

**A META-ANALYSIS OF ARTESUNATE PLUS SULFADOXINE-  
PYRIMETHAMINE VERSUS SULFADOXINE-PYRIMETHAMINE ALONE  
FOR TREATMENT OF UNCOMPLICATED MALARIA IN CHILDREN.**

**Benido Impouma  
Student number: 0418444D**

**A Research Report, submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Science (Medicine) in Epidemiology and Biostatistics.**

**Johannesburg, September 2004**

## DECLARATION

I, Benido Impouma, declare that this research report is my own work. It is being submitted for the degree of Master of Science (Medicine) in Epidemiology and Biostatistics in the University of the Witwatersrand, Johannesburg. To the best of my knowledge, it has not been submitted before for any degree or examination at this or any other University.

 · [Signature of candidate]

.....30 .....day of .....September, 2004

## **DEDICATION**

This report is dedicated to my parents Jean Impouma and Therese Impouma for all the time and resources they put to make me what I am today.

# ABSTRACT

## Study objectives

The objective of this meta-analysis was to review the comparative efficacy and tolerance of sulfadoxine-pyrimethamine (SP) given alone or in combination with one (SPAS1) or three (SPAS3) doses of artesunate in children with uncomplicated *P. falciparum* malaria, aged 6 months to 10 years. Specifically, it assessed cure rate, fever and parasite clearance time, gametocyte carriage and tolerability.

## Methods

The methodology used was a systematic review and a meta-analysis of four randomised controlled trials. The primary endpoint was the parasitological cure rate at day 28. Secondary endpoint included the parasitological cure rate at day 14, time to fever and parasite clearance, gametocyte carriage and occurrence of adverse events.

## Results

Cure rate at day 28 corrected by PCR was 2.5 times higher in the combination of SPAS3 than in SP alone (pooled OR=2.55, 95% CI 1.93 to 3.37). There was no difference in cure rate at day 28 corrected by PCR between the combination of SPAS1 and SP alone (pooled OR=1.06 95% CI 0.98 to 1.15). Fever and parasite clearance times were significantly faster in both SPAS1 and SPAS3 compared to SP alone ( $p<0.001$ ). By day 28 all children on the combination therapy were agametocyaemic as opposed to those on SP alone ( $p<0.001$ ). All drug regimens were well tolerated and safe.

## Conclusion

The combination of SPAS3 is more efficacious than SP alone in treatment of children with uncomplicated *P. falciparum* malaria. The combination is recommended for adoption as a replacement for SP alone in areas where malaria is endemic.

## **ACKNOWLEDGEMENTS**

This thesis was written on the basis of the knowledge and experience that I have acquired during the one year training at the School of Public Health, University of the Witwatersrand.

Special thanks to my supervisors, Drs Ronel Kellermann and Gill Schierhout, who guided me through the protocol development and report writing. They were available each time I needed them to review my drafts.

I also wish to acknowledge the following agencies: UNDP / WORLD BANK / WHO Special Programme for Research and Training in Tropical Diseases (TDR) for providing the funding for my training at Wits School of Public Health, The National Laboratory of Public Health for supporting me with additional resources.

I would like to acknowledge the following persons: Pr Henri Joseph Parra, Dr Jean Vivien Mombouli, Dr Blaise Bikandou, Pr. Brian Greenwood, Pr. Jimmy Withworth Pr. Jimmy Volmink, Pr. Paul Garner, Pr. Arnaud Fontanet, Dr Bob Taylor, Sir Steve Wayling, Sir George Indyke, Dr Joel Breman and Pr. Jonathon Levin.

I would like to thank Ms Bouckoulou Chandra-my fiancée, for her moral support during the one-year of training. I also wish to thank my colleagues for their support and encouragement during the entire study period at the University of the Witwatersrand.

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## LIST OF ABBREVIATIONS

AS	Artesunate
CI	Confidence Interval
CQ	Chloroquine
OR	Odds Ratio
PCR	Polymerase Chain Reaction
RCT	Randomized Controlled Trials
SMD	Standard Mean Difference
SP	Sulfadoxine-Pyrimethamine
SPAS	Sulfadoxine-Pyrimethamine combined with Artesunate
SPAS1	Sulfadoxine-Pyrimethamine and one dose of Artesunate
SPAS3	Sulfadoxine-Pyrimethamine and 3 doses of Artesunate
WHO	World Health Organization

# 1.0 INTRODUCTION

## 1.1 Background

Malaria remains a leading cause of morbidity and mortality, and is endemic in over 100 countries. The World Health Organization (WHO) estimates 2400 million people are at risk, with 200-300 million clinical malaria cases and at least one million annual deaths. Almost 90 % of all deaths occur in sub-Saharan Africa, most of them among young children<sup>1</sup>.

Malaria costs the sub-Saharan African economies over 2 billion USD annually, including costs for malaria control and losses to workdays. This is estimated to be 5% of the region's Gross Domestic Product (GDP) and is causing a slowing of economic growth by about 1.3% per year in malaria endemic countries. <sup>1, 2</sup>

Serious challenges continue to face malaria control in the countries where it is endemic. Traditionally control measures have included early diagnosis and prompt treatment, chemoprophylaxis, insecticide treated nets and vector control.

Over the years, however, there has been an increasing resistance to the common and most affordable anti-malarial drugs such as chloroquine (CQ) and sulfadoxine-pyrimethamine (SP).<sup>3</sup> In Ghana, for example, a study showed resistance I (asexual parasitaemia reduction <25% of pretreatment level in 48 hours) and II (asexual parasitaemia reduction between 25 and 75%) to CQ and SP to be 45% and 37%

respectively and resistance III (mild reduction in parasitaemia or increase in parasitaemia after 48 hours) to be 9% and 14 % respectively.<sup>4</sup>

In Tanzania, the level of SP resistance I, II and III was estimated to be 26%, 72% and 5%, respectively.<sup>5</sup> A number of new alternative treatments have been developed to address the problem of resistance.

## **1.2 Statement of the problem**

The increasing resistance of *P. falciparum* to the widely used and cheap drugs such as CQ and SP has led to the increase in malaria related morbidity and mortality.<sup>3, 4</sup> *P. falciparum* is the commonest and most dangerous species of the 4 human malaria parasites.

This increasing level of resistance spells potential disaster, especially for Africa, which has the greatest burden of the disease. Several countries still continue to use CQ or SP even when resistance has been clearly documented. There is an urgent need to assess the efficacy and safety of new antimalarial drugs, if this disaster is to be averted.

The artemisinin derivatives provide a timely solution to the problem. Studies have evaluated their efficacy and safety.<sup>6,7,8,9,10</sup> However, these were randomised controlled trials (RCT) conducted under highly controlled conditions with limited sample sizes, different levels of endemicity and SP resistance. These factors have limited their generalizability and therefore the adoption of the drug in different settings. These studies also report conflicting results on the efficacy of the combination of SP with

either one or three days of artesunate (SPAS1 or SPAS3) compared to SP alone. In addition the effect of the combination in reducing gametocytaemia remains unclear.

### **1.3 Literature review**

The increasing resistance of *P. falciparum* to CQ and SP is well documented in Africa. Resistance to antimalarial drugs is a serious issue faced by several malaria control programs across the world. It increases the cost of the disease, the risk of severe malaria as well as malaria case fatality rate.

