Systematic review of statistical methods for safety data in malaria chemoprevention in pregnancy trials

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Abstract

Background

Drug safety assessments in clinical trials present unique analytical challenges. Some of these include adjusting for individual follow-up time, repeated measurements of multiple outcomes and missing data among others. Furthermore, pre-specifying appropriate analysis becomes difficult as some safety endpoints are unexpected. Although existing guidelines such as CONSORT encourage thorough reporting of adverse events (AEs) in clinical trials, they provide limited details for safety data analysis. The limited guidelines may influence suboptimal analysis by failing to account for some analysis challenges above. A typical example where such challenges exist are trials of antimalarial drugs for malaria prevention during pregnancy. Lack of proper standardized evaluation of the safety of antimalarial drugs has limited the ability to draw conclusions about safety. We have therefore conducted a systematic review to establish the current practice in statistical analysis for antimalarial drug safety in pregnancy.

Methods We searched PubMed, Embase, Scopus, Malaria in Pregnancy Library and Cochrane Central Register of Controlled Trials for original English articles reporting Phase III (randomized controlled trials) RCTs on antimalarial drugs for malaria prevention in pregnancy published from January 2010 to July 2019.

Results

Eighteen trials were included in this review that collected multiple longitudinal safety outcomes including AEs. Statistical analysis and reporting of the safety outcomes in all the trials used descriptive statistics; proportions/counts (n=18, 100%) and mean/median (n=2, 11.1%). Results presentation included tabular (n=16, 88.9%) and text description (n=2, 11.1%). Univariate inferential methods were reported in most trials (n=16, 88.9%); including Chi-square/Fisher`s exact test (n=12, 66.7%), t-test (n=2, 11.1%) and Mann-Whitney/Wilcoxon test (n=1, 5.6%). Multivariable methods, including Poisson and negative binomial were reported in few trials (n=4, 22.2%). Assessment of a potential link between missing efficacy data and safety outcomes was not reported in any of the trials that reported efficacy missing data (n=7, 38.9%).

Conclusion

The review demonstrated that statistical analysis of safety data in antimalarial drugs for malarial chemoprevention in pregnancy RCTs are inadequate. The analysis insufficiently account for multiple safety outcomes potential dependence, follow-up time and informative missing data which can compromise antimalarial drug safety evidence development, based on the available data.

Introduction

Drug safety assessment in randomized controlled trials (RCTs) is integral in development of comprehensive drug safety profile. Recently, there is enhanced quality on clinical trial reporting of safety outcomes through adherence to the Consolidated Standards of Reporting Trials (CONSORT) guideline (1, 2). However, there is scanty literature on standardized way to statistically analyse the safety outcomes in clinical trials. Although there exists some general regulatory guidelines on safety data analysis, such as International Conference on Harmonization that recommends descriptive statistical methods supplemented by confidence intervals (3), the

proposed statistical methods rarely account for complexity of the collected safety data e.g. recurrent adverse events. Effective solutions to statistical analysis of safety data in clinical trials may need to be tailored to specific indications (set of diseases with similar characteristics) under study since safety data collected is also influenced by the medical condition under study. Absence of standardized guidelines for safety data analysis in specific settings may limit the ability to draw rich conclusions about the safety of the investigational product, based on collected data. Standardized guidelines can simplify integration of safety information from multiple outcomes across RCTs (4) and would ensure optimal use of data in developing safety profile of the investigational product.

Statistical analysis of safety data in clinical trials is characterized by a challenge of multiple and related endpoints measured over time. The safety endpoints may include clinical and laboratory defined AEs. Laboratory based AEs are defined based on standard cut-off points for measures such as vital signs (e.g. body temperature) hepa-toxicity measures (e.g. bilirubin level), cardio-toxicity measures (e.g. electrocardiograms) and other tests relevant to the medical indication being studied (4). The safety endpoints may be correlated within patients and over time such that failure to account for this in an analysis may yield biased estimates and false inference. Furthermore, time to occurrence of the safety endpoint may be very informative in profiling the drug safety. Such data presents statistical analysis and interpretation challenges due to the complexity in structure(5). For instance, in case of multiple repeatedly measured safety outcomes, false positives may arise from multiple statistical testing if appropriate longitudinal or time to event methods and/or multiplicity adjustments are not considered.

