-variates examined in each analysis will differ by outcome examined and depend on availability, but will include maternal age, gravidity, season, setting (urban vs. rural), maternal HIV infection, infant HIV infection if available, use of malaria prevention (ITNs, IPTp or other regimen, IRS) by the mother and infant, use of haematinics by the infant, use of antimalarials by the infant, and type of malaria test (mother and infant). For infant growth, information on maternal anthropometry will be used if available.

***Sub-group analysis***

Subgroup analyses will be conducted by region (Africa vs. other regions), for time of infection during pregnancy, maternal density of infection, maternal HIV status, gravidity, level of malaria transmission, use of malaria prevention by mother or by the infant, and infant sex.

***Missing data***

There are different types of missing data: 1) the variable may not have been collected; 2) the variable was collected but incomplete; 3) the variable was collected but not included in the dataset. In the last case, we will contact the original authors of the study to obtain the relevant missing data.

If a covariable was collected but incomplete, missing baseline covariates will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions. For a continuous variable, missing values will be imputed from random values from a normal distribution with mean and SD calculated from the available sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities *P*1, *P*2, …, and *P*k from the sample. The seed for the imputation is set as 128.

Missing outcomes or exposure data will not be imputed.

***Sensitivity analyses***

To assess the robustness of the results, we will conduct several sensitivity analyses, including:

* Inclusion of study quality variable and study design (cohort, trial), or different malaria tests where applicable
* Imputation of partially missing data
* Include aggregated data if possible
* For binary non-repeated outcomes, we will use a two-stage approach whereby each estimate is optimally adjusted using the co-variates available by study and compare this with the results of the one-stage analysis

## Meta-bias

Some studies or outcomes may be more likely to be reported in publications than others, e.g. because they showed specific (significant) associations in either direction or because of the perceived importance of specific finding by the authors (publication bias across studies, selective reporting within studies). We will assess which outcomes have been more frequently reported than others to assess for potential sources of meta-bias. Also, we will verify trial registries for completion of study reporting. Lastly, we will minimise reporting bias by asking authors to provide a complete set of outcomes where available.

## Confidence in cumulative evidence

In the absence of a grading system comparable to GRADE, the system used for meta-analyses of trials, we will describe the strength of the body of evidence across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate.

## Ethics and dissemination

All individual studies have ethical approval from relevant local ethics committees and results are or will be available in one or more publications. Interim and final IPD results will be presented to the working group participants prior to publication and public dissemination for review. Results of the study will be published in peer-reviewed journals and presented at national and international conferences, whereby all members of the working group will be listed in slides or in the publication.

## References

1 Walker, P. G., Floyd, J., ter, K. F. & Cairns, M. Estimated impact on birth weight of scaling up intermittent preventive treatment of malaria in pregnancy given sulphadoxine-pyrimethamine resistance in Africa: A mathematical model. *PLoS Medicine* **14**, e1002243 (2017).

2 Moore, K. A., Simpson, J. A., Scoullar, M. J. L., McGready, R. & Fowkes, F. J. I. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. *Lancet Global Health* **5**, e1101-e1112 (2017).

3 Radeva-Petrova, D., Kayentao, K., ter Kuile, F. O., Sinclair, D. & Garner, P. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. *Cochrane. Database for Systematic Reviews* **10**, CD000169 (2014).

4 Harrington, W. E., Kakuru, A. & Jagannathan, P. Malaria in pregnancy shapes the development of fetal and infant immunity. *Parasite immunology*, e12573 (2018).

5 Yeo, K. T. *et al.* HIV, Cytomegalovirus, and Malaria Infections during Pregnancy Lead to Inflammation and Shifts in Memory B Cell Subsets in Kenyan Neonates. *Journal of Immunology* **202**, 1465-1478 (2019).

6 Brabin, B. An analysis of malaria parasite rates in infants: 40 years after macdonald. *Tropical Diseases Bulletin* **87**, R1-R21 (1990).

7 Amaratunga, C. *et al.* A role for fetal hemoglobin and maternal immune IgG in infant resistance to *Plasmodium falciparum* malaria. *PLoS ONE* **6**, e14798 (2011).

8 Hviid, L. & Staalsoe, T. Malaria immunity in infants: a special case of a general phenomenon? *Trends in Parasitology* **20**, 66-72 (2004).