A review of the public health impact of CQ resistance in Africa showed an association between CQ resistance and malaria related morbidity and mortality.<sup>3</sup> In Senegal for example, the emergence and development of CQ resistance has been associated with a 5.5 fold increased malaria case fatality rate. CQ resistance was also associated with an increased incidence of severe malarial anaemia which contributed to human immunodeficiency dissemination among children. Children who received one transfusion were 2.8 times more likely to be HIV seropositive, those who received two transfusions were 7.9 times more likely to be HIV seropositive than those who did not.<sup>3</sup>

In a study evaluating the effect of changing drug treatment policy on the case fatality rates of children hospitalized with malaria over a four year period, Zucker et al found a reverse relationship between changing antimalarial drug policies and mortality due to malaria.<sup>11</sup> The case fatality rate for malaria declined from 1991 through 1994 as the percentage of children who received an effective treatment regimen increased.

Several countries still continue to use CQ or SP even when resistance to them has been clearly documented. The argument for continuing to use CQ has been the cost of second-line therapy. However the debate about CQ drug resistance is no longer about the increased cost of second-line medications. It is about the cost of life. We cannot justify allowing children to die in Africa because they are not receiving effective treatment.<sup>11</sup>

The artemisinin derivatives have been introduced in a number of countries. Artesunate, an artemisinin derivative, is a new and promising antimalarial drug extracted from a Chinese plant *Artemisia annua* L. It has potent antimalarial activity and an attractive safety profile and has yet to be associated with resistance.<sup>12</sup> Artesunate is active orally, has a short half-life and reduces gametocytes carriage and may therefore reduce infectivity. To avoid the problem of the emergence of resistance of *P. falciparum*, the drug is being administered in combination with other antimalarial drugs.

In combination treatment of malaria the artemisinin derivative which has a short half-life may be combined with another antimalarial drug which has a long half life (eg SP). The artemisinin derivative would act rapidly to reduce the initial parasite load while the drug with a long half life would remain in the bloodstream to clean the remaining parasites.<sup>13</sup>

In Asia, where resistance of *P.falciparum* to drugs such as mefloquine has spread over the past decades, studies have been conducted to assess the effect of adding artesunate to mefloquine in treating multi-drug resistant *P. falciparum* malaria. A prospective

study by Nosten and colleagues, on the Thai Myanmar border provided strong evidence in support of using artesunate in combination with mefloquine, particularly in areas with resistance to the partner drug.<sup>14</sup> Before the introduction of artemisinin derivatives in this area, mefloquine was the drug of choice for treating patients with malaria. Parasitological failure rate after administration of mefloquine exceeded 25%. The introduction and extensive use of artesunate in combination with mefloquine in this area, over time, produced four main effects:

- i. An efficacy exceeding 95%; the efficacy of high- dose mefloquine monotherapy (25mg/kg bodyweight) had fallen to approximately 75%
- ii. At least 7 years of high sustained efficacy.
- iii. Reduction in the transmission of *P. falciparum* due to the antigametocidal effect of artesunate.
- iv. Increased *in vitro* sensitivity of mefloquine, suggesting that the combination had reversed the previous decline in mefloquine sensitivity.<sup>14</sup>

These results, particularly the high and sustained efficacy of the cocktail and the alteration in the pattern of resistance to the commonly used drug, were a major breakthrough in the fight against malaria. A number of questions arose from these results. Firstly, could this experience be replicated in the other malaria endemic areas, e.g. Africa, where drug resistance is currently curtailing malaria control programs? Secondly, what would the safety and tolerability of these artemisinin derivatives be if combined with the standard antimalarial drugs used in these other settings?

In response to these questions, WHO (1998) set up a task force to achieve the following: provide reliable data on the efficacy and safety of the drug regimens under trial and present these data in an understandable format, conduct large field trials using those combinations of proven value and bridge the gap between malaria research and control.<sup>15</sup> Since then, several trials mainly sponsored by WHO have been concluded to assess the effectiveness of the combination of artemisinin derivatives with the existing antimalarial drugs.

In Africa, the combination of artesunate with SP (SPAS) could delay or prevent the emergence of resistance to SP and have an impact on malaria transmission by lowering rates of gametocytaemia after treatment.<sup>16</sup> Further research is needed.

This meta-analysis reviewed the efficacy and safety of the combination of SPAS versus SP alone in treating children with uncomplicated *P. falciparum* malaria.

#### **1.4 Justification**

If the meta-analysis shows that the combination of SPAS is more efficacious than SP alone, we can expect that it will have significant policy implications. The combination will be recommended as first-line therapy in countries where alternatives to the use of SP have not emerged. Its use will significantly reduce malaria transmission, and prevent or delay the development of resistance in children, thereby reducing the morbidity and mortality due to malaria. This meta-analysis will also provide additional scientific resource to the existing body of knowledge.

The purpose of this meta-analysis, therefore, was to improve the generalizability of the different study results by reviewing the separate studies that have assessed the efficacy and tolerability of the combination of SPAS (SPAS1 or SPAS3) as compared to using SP alone in the treatment of uncomplicated *P. falciparum* malaria in children.

## **1.5 Objectives**

### **1.5.1 General objective**

To review the efficacy and safety of the combination of SPAS1 or SPAS3 compared to SP alone in the treatment of uncomplicated *P. falciparum* malaria in children.

### **1.5.2 Specific objectives**

- i. To compare the parasitological cure rates by day 14 and day 28 of the combination of SPAS1 or SPAS3 compared to SP alone.
- ii. To compare the parasitological clearance time in the combination of SPAS1 or SPAS3 against the parasitological clearance time in SP alone.
- iii. To compare the fever clearance time in the combination of SPAS1 or SPAS3 against the fever clearance time in SP alone.
- iv. To compare the rates of adverse events in the combination of SPAS1 or SPAS3 against the rates in SP alone.
- v. To compare the effect of SPAS1, SPAS3 and SP alone in reducing gametocyte carriage on day 7, 14 and 28

### **1.5.3 Implementation objective**

To make recommendations for the use of the combination of SPAS as first-line therapy in countries where alternative to the use of SP has not emerged.

## **2.0 METHODS**

The methods used for this review followed the recommendations of the QUORUM statement<sup>17</sup> on reporting of meta-analysis and the guidelines developed by the Cochrane Library available at [www.cochrane.org](http://www.cochrane.org)

### **2.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

#### **2.1.1 Types of studies**

RCT across the world comparing the combination of SPAS1 or SPAS3 against SP alone for treatment of uncomplicated *P. falciparum* malaria in children.

#### **2.1.2 Types of participants**

Children males and females, aged 6 months to 10 years with uncomplicated *P. falciparum* malaria in the selected studies.

#### **2.1.3 Types of intervention**

Experimental group: Combination of SPAS1 or combination of SPAS3.

Control group: SP alone.

All selected RCTs compared 3 arms: children in the first arm received SP alone (25mg/kg sulfadoxine, 1.25 mg/kg pyrimethamine); in the second arm SP plus one dose of artesunate (4mg/kg bodyweight, SPAS1) and in the third SP plus three doses of artesunate (4mg/kg bodyweight once daily for 3 days, SPAS3).