In clinical trials, AEs may impact compliance and study participation which may further affect treatment efficacy estimates (6, 7). Occurrence of (even mild) AEs due to a drug would lead to non-adherence, leading to informative censoring. The dropping of the patients from the study generates missing data that may lead to biased results if poorly accounted for. Therefore, safety data analysis accounting for missing data is useful to facilitate identification and characterization of the safety profile of the drug as early as possible. Other analysis challenges include lack of adequate ascertainment and classification of adverse events, limited generalizability of results (8) since some AEs cannot be pre-specified at study design stage.

There are many populations where drug safety assessment is complex. One of the special settings in safety data assessment is the use of drugs to prevent adverse outcomes in pregnancy, currently referred to as intermittent preventive treatment of malaria in pregnancy (IPTp). For example, the World Health Organization recommends that pregnant women receive routine treatment with antimalarial drugs to clear any malaria infection that is present and also to prevent infection in the weeks after administration (9). Unfortunately, recent review indicates that methodological issues, in studying antimalarial drugs in pregnancy, have prevented firm conclusions on the safety of new antimalarial drugs in pregnancy (10). Previous efforts have attempted to standardize safety assessment methodology for antimalarial drug trials in pregnancy including study designs and data collection (11, 12). However, literature remains limited in describing the standard practice in the statistical analysis of safety data that are collected on antimalarial drugs during pregnancy trials.

The current review focusses on safety assessment in antimalarial drugs for chemoprevention in pregnancy trials. Since antimalarial drug for malaria chemoprevention is given repeatedly to healthy pregnant women, it is critical to improve safety assessment in this vulnerable population. Specifically, appropriate statistical analysis of safety outcomes can improve development of antimalarial drug safety profile. This can be achieved through

sufficient use of the data generated during the RCT which provides a comprehensive drug safety insight. This review therefore aims at identifying statistical methods used in the analysis of safety data in antimalarial drugs for prevention used in treatment clinical trials in pregnancy and their appropriateness.

Methods

The systematic review was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (13) which outlines minimum standards for reporting systematic reviews and meta-analysis. The protocol for this review was registered and published with PROSPERO (CRD42019120916). The study population is pregnant women on any antimalarial drug for malaria chemoprevention.

Search Strategy

Inclusion criteria

Primary original articles published in English from Phase III RCTs were considered for inclusion. The articles were from RCTs assessing the efficacy and safety of malaria chemoprevention in pregnancy. We focussed on Phase III RCTs, since they have the largest sample size among premarketing trials and accommodates multidisciplinary support in safety evaluation. Further, the data is also systematically collected and they have the benefit of being randomized, which aids a fair comparison of treatment groups.

Exclusion criteria

Observational studies, case reports, letters to the editor, narrative reviews, systematic reviews and trials in Phase I or Phase II or Phase IV were excluded from this review. Non-English publications were excluded since we had no resources for interpretation.

Selection of studies

Studies published between 1st January 2010 and 31st July, 2019 were searched from five databases (PubMed, Embase, Scopus, Malaria in Pregnancy Libray (MiPL) and Cochrane Central Register of Controlled Trials (CENTRAL). The MiPL is an excellent scholarly source of articles on Malaria in Pregnancy that enabled us to capture both indexed and non-indexed articles beyond the searched databases. Additionally, we searched reference lists of the identified trials and relevant reviews to identify trials potentially missed in the databases search. The year 2010 was selected since it is when CONSORT guideline updated and emphasized on appropriate statistical analysis and reporting of clinical trials (14). Conference proceedings were not included because they usually contain abstracts that do not give detailed analysis of the presented results and they are not rigorously peer-reviewed. We did not reach out to experts who may have unpublished studies because the review focussed on published studies only. The key search items included; *malaria, antimalarial drug, pregnancy, efficacy safety or tolerability.* The detailed search strategy is presented in Table S1. The search was customized per database. Based on PRISMA procedure, after removing duplicates, two reviewers (NP and ANK) independently screened titles and abstracts initially before arriving at a final list of eligible articles. Based on the

eligible studies list, full text articles were retrieved studies. The references were managed using Endnote X7.1 (Thomson Reuters). If there were disagreements, the two reviewers discussed the paper to reach a consensus and reasons for exclusion were provided for ineligible publications/studies