9 Malhotra, I. *et al.* Can prenatal malaria exposure produce an immune tolerant phenotype? A prospective birth cohort study in Kenya. *PLoS Medicine* **6**, e1000116 (2009).

10 Wilson, P. T., Malhotra, I., Mungai, P., King, C. L. & Dent, A. E. Transplacentally transferred functional antibodies against *Plasmodium falciparum* decrease with age. *Acta Tropica* **128**, 149-153 (2013).

11 Gbedande, K. *et al.* Malaria modifies neonatal and early-life toll-like receptor cytokine responses. *Infection and Immunity* **81**, 2686-2696 (2013).

12 Le Hesran, J. Y. *et al.* Maternal placental infection with *Plasmodium falciparum* and malaria morbidity during the first 2 years of life. *American Journal of Epidemiology* **146**, 826-831 (1997).

13 Haghdoost, A. A., Alexander, N. & Smith, T. Maternal malaria during pregnancy and infant mortality rate: Critical literature review and a new analytical approach. *Journal of Vector Borne Diseases* **44**, 98-104 (2007).

14 Schwarz, N. G. *et al.* Placental malaria increases malaria risk in the first 30 months of life. *Clinical Infectious Diseases* **47**, 1017-1025 (2008).

15 Mutabingwa, T. K. *et al.* Maternal malaria and gravidity interact to modify infant susceptibility to malaria. *PLoS Medicine* **2**, e407 (2005).

16 Borgella, S. *et al.* Impact of pregnancy-associated malaria on infant malaria infection in southern benin. *PLoS ONE* **8**, e80624 (2013).

17 Bardaji, A. *et al.* Impact of malaria at the end of pregnancy on infant mortality and morbidity. *The Journal of infectious diseases* **203**, 691-699 (2011).

18 Sylvester, B. *et al.* Prenatal exposure to *Plasmodium falciparum* increases frequency and shortens time from birth to first clinical malaria episodes during the first two years of life: prospective birth cohort study. *Malaria Journal* **15**, 379 (2016).

19 Boudova, S. *et al.* Placental but not peripheral Plasmodium falciparum infection during pregnancy is associated with increased risk of malaria in infancy. *The Journal of infectious diseases* **216**, 732-735 (2017).

20 Le Port, A. *et al.* Importance of adequate local spatiotemporal transmission measures in malaria cohort studies: application to the relation between placental malaria and first malaria infection in infants. *American Journal of Epidemiology* **178**, 136-143 (2013).

21 Asante, K. P. *et al.* Placental malaria and the risk of malaria in infants in a high malaria transmission area in Ghana: a prospective cohort study. *The Journal of infectious diseases* **208**, 1504-1513 (2013).

22 Apinjoh, T. O. *et al.* Determinants of infant susceptibility to malaria during the first year of life in South Western Cameroon. *Open Forum Infectious Diseases* **2** (2015).

23 Awine, T. *et al.* The risk of malaria in Ghanaian infants born to women managed in pregnancy with intermittent screening and treatment for malaria or intermittent preventive treatment with sulfadoxine/pyrimethamine. *Malaria Journal* **15**, 46 (2016).

24 Agbota, G. *et al.* Increased risk of malaria during the first year of life in small-birth-weight-for-gestational age infants: a longitudinal study in Benin. *The Journal of infectious diseases* (2018).

25 Kakuru, A. *et al.* Infant sex modifies associations between placental malaria and risk of malaria in infancy. *Malar J* **19**, 449 (2020).

26 Kakuru, A., Staedke, S. G., Dorsey, G., Rogerson, S. & Chandramohan, D. Impact of Plasmodium falciparum malaria and intermittent preventive treatment of malaria in pregnancy on the risk of malaria in infants: a systematic review. *Malar J* **18**, 304 (2019).

27 Kakuru, A. *et al.* Impact of intermittent preventive treatment of malaria in pregnancy with dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine on the incidence of malaria in infancy: a randomized controlled trial. *BMC Med* **18**, 207 (2020).

28 De Beaudrap, P. *et al.* Timing of malaria in pregnancy and impact on infant growth and morbidity: a cohort study in Uganda. *Malaria Journal* **15**, 92 (2016).

29 Rachas, A. *et al.* Placental malaria is associated with increased risk of nonmalaria infection during the first 18 months of life in a Beninese population. *Clinical Infectious Diseases* **55**, 672-678 (2012).