## **2.1.4 Types of outcomes measured**

### **Primary endpoints**

- Cure rate by day 28 defined as *P. falciparum* negative blood slide on day 28.
- Polymerase Chain Reaction (PCR)-corrected cure rate by day 28 to differentiate reinfection from recrudescence.

### **Secondary endpoints**

- Cure rate by day 14 defined as *P. falciparum* negative blood slide on day 14.
- Time to fever clearance: Time (days) from the initiation of treatment to fever clearance.
- Time to parasite clearance: Time (days) from the initiation of treatment to parasite clearance.
- Gametocyte carriage on days 7, 14 and 28 stratified by the presence of gametocytes on day 0.
- Tolerability: any reported adverse events, including serious adverse events and adverse drug reactions.

To assess the eligibility of each trial we used a modified sample eligibility form (appendix 1) from the Cochrane review Artemeter-Lumefantrine.<sup>18</sup>

This was done by the author and two experienced persons under the facilitation of the supervisor. Disagreement was resolved by involving a third person. Studies that did not meet inclusion criteria were accounted for in the “characteristics of excluded studies” section of the report (see section 3.1.2).

## **2.2 SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES**

The following databases were searched:

- Cochrane Library, especially the Cochrane Infectious Diseases Group. Access to the database was achieved through [www.sahealthinfo.net](http://www.sahealthinfo.net)
- MEDLINE (1966 to 2004).
- EMBASE (1982 to 2004).
- LILACS (La Literatura Latinoamericana y del Caribe de Informacoin en Ciencias de la Salud).
- African Index Medicus.
- WHO and CDC websites.

All potentially relevant trials were retrieved using the search terms artesunate, SP, Fansidar, malaria or the combined search terms artesunate and/plus SP, artesunate and/plus Fansidar, artesunato, SP resistance, SP, artesunate adverse effects. All related links to the retrieved articles published in either English or French were checked. Also the reference lists of full text articles were scanned to retrieve potentially relevant trials. The first or corresponding authors of retrieved articles, investigators in the field, agencies and pharmaceutical companies were contacted for additional information if required.

## **2.3 QUALITY ASSESSMENT**

The methodological quality of the trial design was assessed based on the following key factors described in the Cochrane Library guidelines:

- i. Generation of allocation sequence.
- ii. Allocation concealment.
- iii. Blinding.
- iv. Loss to follow-up (comparison between the number of patients seen on day of admission and those analysed at day 28).

Generation of allocation sequence, allocation concealment and loss to follow-up was classified as adequate, inadequate or unclear (refer to appendix 2 for more details).

The blinding process was described as single-blind, double-blind or open label.

This assessment was done by two independent reviewers who used a pre-designed form (Appendix 2).

## **2.4 DATA EXTRACTION**

Data for all potentially relevant trials were extracted using a pre-designed and modified data extraction form (Appendix 3).

This extraction was done by the author and two independent reviewers, checked by the supervisor.

After piloting the extraction form the following information was extracted and tabulated:

- Trial information (study site, including malaria transmission characteristics and period, number of participants assessed for eligibility, randomised, seen at day 14 and 28).
- Demographic characteristics of the study population (age, sex).
- Treatment (regimen, doses).

- Validity assessment of key factors (randomization, blinding, concealment of allocation sequence and generation of allocation sequence).
- Follow-up.
- Outcome variables (efficacy at day 14 and 28, gametocytaemia, time to clear fever and parasitemia).

For studies where information were missing or not reported the corresponding authors were contacted. For binary outcomes (e.g. cure rate at day 28) the total number of participants and the number of participants experiencing the events were extracted. For continuous data (e.g. weight) the measures of central tendency (mean) and spread (standard deviation and range) were extracted.

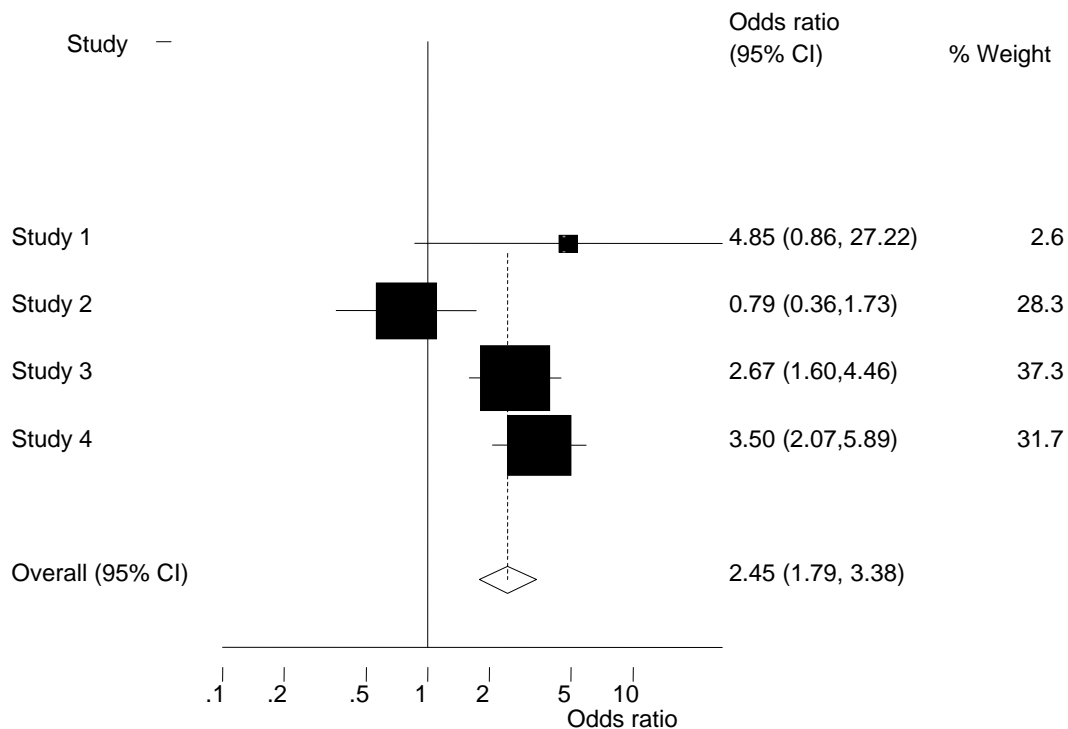
## **2.5 DATA MANAGEMENT AND ANALYSIS**

Data were entered in Epi-Info version 3.2, double checked and analysed in Intercooled Stata 8. The efficacy of SP alone was compared with that of either the combination of SPAS1 or the combination of SPAS3.

The association between the exposure (treatment) and outcome (cure rate) was assessed using the odds ratio as the main measure of association. Since the stata commands used in the analysis works on the log ratio scale, we calculated odds ratio on a log ratio scale and used the exponential function to obtain an odds ratio scale. The standard error of odds ratio was calculated using the Woolf's method.

After listing the number of patients with the outcome and the total number of patients randomised in each arm, we generated and interpreted the forest plot.

As shown in Figure 2.1 below, the unbroken vertical line is at the null value of the odds ratio and represents no treatment effect. The broken line is at the pooled odds ratio which corresponds to the summary estimate of all included trials. The horizontal lines depict the width of the 95% confidence interval while the black squares reflect the weight of the individual trial in the meta-analysis. The diamond represents the pooled odds ratio with its 95% confidence interval.