Data Extraction

The data extraction file was created in Microsoft Excel was used to record all key variables from the selected articles. Some of the collected variables such as mode of safety data collection, participants' withdrawal due to AE and handling of continuous measures were based on CONSORT guideline. The following key variables were extracted from the papers: main author, publication date, study design, study location, main efficacy outcome, sample size, list of safety parameters collected (including laboratory data), nature of safety data collection (i.e. passive or active), list of statistical methods used for respective safety outcomes, how the results were presented, retention rate at the end of the follow up and how missing safety or efficacy data was handled. The primary hypothesis type (as superiority, non-inferiority or equivalence) was defined based on what was reported in the actual manuscript or inferred by NP based on how the study framed the primary hypothesis. Superiority hypotheses aim to show whether treatment is better than control, non-inferiority hypotheses intend to show that one treatment is not worse than the other and equivalence hypotheses intend to show that a given treatment is similar to another for defined characteristics (15). The statistical methods were classified as descriptive or inferential and univariate or multivariate depending on the purpose and nature of the statistical methods based on previous similar reviews (16, 17), reviewing statistical methods.

Data Synthesis

The extracted quantitative data was reported as percentages in tables. The commonly reported safety parameters, suitability of the used statistical methods and other findings were also summarized narratively.

Results

The search identified 1103 articles. After removing duplicates, 722 unique articles were identified and considered for possible inclusion in the review. The duplicates (i.e. repeated citations) were the same articles but identified in multiple search databases. Figure 1 presents details of the selection process. During screening, a total of 637 articles were excluded based on relevance of their titles and abstracts. The remaining 85 full text articles were assessed for possible inclusion and 18 articles satisfied the inclusion criteria, hence they are included in this review as shown in Table 1. Reasons for exclusion are shown in Figure 1.

Characteristics of the trials

The trials included reviewed were conducted in Oceania (2 trials, 11.1%) and Sub-Saharan Africa (16 trials, 88.9%) regions. The 18 RCTs reviewed recruited 26,281 pregnant women with a median sample size of 374 (Interquartile range (IQR): 173, 648) women per treatment arm in a trial. Thirteen trials (72.2%) recruited more than 200 patients per arm. As expected, all trials (18 trials, 100%) computed sample size based on the efficacy outcome(s). The majority of the trials (11 trials, 65.4%) had two treatment arms and the rest had three treatment

arms. All 18 trials had an active comparator and IPTp-SP was studied as a standard malaria chemoprevention in the majority of trials (14 trials, 77.8%). Although we focussed on published trials from 2010 to 2019, the trials were conducted between 2003 and 2017. Based on the primary hypothesis tested, superiority design RCTs were the most common (15 trials, 83.3 %) and the other trials had a non-inferiority hypothesis. Over half of the trials (10 trials, 55.6%) were open-label; one trial did not state the blinding status but the other seven trials (38.9%) were blinded. Majority of the trials (14 trials, 77.9%) reported that they had a Data Safety and Monitoring Board (DSMB).

Characteristics of the reported safety data

Over half of the trials (10 trials, 55.6%) reported that they collected safety data using a combination of scheduled and non-scheduled visits (Table 2), while a third of the trials (6 trials, 33.3%) did not specify the safety data collection approach used. The median retention rate (based on the main efficacy outcome) was 89.4% (IQR: 82.5%, 92.4%) and 10 trials (55.6%) had a retention rate below 90%.