30 Agbota, G. C. *et al.* in *67th ASTMH Annual Meeting, New Orleans, USA.* 235-235 (American Journal of Tropical Medicine and Hygiene).

31 Redd, S. C., Wirima, J. J. & Steketee, R. W. Risk factors for anemia in young children in rural Malawi. *American Journal of Tropical Medicine and Hygiene* **51**, 170-174 (1994).

32 Cornet, M. *et al.* Prevalence of and risk factors for anemia in young children in southern Cameroon. *American Journal of Tropical Medicine and Hygiene* **58**, 606-611 (1998).

33 van Eijk, A. M. *et al.* Malaria and human immunodeficiency virus infection as risk factors for anemia in infants in Kisumu, western Kenya. *American Journal of Tropical Medicine and Hygiene* **67**, 44-53 (2002).

34 van Rheenen, P., de Moor, L., Eschbach, S., de Grooth, H. & Brabin, B. Delayed cord clamping and haemoglobin levels in infancy: a randomised controlled trial in term babies. *Tropical Medicine and International Health* **12**, 603-616 (2007).

35 Koura, K. G. *et al.* Maternal anaemia at delivery and haemoglobin evolution in children during their first 18 months of life using latent class analysis. *PLoS ONE* **7**, e50136 (2012).

36 Accrombessi, M. *et al.* Malaria in pregnancy is a predictor of infant haemoglobin concentrations during the first year of life in Benin, West Africa. *PLoS ONE* **10**, e0129510 (2015).

37 Kaali, S. & The Kintampo Birth Cohort Study team members. in *67th Annual Meeting of the ASTMH, New Orleans, USA.* 103 (American Journal of Tropical Medicine and Hygiene).

38 McElroy, P. D. *et al.* Analysis of repeated hemoglobin measures in full-term, normal birth weight Kenyan children between birth and four years of age. III. The Asemobo Bay Cohort Project. *American Journal of Tropical Medicine and Hygiene* **61**, 932-940 (1999).

39 Kalanda, B. F., Van Buuren, S., Verhoeff, F. H. & Brabin, B. Anthropometry of fetal growth in rural Malawi in relation to maternal malaria and HIV status. *Archives of Disease in Childhood. Fetal and Neonatal Edition* **90**, F161-F165 (2005).

40 Ayoola, O. O., Omotade, O. O., Gemmell, I., Clayton, P. E. & Cruickshank, J. K. The impact of malaria in pregnancy on changes in blood pressure in children during their first year of life. *Hypertension* **63**, 167-172 (2013).

41 Walther, B. *et al.* Placental malaria is associated with reduced early life weight development of affected children independent of low birth weight. *Malaria Journal* **9**, 16 (2010).

42 Boudova, S. *et al.* in *67th Annual Meeting of the ASTMH, New Orleans, USA.* 97-98 (American Journal of Tropical Medicine and Hygiene).

43 Riley, R. D., Lambert, P. C. & Abo-Zaid, G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* **340**, c221 (2010).

44 van Eijk, A. M. *et al.* The Malaria in Pregnancy Library: a bibliometric review. *Malar J* **11**, 362 (2012).

45 van Eijk, A. M. *et al.* Risk factors for malaria in pregnancy in an urban and peri-urban population in western Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **96**, 586-592 (2002).

46 Kayentao, K. *et al.* Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA* **309**, 594-604 (2013).

47 Gamble, C., Ekwaru, P. J., Garner, P. & ter Kuile, F. O. Insecticide-treated nets for the prevention of malaria in pregnancy: A systematic review of randomised controlled trials. *PLoS Medicine* **4**, e107 (2007).

48 Roh, M. *et al.* in *ASTMH 66th Annual Meeting, November 5-9, 2017, Baltimore, Maryland USA.* (2017).

49 Dewey, K. G. & Oaks, B. M. U-shaped curve for risk associated with maternal hemoglobin, iron status, or iron supplementation. *Am J Clin Nutr* **106**, 1694S-1702S (2017).

50 van Eijk, A. M. *et al.* Human immunodeficiency virus seropositivity and malaria as risk factors for third-trimester anemia in asymptomatic pregnant women in western Kenya. *American Journal of Tropical Medicine and Hygiene* **65**, 623-630 (2001).