**Figure 2.1 Forest plot illustration**

The statistical level of significance used in all the analysis was 5%. In interpreting a z-test related to a forest plot, a p-value of less than 5% meant heterogeneity of included trials. In case of heterogeneity we used meta-regression to estimate the effect of

treatment after controlling for potential confounders. Based on the meta-regression outputs all variables that were statistically significant were added into the model.

Bias in ascertaining included studies was investigated using the funnel plot and the Egger's test at 5% level of statistical significance. An asymmetrical funnel plot was suggestive of either publication bias, difference in methodological quality or heterogeneity. A p-value of greater than 5 % gave no evidence of bias.

A sensitivity analysis was conducted as part of the analysis for each of the above key factors to determine the robustness of validity assessment. This was done by examining the extent to which results were affected by changes in the methods, values or variables.<sup>19, 20</sup>

Both fixed and random effect models were used. All analyses were based on the intention to treat approach which consists of analyzing all patients included in the study in their respective treatment arm, regardless of events that may occur during the follow-up.

## **2.6 ETHICAL CONSIDERATION**

The study was approved by the Wits Human Research Ethics Committee.

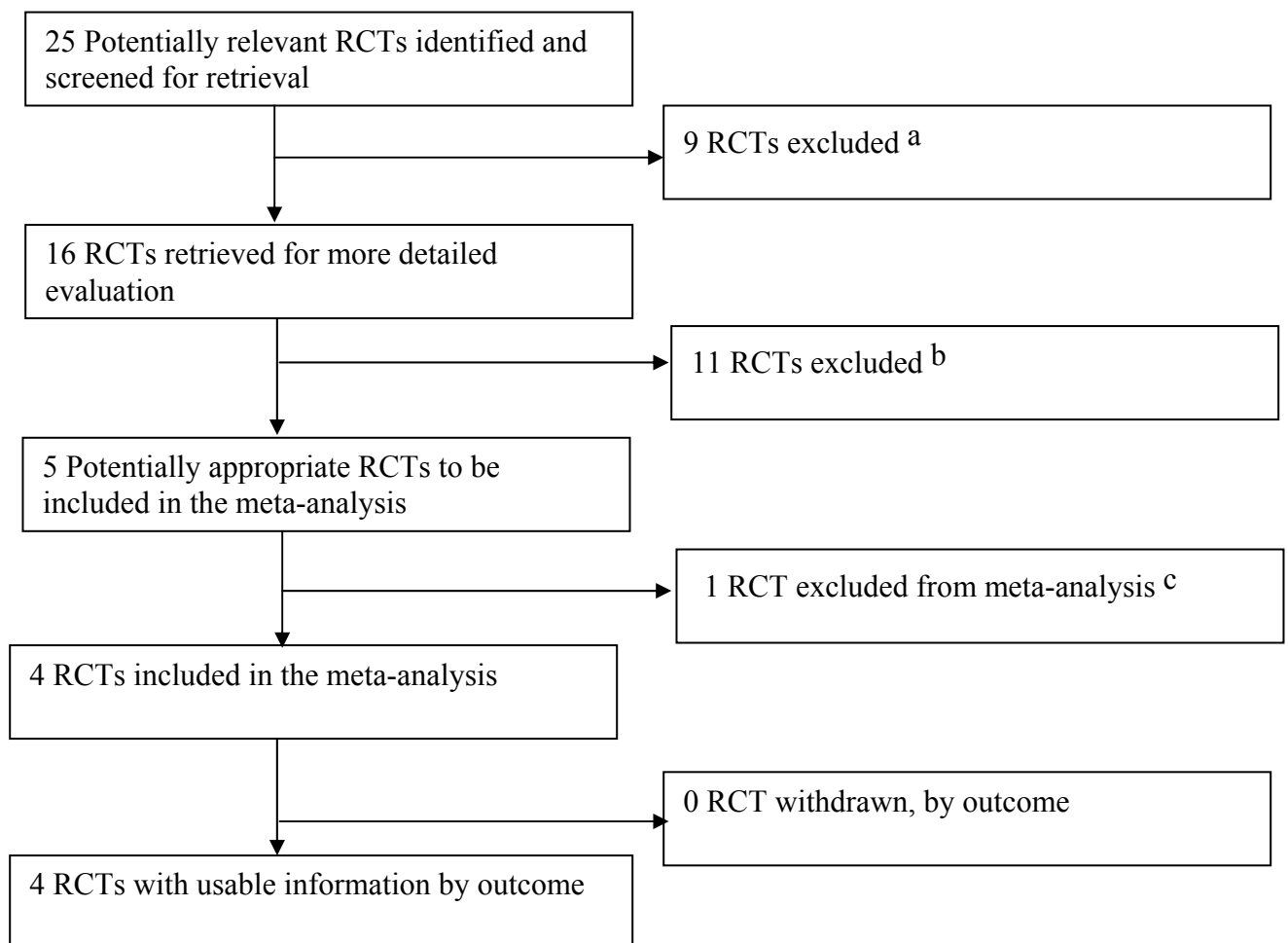
### 3.0 RESULTS

The results of this study are presented according to the QUORUM statement format for meta-analysis.<sup>17</sup>

#### 3.1. Qualitative extraction

##### 3.1.1. Steps used for identification and selection of included RCTs.

Figure 3.1 below is a summary of the steps that were taken to select the four papers out of the 25 RCTs initially identified. These RCTs were approved by the relevant ethics committees.



**Figure 3.1** Flow diagram of steps used for selection of studies.

### 3.1.2 Characteristics of excluded studies

The flow diagram in figure 3.1 shows three categories of excluded studies:

- a. Studies that did not match the initial criteria for inclusion.
- b. Trials that were excluded for one or more of the following reasons:
  - Comparison of the combination of SPAS with either placebo or other antimalarial drugs such as CQ, amodiaquine and/or primaquine (8 trials).
  - Inclusion of healthy children (2 trials).
  - Inclusion of pregnant women as the main inclusion criteria (1 trial).
  - 2 trials assessing the combination of SPAS were not RCTs.
- c. Studies that were excluded by the reviewers because of inadequate follow-up, bias in ascertaining the exposure and outcome (open label trial), inclusion of both adults and children, results such as secondary endpoints were not reported separately for children and adults making extraction of data difficult.

The 4 included RCTs are listed in Table 3.1 below along with their references.

**Table 3.1 Site and references of included studies.**

Study site	References
1. Gambia <sup>21</sup>	Doherty et al. A randomized safety and tolerability trial of artesunate plus sulfadoxine – pyrimethamine versus sulfadoxine-pyrimethamine alone for the treatment of uncomplicated malaria in Gambian children. <i>Trans R Soc Trop Med Hyg</i> 1999; 93(5): 543-6.
2. Gambia <sup>6</sup>	Seidlein et al. Efficacy of artesunate plus pyrimethamine – sulfadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial. <i>Lancet</i> 2000; 355(9201): 352-7.
3. Kenya <sup>22</sup>	Obonyo et al. Artesunate plus sulfadoxine-pyrimethamine for uncomplicated malaria in Kenyan children: a randomized, double-blind, placebo-controlled trial. <i>Trans R Soc Trop Med Hyg</i> 2003; 97 (5): 585-91.
4. Uganda <sup>23</sup>	Priotto et al. Artesunate and sulfadoxine-pyrimethamine combinations for the treatment of uncomplicated <i>Plasmodium falciparum</i> malaria in Uganda: a randomized, double-blind, placebo-controlled trial. <i>Trans R Soc Trop Med Hyg</i> 2003; 97(3): 325-30.