All the reviewed trials indicated that they had collected multiple longitudinal safety endpoints. As expected, almost all the trials (17 trials, 94.4%) reported obstetric safety outcomes such as foetal loss. Table S2 and S3 in the additional file provides a detailed list of safety outcomes reported in each reviewed trial. Despite the reported occurrence of multiple AEs, none of trials seemingly reported recurrence of AEs during pregnancy. In total, 12 trials (66.7%) reported adverse events with different severity levels e.g. mild, moderate and severe. All trials reported occurrence of AEs by treatment arm. Almost all trials (17 trials, 94.4%%) reported laboratory data in their safety assessment of the drug and 16 trials of these (88.9) dichotomized at least a single continuous safety outcome (e.g. haemoglobin) based on standard cut-off points, to define an AE.

Statistical analysis for safety data analysis

Analysis population and missing data

The safety analysis approach (based on treatment allocation and adherence) was specified and reported in 11 trials (61.1%). Per protocol (PP) and intention to treat (ITT) analysis approaches were used in five trials (27.7%) and four trials (22.2%) respectively. Two trials indicated that they used both PP and ITT to analyse the safety data. Although all the reviewed trials had at least one patient lost to follow-up, only seven trials (38.9%) reported missing efficacy data and two of the seven trials indicated that the missingness was ignorable after exploring data missingness patterns (Table 3). None of the reviewed trials conducted an advanced sensitivity analysis on the relationship between missing data and drug safety. For example, none of the studies assessed the safety outcomes (e.g. adverse events) in relation to missing efficacy outcomes. This review found that most trials (16 trials, 88.9%) had at least one participant who experienced an AE leading to discontinuation from the trial although the studies did not formally investigate/quantify the relationship between the AEs and trial completion.

Reported statistical methods

All the trials included reviewed used descriptive statistics as one of the methods to summarize adverse events (Table 3). Proportions or counts were the descriptive statistics used in all of the studies to report safety data. Incidences were reported in six trials (33.3%). Most trials (16 trials, 88.9%) reported univariate inferential statistical methods; these included Chi-square or Fisher`s exact test (12 trials, 66.7%), t-test (n=4, 22.2%). Only three trials reported multivariate statistical methods. The multivariable methods were Poisson regression (n=3, 16.7 %), and negative binomial regression (n=1, 5.6%). Usage of at least two inferential statistical methods to compare safety outcomes was reported in five trials (27.8%). Although all studies reported multiple safety outcomes, none reported adjustment for multiplicity during analysis.

The review showed that at least a single optimal statistical methods was reported in three trials (16.7%) that considered multivariable modelling. The statistical methods reported in the rest of the trials were suboptimal for the type of data being collected. For further details, additional file under Tables S2 and S3 provide a detailed list of reported statistical methods with their respective safety outcome(s).

Presentation of safety outcomes estimates

In terms of presentation of results, none of the trials presented adverse events in a graph. Only two trials (11.1%) narratively presented the safety results; the other 16 trials (88.9%) presented the results in tabular format. A total of 14 trials reported p-values after comparing treatments and there were only 10 trials (55.6%) that reported point estimates with their respective confidence intervals

Discussion

This review sought to provide a detailed overview of the actual practice of the statistical analysis of safety data in the unique setting of drug trials for the preventions of malaria in pregnancy as reflected published literature. Our work has shown that there is limited reporting of statistical analyses of safety data, at the end of the trial, in these published reports. Our findings are useful to advance the development of standardized guidelines for safety data statistical analysis in analysis in antimalarial drugs in pregnancy trials and related fields. Such guidelines will not replace but rather complement the CONSORT guidelines that are general (i.e. not providing specific statistical methods in analysing harms in RCTs). To our knowledge, this is the first paper to review statistical methods for safety data in antimalarial drugs in pregnancy.

Descriptive methods were commonly used to summarize safety data. Our review found that each clinical trial used at least one descriptive method to summarize safety data. Univariate statistical methods such as Chi-square or Fishers exact tests were used in two thirds of the articles reviewed. Such descriptive statistics and univariate statistical inference ignored useful information such as variability in follow-up time, missing data and correlation (for those trials which had their multiple safety outcomes repeatedly measured). Hence there was inefficient data use during analysis that may lead to a loss of useful information for improved and informative conclusions. Although a third of the reviewed trials attempted to use crude incidence, they failed to adequately account for individual patient follow-up-time and potential confounders.