51 Bhatt, S. *et al.* Coverage and system efficiencies of insecticide-treated nets in Africa from 2000 to 2017. *Elife* **4** (2015).

52 *Nathan and Oski's hematology and oncology of infancy and childhood (Eight edition)*. (Elsevier/Saunders, 2015).

53 WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* **450**, 76-85 (2006).

54 Hartling, L. *et al.* Testing the Newcastle Ottawa Scale showed low reliability between individual reviewers. *J Clin Epidemiol* **66**, 982-993 (2013).

## Supplement 1: Variables of interest

|  |  |
| --- | --- |
| ***Pregnancy or enrolment*** | ***Delivery (cont’d)*** |
| maternal ID | Peripheral malaria by PCR |
| Country of study | Peripheral species by PCR |
| Date of malaria test | Peripheral malaria by RDT |
| Malaria by microscopy | Peripheral species by RDT |
| Species by microscopy | Placental malaria by microscopy |
| Count by microscopy | Placental species by microscopy |
| Malaria by PCR | Placental count by microscopy |
| Species by PCR | Placental malaria by PCR |
| Malaria by RDT | Placental species by PCR |
| Species by RDT | Placental malaria by RDT |
| LAMP | Placental species by RDT |
| Gravidity | Placental histology |
| Age | Cord malaria (test type and result) |
| Fever (documented fever or history of fever) | Cord haemoglobin |
| History of recent antimalarial treatment | Maternal haemoglobin |
| Gestational age | Maternal haemoglobin test |
| How gestational age was measured | Gravidity |
| Net use (during pregnancy or last night) | Age |
| ITN use | Fever (documented fever or history of fever) |
| Treatment arm if part of a trial  IPTp use, number of doses | History of recent antimalarial treatment |
| Hemoglobin (and type of test) | bednet use |
| HIV status | ITN use |
| Residence (rural/periurban/urban) | Singleton |
| Maternal height/weight/MUAC if available | Birth outcome (stillbirth, live birth) |
| **For each data point in pregnancy** | Birthweight and other newborn anthropometrics where available (length, head circumference, chest or abdominal circumference) |
| Date of visit | Newborn id |
| Scheduled or unscheduled visit | Newborn sex |
| gestational age | Gestational age at delivery |
| How gestational age was measured | Method of assessment of gestational age |
| fever (history) | Maternal HIV-status |
| Body temperature (and how measured) | Smoker |
| Haemoglobin | IRS |
| Use of malaria prevention (ITN, IPTp other) | Iron and folate supplementation |
|  | Residence (rural/periurban/urban) |
| ***Delivery*** | Number of ANC visits |
| ID | Maternal height/weight if available |
| Date of delivery | **Optional** |
| Peripheral malaria by microscopy | Test results of other diseases (date, and test result) |
| Peripheral species by microscopy |  |
| Peripheral count by microscopy |  |

|  |  |
| --- | --- |
| ***Infant data elements*** |  |
| **Infant follow up visits** | ***Infant follow up continued*** |
| Date of visit | Malaria by microscopy |
| Scheduled or unscheduled visit | Species by microscopy |
| age in months | Count by microscopy |
| fever (history) | Malaria by PCR |
| Body temperature (and how measured) | Species by PCR |
| Haemoglobin | Malaria by RDT |
| Haemoglobin test | Species by RDT |
| Infant anthropometry (height, weight, MUAC, head circumference) | LAMP |
| Infant HIV-status (if known) | Infant/child death |
| Use of malaria prevention | Date of child death |
| ITN use and definition of use | Reason of study departure |
| IRS use and definition of use | **Optional** |
| Recent malaria treatment | Test results of other diseases (date, and test result) |
| Trial arm (where applicable) | Other complaints at infant visit (vomiting, cough, diarrhea) |

|  |  |
| --- | --- |
| ***Other definitions*** |  |
| Infant | Child in the first 12 months of life |
| Maternal anaemia | Haemoglobin (Hb) < 11 g/dl |
| Infant documented fever | A measured axillary body temperature or an equivalent measurement (e.g. ear or front of the head) of ≥37.5°C (for measurements of other body parts adjustments to the lower cut-off value may be made) |
| Low birth weight | <2500 grams at birth |
| Prematurity  Small for gestational age at birth | < 37 weeks of gestation at delivery |