### **3.1.3. Assessment of methodological quality of included RCTs.**

The four validity assessment criteria recommended by the Cochrane guidelines were used in this study as opposed to the assessment based on the use of checklists. The four criteria are: concealed allocation, generation of allocation, blinding and loss to follow-up. Concealed allocation was not described in the Gambia-S and Uganda studies. The corresponding authors of these two papers were contacted but they did not reply. However, the reviewers agreed to include these two studies after assessment of the other three criteria (Table 3.2).

**Table 3.2 Assessment of methodological quality of included studies**

<b>Trial name</b>	<b>Year of publication</b>	<b>Concealed allocation</b>	<b>Generation of allocation</b>	<b>Blinding</b>	<b>Loss to follow-up</b>
<b>Gambia-D<sup>21</sup></b>	1999	Adequate	Adequate	Single	Adequate
<b>Gambia-S<sup>6</sup></b>	2000	Not described	Adequate	Double	Adequate
<b>Kenya<sup>22</sup></b>	2003	Adequate	Adequate	Double	Adequate
<b>Uganda<sup>23</sup></b>	2003	Not described	Adequate	Double	Adequate

## **3.2 Quantitative data synthesis**

### **3.2.1 Baseline characteristics of children in the included studies.**

Six thousands one hundred and thirty three (6133) children were screened for eligibility, out of which 27% (1660/6133) who met the inclusion criteria were recruited and assigned to receive either SP alone or the combination of SPAS1 or SPAS3. The proportions of males and females in the study were 50.4% (837/1660) and 49.6% (823/1660), respectively.

The mean age of children in the selected trials ranged from 1.3 to 5.9 years. There was no difference in the weighted mean between children who received the combination of SPAS in comparison to those who received SP alone (pooled standard mean difference (SMD) = -0.07, p = 0.520, 95% CI: -0.27 to 0.01).



The mean weight of children in the selected trials ranged between 9.2 and 18.4 kgs. There was a statistically significant difference in the baseline weight of children enrolled into the study (pooled SMD = -0.49, p value <0.001, 95% CI -0.70 to -0.28). The weighted mean temperature was the same in both regimen groups (p value =1.00, 95% CI -0.21 to 0.21).

The table 3.3 above summarises the baseline characteristics of the included studies.

All the children received either SP alone (25 mg/kg pyrimethamine and 1.25 mg/kg sulfadoxine) or SP and artesunate (4mk/kg bodyweight) for one day (SPAS1) or SP and 4mg/kg bodyweight of artesunate for 3 days (SPAS3).

It should be noted that the Gambia-D study only compared the SP alone regimen to the combination of SPAS3.

The total number of children seen at day 14 and 28 were 87.2% (1448/1660) and 86.2% (1431/1660), respectively. These are presented in Table 3.4

**Table 3.4 Total number of children seen at day 14 and 28**

<b>Trial name</b>	<b>Gambia-D</b>	<b>Gambia-S</b>	<b>Kenya</b>	<b>Uganda</b>	<b>Combined</b>
<b>Assessed for eligibility</b>	74	2186	2492	1381	6133
<b>Number randomised</b>	40	600	600	420	1660
<b>Number seen at day 14</b>	35	561	581	271	1448
<b>Number seen at day 28</b>	37	552	572	270	1431

### **3.2.2 Primary endpoint**

The primary endpoint was cure rate at day 28. The results of the comparison are presented in Table 3.5 below.

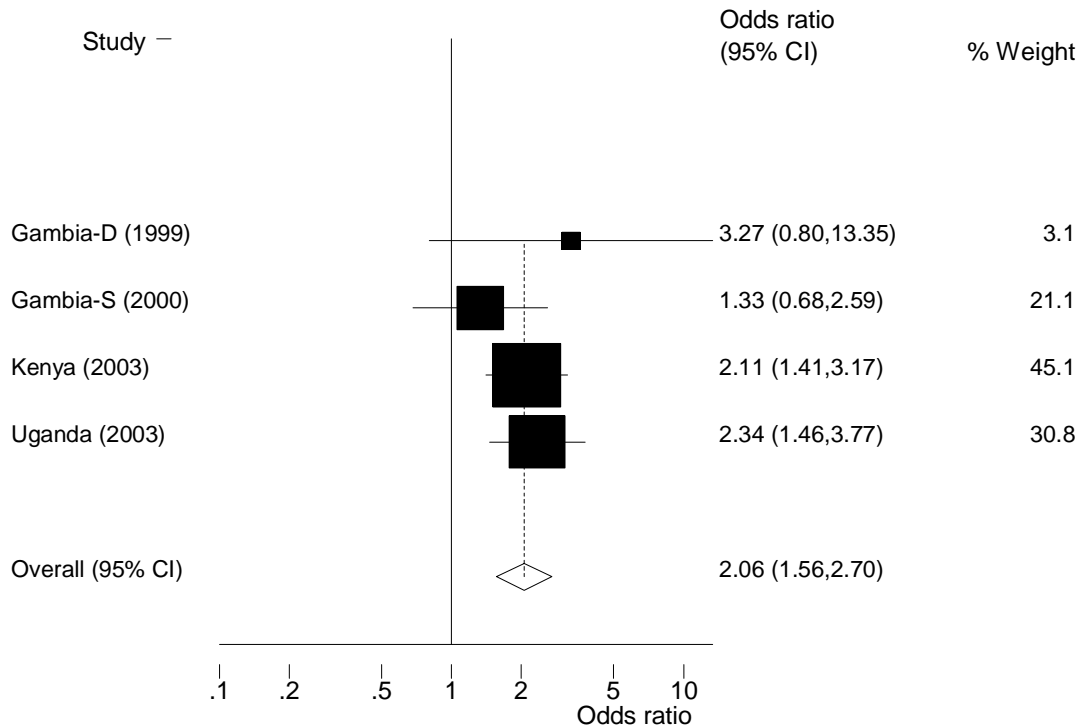
All the studies compared the safety and efficacy of SP alone and the combination of SPAS. Artesunate was given for either 1 day (SPAS1) or 3 days (SPAS3). The numbers assigned to receive SP alone or the combination were similar in all studies except for study 4 (Uganda) where the number of patients who received SP were higher than those in the experimental group. The authors did not justify this difference.

The cure rate at day 28 corrected by PCR was dramatically different from the crude cure rate at day 28 for the Kenyan study. For example, the crude cure rate and the corrected cure rate for the SP alone treatment arm were 33% (66/200) and 51% (102/200), respectively. This difference was not explained by the authors.