All trials dichotomized at least a single continuous clinical laboratory safety outcome (i.e. where AE was defined based on standard cut-off points for adult toxicity). Although this aids in providing time-specific drug safety status and easy interpretation, the dichotomized outcome may miss some information on the magnitude of the

temporal changes, overtime during the trial. The information loss may lead to reduction in statistical power to detect safety signal if it exists. Valid longitudinal methods (used without restriction on cut-off points) can address the information loss by exploiting potential within-subject correlations for the repeated clinical laboratory measurements. (18–20). Furthermore, the longitudinal methods can provide the basis for developing improved cut-off points tailored to pregnant women in malaria-specific settings. To ensure improved uptake of such methods, future work needs to strive towards making the results from the longitudinal methods feasibly interpretable to the medical practitioners.

Only three studies appropriately used multivariable statistical methods. Since use of crude methods can lead to false findings, multivariable methods (e.g Poisson regression) help in adjusting for patient characteristics (e.g. confounders such as age). Of specific interest in this review, the Poisson model was more suitable in the context of rare AEs which usually have low event rates (20, 21). Since Poisson regression assumes a constant rate of occurrence of a rare event, it is not ideal for other multiple transient AEs that were common or recurred and would vary in occurrence overtime (22). Alternatively, mixed effects models could be considered to characterize the safety events over time since they capture patient-specific effects (23, 24). Whenever time to AE occurrence information is available, survival analysis models may also be preferred to characterize the time to AE occurrence. For recurrent safety events, that may induce dependence, methods that extend the Cox regression model may be preferred; such models include survival mixed effects models (e.g. frailty models) (25).

Almost half of the reviewed trials did not explicitly define the population on which the safety analysis was based. If per protocol analysis is used to address non-adherence there is potential selection bias since it destroys the balance due to randomization. Although CONSORT recommends ITT, as an alternative, for analysis of safety endpoints, non-adherence cannot be explicitly addressed with ITT approach since it ignores dropouts, withdraw or loss-to-follow up for various reasons including safety concerns; ITT-based inference ignores causal effect of the actual treatment received (26). Patient withdrawal or dropout due to adverse events can induce informative censoring useful in quantifying antimalarial drug safety. For example, if a patient withdraws due to vomiting after taking an antimalarial drug, their obstetric efficacy outcomes such as birth weight may appear as missing data. In the context of antimalarial drug for malaria prevention, even mild AE can lead to drug non-adherence. Since the patient has no disease symptoms, they would judge it less costly for them to discontinue the drug than continue experiencing AEs. Hence, inclusion of information on treatment/trial completion status in relation to antimalarial safety, would enrich development of the safety profile of antimalarial drug in pregnancy. Although study completion status, antimalarial drug safety and missing data may be interlinked, missing data received limited attention such that in the few trials that considered efficacy missing data did not explicitly explore the potential link. Studying such complex associations requires statistical methods that can appropriately estimate the pathway from the antimalarial chemoprevention to study completion. Advantageously, methods based on causal inference framework, such as mediation analysis (27–30) could be adapted/extended to assess the influence of the adverse events on non-adherence in RCTs.

Despite the about three quarters of the trials reporting p-values after comparing safety outcomes by treatment arms, only about half of the reviewed trials adhered to International Harmonisation Conference Guideline E9 in reporting of confidence intervals in quantifying the safety effect size (31). Use of confidence interval aids in interpretation of results by providing a measure of precision. Furthermore, graphical displaying of safety data to aid in summarizing of safety data was inadequate. Graphs on safety data have a greater ability to convey insight about patterns, trends, or anomalies that may signal potential safety issues compared to presentation of

such data in tabular form only(32). For example, the graphs could help to visualize frequency and changes in adverse events over time by treatment arm. The graphs could further help in assessing assumptions for some statistical methods.

Over three-quarters of the reviewed trials were designed as superiority trials based on efficacy outcomes. Although the statistical approach for safety assessment was mainly on superiority hypotheses (for both the superiority and non-superiority trials), clinical and statistical justification of assessing safety based on superiority hypotheses may be invalid. Superiority hypotheses concentrate on the absence of difference in drug safety effect/risk between or across the treatment arms which may be challenging (15). For example, when comparing high AE incidences, non-significant difference (when using a superiority hypothesis) would not necessarily translate to a conclusion that a drug is safe and well-tolerated since sometimes all compared treatment arms may have high AE incidence. Perhaps, drug safety evaluation should strive to prove that there is no risk beyond a protocol-defined/hypothesized priori clinical safety margin (i.e. no excessive safety risk). Based on our findings, we encourage researchers to consider defining safety margins in safety assessment of antimalarial drugs. Since safety is mostly a secondary outcome, it is not straight forward on how to define a non-inferiority margin and the appropriate analysis population. Currently, it is still unclear and debatable how to implement this, such that further research is needed (4).

Interestingly, we observed that over half of the trials were open-label which may influence physician's clinical safety assessment on a patient and patient`s reporting of AEs based on their expectations since they know the treatment assigned. Appropriate reporting of the AEs would be guided by DSMBs right from early stages of the trial. However, availability of DSMBs in over three-quarters of the trials did not translate to improved reporting and analysis. Therefore, it is important for DSMB member to understand improved analysis approaches for AEs since they influence on how safety data is analysed and reported.

This review agrees with other similar publications focusing on drug safety assessment in clinical trials that have noted the need for further improvement in the statistical analysis of the safety data (8, 33). This review concurs with a recent review that has noted that inappropriate handling of multiple test is prevalent, although their review focussed on four high impact journals, AE in general and a short time of review period (34). Issues raised in this review include time-dependence of AEs, informative censoring due to discontinuation of treatment because of AEs, safety graphs, and repeated occurrence of AEs and multivariate longitudinal structure of laboratory data that yields complex correlation. This is an ongoing work whereby further analysis will be explored to address the identified statistical issues above.

The application of the systematic review protocol in gathering the current practice in our context is more reliable since it exhaustively identified the published antimalarial drug clinical trials in pregnancy for studied period. However, our review covered only the last decade of publications and may have missed studies published in other languages or that did not appear in our search. Because the trials reported in the publications spanned for a decade, it was difficult to assess temporal trends. This review represents the most comprehensive review of safety data analysis practice for this important indication.

Conclusion

Although useful safety data is collected in malaria chemoprevention in pregnancy clinical trials, the analysis remains sub-optimal and this hinders definitive conclusions about drug safety in this setting. Descriptive statistical methods and dichotomization of continuous outcomes are predominant which may lead to loss of useful information. The definition of analysis population and informative presentation of results are not standardized. Further work in addressing the highlighted gaps, underway within our team, can enhance drug safety decisions/conclusions.

List Of Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

AE: adverse event

RCT: randomized clinical trial

ECG: electro-cardiograph

ICH: International Conference on Harmonization

IPTp-SP: Intermittent Preventive Treatment of Malaria in Pregnancy using Sulfadoxine-Pyrimethamine

WHO: World Health Organization

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

PROSPERO: Prospective Register of Systematic Reviews

CTX: cotrimoxazle

MiPL: Malaria in Pregnancy Library;

CENTRAL: Cochrane Central Register of Controlled Trials

DSMB: Data Safety and Monitoring Board

PP: Per protocol

ITT: Intention to Treat

Declarations

Availability of data and materials

All data analysed in this paper are provided in the *additional file*.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

NP, MKL and TC conceived the study idea and NP, AK and TB collected, analysed and interpreted the data

NP, MKL and TC led the manuscript writing;

LK, MM, KNO, ANK, VM, MJCE and DPM contributed towards the study design, data interpretation and rigorous manuscript review

All authors read and approved the final manuscript.