**i. Cure rate of SPAS3 vs. SP alone at day 28.**

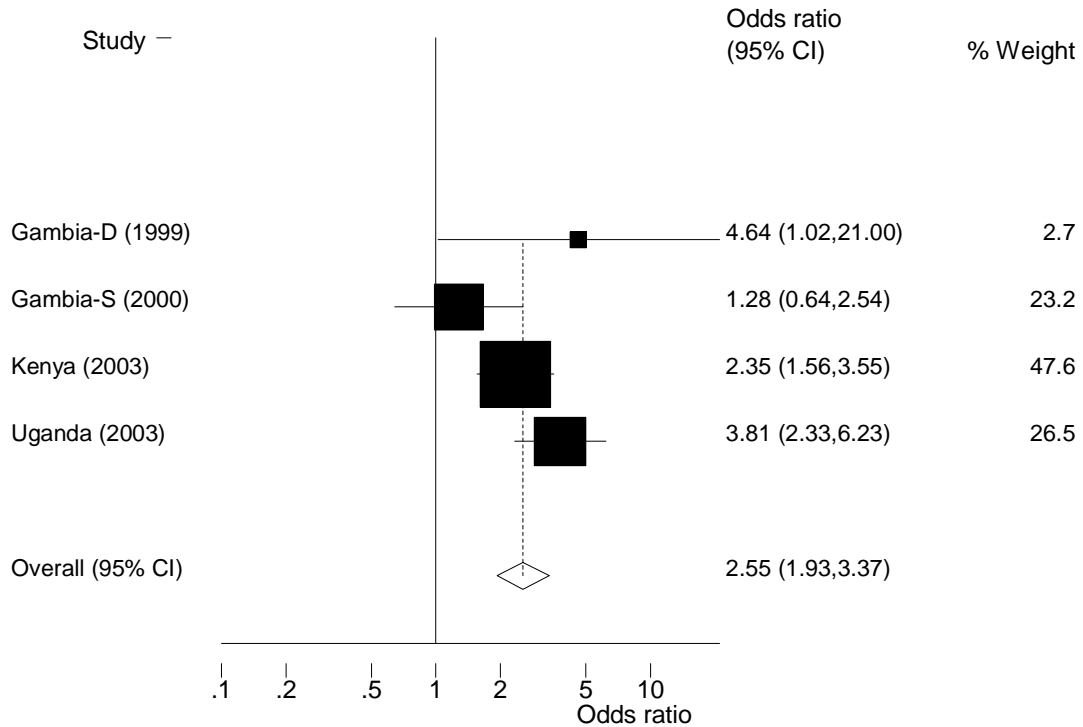
The pooled odds ratio of 2.06 (95% CI 1.56 to 2.70) showed the combination of SPAS 3 to be more efficacious than SP alone. Children who received the combination were approximately 2 times more likely to get cured by day 28 than those who received SP alone. This finding was statistically significant (Figure 3.2); the probability of the null hypothesis of no heterogeneity between the RCTs was 0.49 (Heterogeneity chi-squared= 2.37, p=0.49). The null hypothesis was therefore accepted and it was concluded that there was no heterogeneity between RCTs.



**Figure 3.2 Forest plot showing the results of trials comparing the cure rate at day 28 of SPAS3 vs. SP alone.**

**ii. Cure rate of SPAS3 vs. SP alone at day 28, corrected by PCR.**

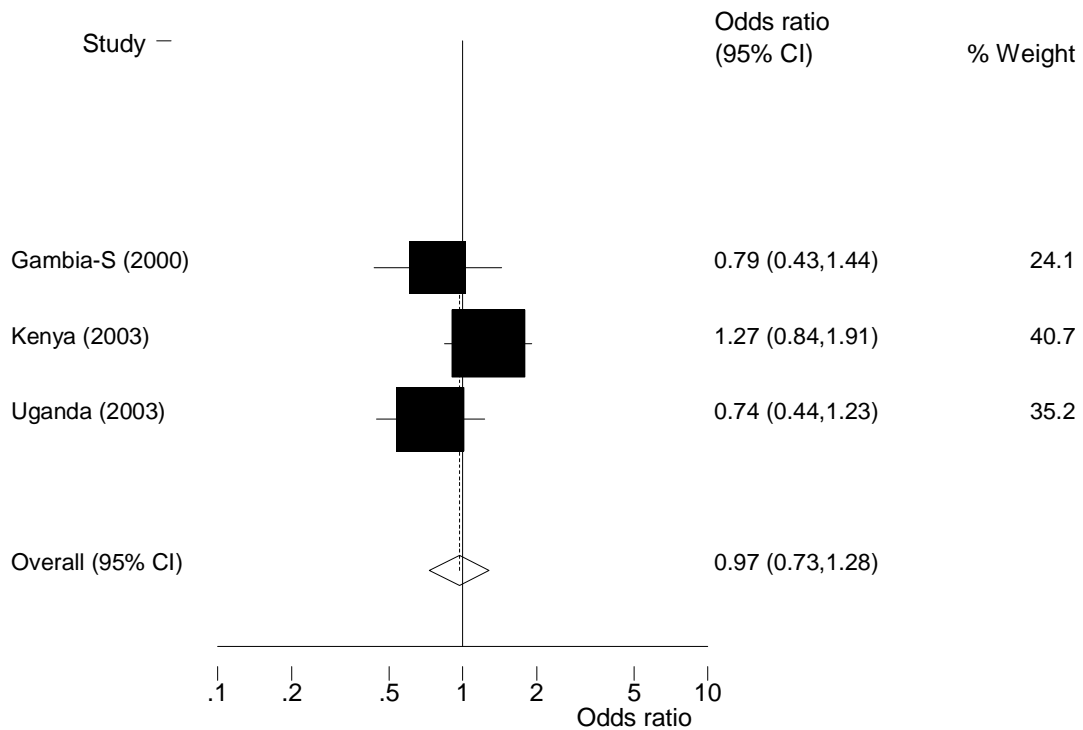
After correcting the cure rate at day 28 by PCR, the efficacy of the combination of SPAS3 remained significantly higher than that of SP alone (OR=2.55, 95% CI 1.93 to 3.37) as shown in Figure 3.3 below. There was no heterogeneity (Heterogeneity chi-squared=7.20, p=0.07).



**Figure 3.3 Forest plot of the results of RCT comparing the cure rate of SPAS3 vs. SP alone at day 28, corrected by PCR.**