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Tables

Table 1: Overview of randomized clinical trials included in the systematic review

uthor, rence)	Study site	DSMB	Hypothesis	Masking	Comparator drug(s)	Experimental drug(s)
amo. (35)	Malawi	Yes	Superiority	Single-blinded	two-dose IPTp-SP	1. AZ-SP 2. Monthly SP
ı) (36)	Burkina Faso	No	Superiority	Not stated	two-dose IPTp	three IPTp-SP
te. (37)	Mali	Yes	Superiority	open-label	two-dose IPTp	three IPTp-SP
mugyenyi l (38)	Uganda	Yes	Superiority	double blinded	1. IPTp-SP 2. ITN+placebo	IPTp-SP+ITN
3 (39)	Solomon Islands	Yes	Superiority	open-label	IPTp-SP	-CQ prophylaxis
eud-ı ł (40)	Benin	Yes	Noninferiority	open-label	1. IPTp-MQ, 2. (IPTp-MQ) and CTX (low CD4)	1. CTX(low CD4) 2. CTX(high CD4)
ález ł (41)	Benin, Gabon, Mozambique, and Tanzania	Yes	Superiority	open-label	IPTp-SP	1. two-dose MQ 2. split-dose MQ
ález ł (42)	Kenya, Mozambique, and Tanzania	Yes	Superiority		CTX and Placebo	CTX and (IPTp-MQ)
ent ł (43)	Togo	Yes	Noninferiority	open-label	IPTp-SP	CTX
ando ł (44)	Zambia	Yes	Noninferiority	open-label	IPTp-SP	CTX
i 5 (45)	Kenya	No	Superiority	open-label	IPTp-SP	1. IPTp-DP 2. IST-DP
er 5 (46)	Papua New Guinea	Yes	Superiority	single blinded	IPTp-AZCQ	one-dose SP-CQ
ru 5 (47)	Uganda	No	Superiority	double blinded	IPTp-SP,	1. IPTp-DP 2. IPTp-IPTp-DP
ni 5 (48)	Benin, Kenya, Malawi, Tanzania, and Uganda	Yes	Superiority	open-label	IPTp-SP	IPTp-AZCQ

reeba 7 (49)	Uganda	No	Superiority	double blinded	TMP-SMX	TMP-SMX+ DP
a 3 (50)	Malawi	Yes	Superiority	open-label	IPTp-SP	1. IPTp-CQ 2. CQ prophylaxis
rotu (51)	Nigeria	No	Superiority	Single-blind	IPTp-SP	IPTp-MQ
ɔi (52)	Uganda	No	Superiority	Double-blind	IPTpSP	IPTpDP

AL: Atermether Lumafentrine, CTX: Cotrimoxazle, Q: Quinine, AS: Atersunate, AQ: Amodiquine, MQ:Mefloquine, CQ: Chloroquine, DP: Dihydroartemisinin-piperaquine, TMP-SMX:Trimethoprim-Sulfamethoxazole, PQ: piperaquine, AZ: Azithromycin

Table 2: Characteristics and structure of reported safety data (n=18)

Characteristic	Number of articles (%)
Data Monitoring and Safety Board	14 (77.8)
Data collection approach	
Scheduled visits	1 (5.6)
Scheduled and non-scheduled visits	10 (55.6)
Non-scheduled visits	1 (5.6)
Not Specified	6 (33.3)
Reported AE severity levels	13 (72.2)
Assessed AE vs adherence	3 (16.7)
Discontinue treatment due to AE	18 (100)
Reported continuous outcome dichotomization	18 (100)
Reported laboratory data	18 (100)
Multiple safety endpoints	18 (100)
Longitudinal safety endpoints	18 (100)
Reported recurrent AEs	0 (0.0)
Retention rate (IQR)[b]	89.4% (IQR: 82.5%, 92.4%)

b IQR is interquartile range. The retention rate is based on primary outcome reported in trial flow diagram

Table 3: Statistical approaches for safety data analysis

Statistical method/approach	Number of articles (%)
Descriptive statistics	18 (100)
Proportion/count	18 (100)
Mean/median	1 (5.6)
Incidence rate	6 (33.3)
Inferential methods	
Univariate methods	
Fisher`s exact test/Chi square	12 (66.7)
t-test	4 (22.2)
Linear regression	1 (5.6)
Mann-Whitney/Wilcoxon	1 (5.6)
Multivariable modelling	
Poisson regression	3 (16.7)
Negative binomial	1 (5.6)
Number of inferential methods used	
None	3 (16.7)
One method	10 (55.6)
More than one method	5 (27.8)
Analysis approach	
Reporting missing data	
Missing efficacy data reported	7 (38.9)
Handling missing efficacy data	
Imputation	1 (5.6)
Analysis population definition	
ITT	4 (22.2)
PP	5 (27.8)
ITT+PP	2 (11.1)
Not specified	7 (38.9)
Multiplicity adjustment	0 (0.0)
Results presentation	
Graphs	0 (0.0)
Tables	16 (88.9)
Point estimate and confidence interval	10 (55.6)
P value	16 (88.9)

Note: ITT=Intention to treat; PP=Per protocol; Entries in this table are mutually exclusive and may not add up to the total 26 articles since some articles used more than one approach

Figures

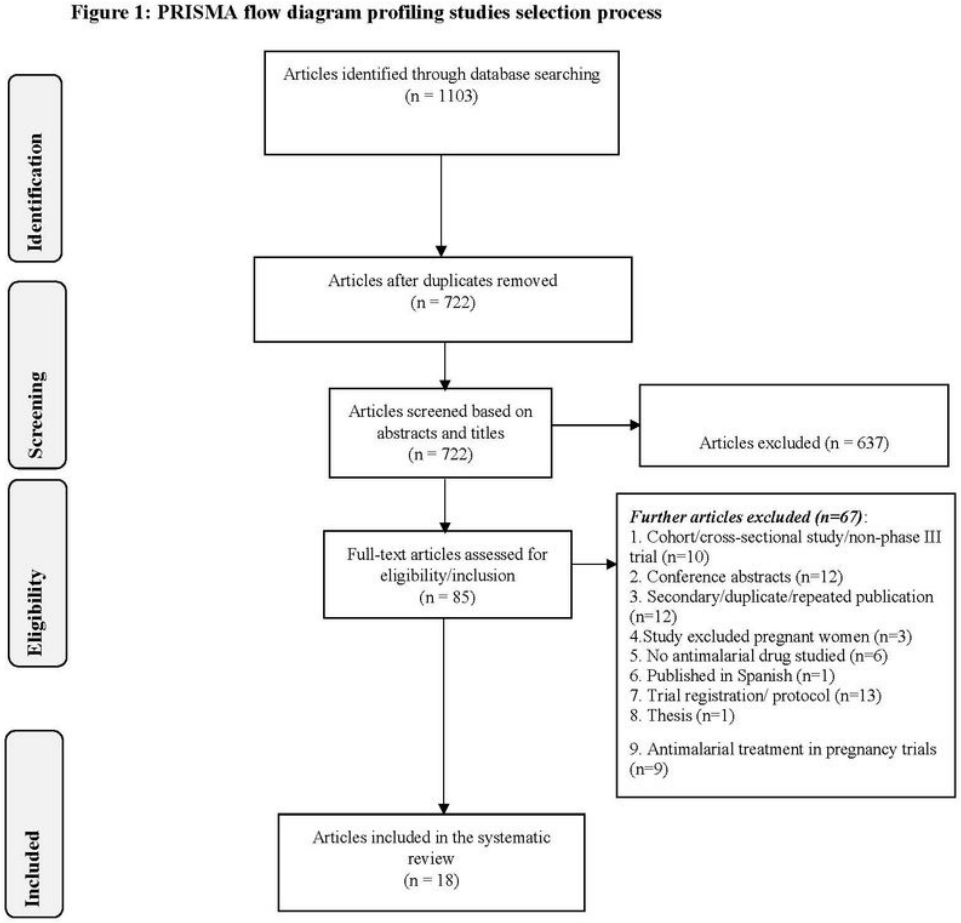

Figure 1

PRISMA flow diagram for study selection process