### iii. Cure rate of SPAS1 vs. SP alone at day 28.

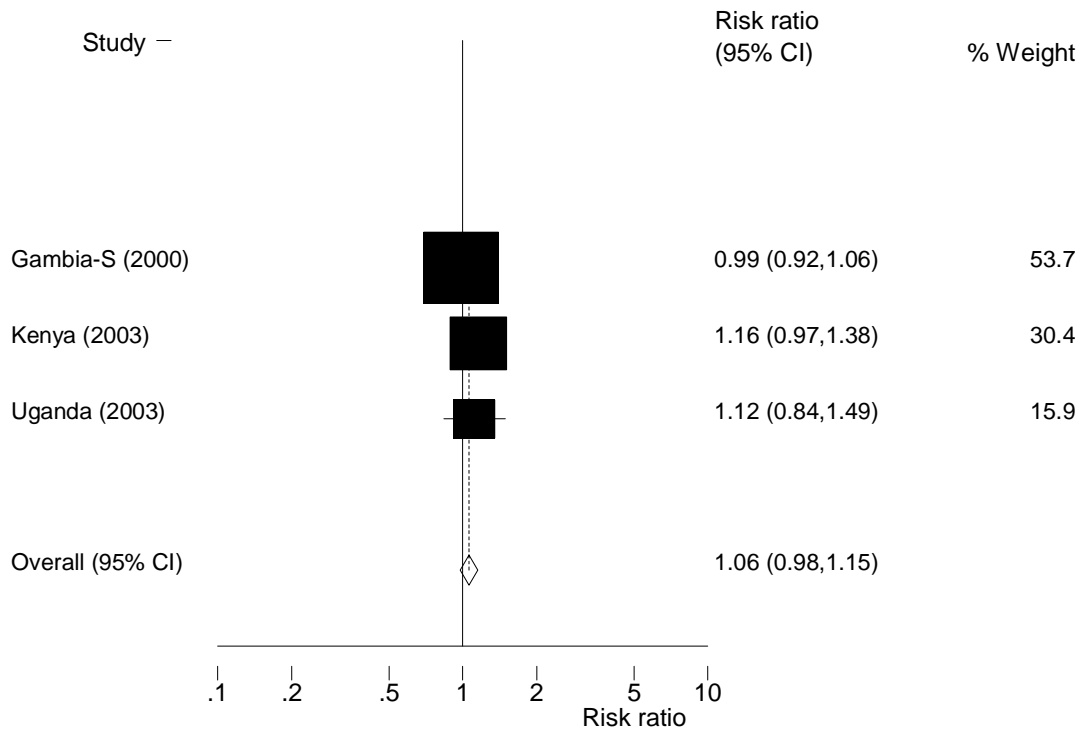
The pooled odds ratio of the comparison of the efficacy of SPAS1 vs. SP alone was 0.97, which estimate ranged from 0.73 to 1.28 in the underlying population. This result shows no evidence of difference in efficacy between SPAS1 and SP alone since the 95% CI contained the null value 1. Neither was there heterogeneity between included studies (Heterogeneity chi-squared =3.21, p = 0.20). It should be noted that these results do not include the data from the Gambia-D study.



**Figure 3.4 Forest plot of the results of RCT comparing SPAS1 vs. SP alone at day 28.**

**iv. Cure rate of SPAS1 vs. SP alone at day 28, corrected by PCR.**

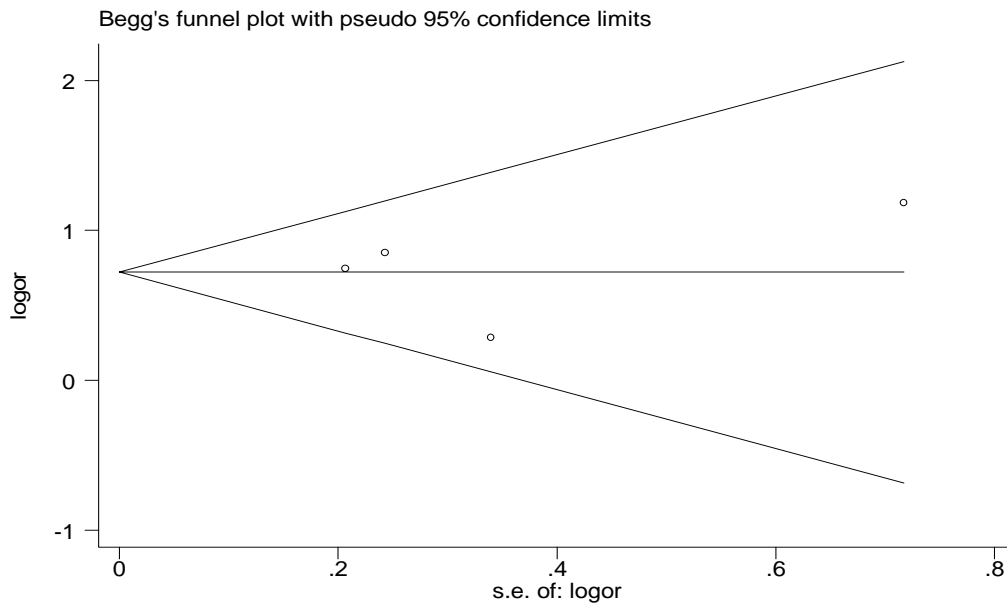
Figure 3.5 below shows the efficacy corrected by PCR at day 28 of SPAS1 vs. SP alone. There was no difference in the efficacy between the two regimens (pooled odds ratio=1.06, 95% CI 0.98 to 1.15). Neither was there heterogeneity (H chi-squared = 5.21, p = 0.07).



**Figure 3.5 Forest plot of the results of RCT comparing the cure rate of SPAS1 vs. SP alone at day 28, corrected by PCR.**

## Biases and Potential confounders

Biases and potential confounders were ascertained using a funnel plot and meta-regression. The Begg's funnel plot showed no evidence of bias since all observations lied between  $\pm 2$  standard deviation (Figure 3.6). Similar results were found with the Egger's test. The probability of the null hypothesis being true (that is there was no bias) was greater than the critical value 0.05 (p value 0.60). The null hypothesis was not rejected which implies that the study was not biased.



**Figure 3.6 Funnel plot examining bias.**

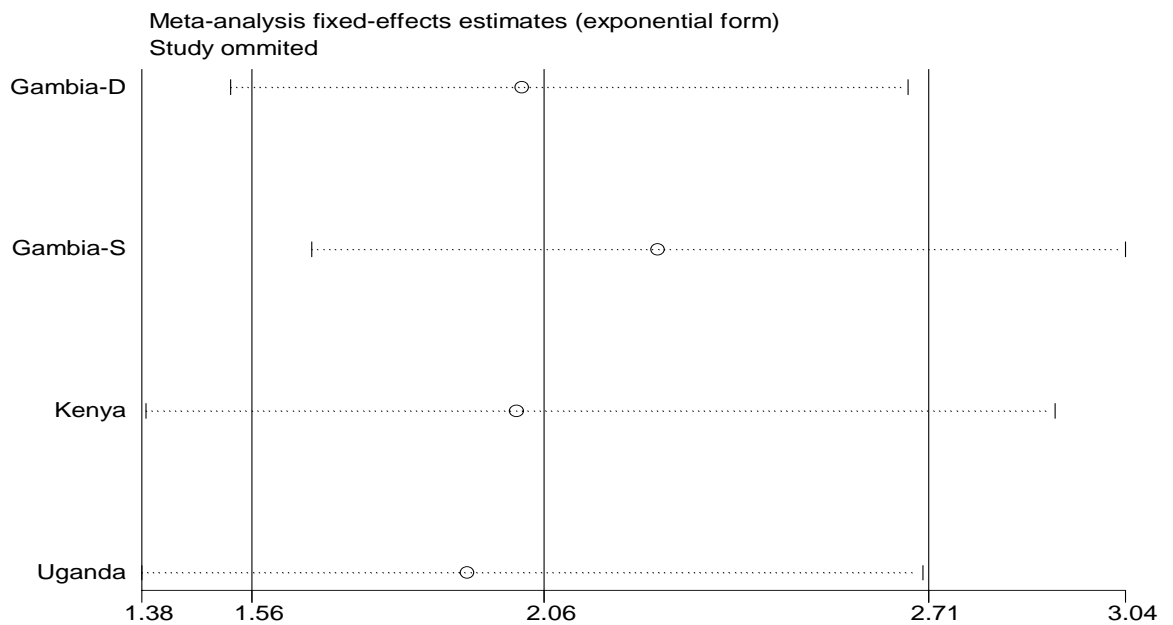
Since the baseline characteristics of weight differed between studies, the effect of this explanatory variable was assessed using a meta-regression. Having controlled for weight, it was found that weight had no influence on the relationships between the treatments (SPAS1 vs. SP alone or SPAS3 vs. SP alone) and cure rates. The effect of weight on SPAS3 cure rate is shown as an example in Table 3.6.

**Table 3.6 Effect of weight on SPAS3 cure rate.**

	Coef.	Std.Err.	z	P> z	95% Conf.Interval	
<b>weight</b>	-0.03	0.06	-0.57	0.57	-0.15	0.08
<b>_cons</b>	1.10	0.67	1.63	0.10	-0.22	2.42

Sensitivity analysis

The effect of each included RCT on the pooled estimated odds ratio was assessed by omitting one study at a time. The pooled odds ratio did not change much and remained around 2.06. This is shown in Figure 3.7

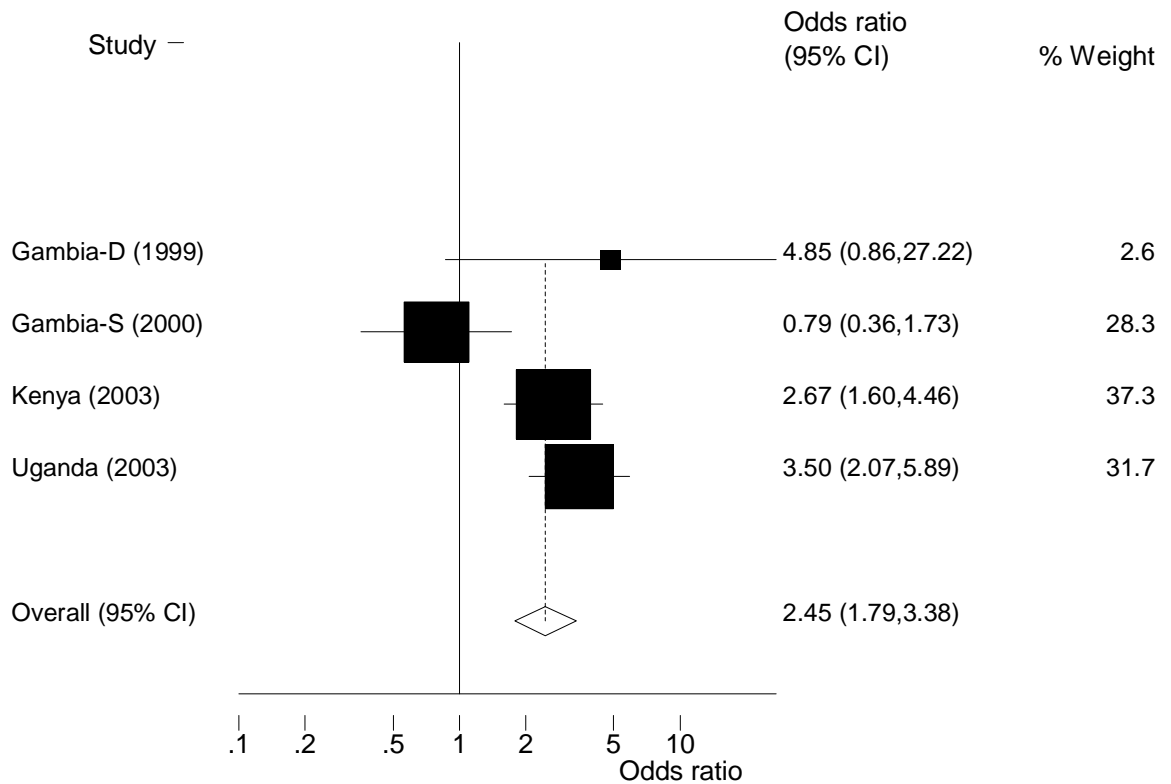


**Figure 3.7 Sensitivity analysis of RCT comparing SPAS3 and SP alone.**

### 3.2.3 Secondary endpoints

#### i. Cure rate of SPAS3 vs. SP alone at day 14.

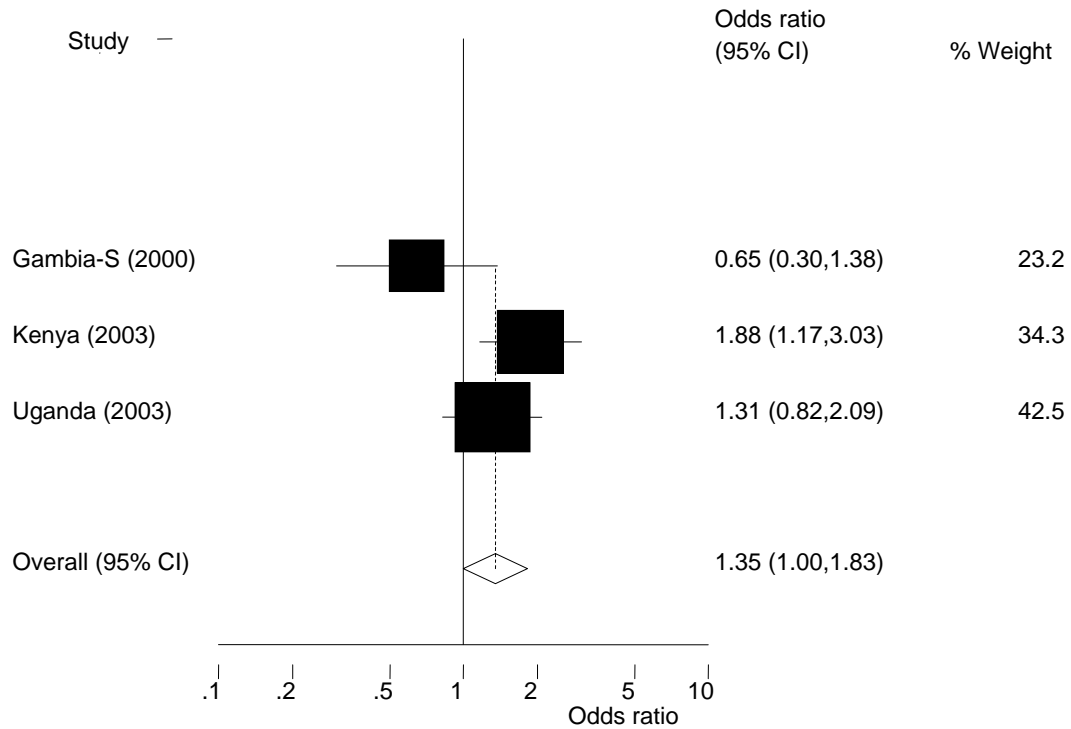
At day 14, children who received the combination of SPAS3 were about 2.5 times more likely to be cured than those who received SP alone. The difference in cure rate between the regimens was statistically significant (95% CI 1.79 to 3.38). Neither was there heterogeneity (H chi-squared = 10.51, p = 0.05).



**Figure 3.8** Cure rate at day 14 of SPAS3 vs. SP alone

**ii. Cure rate of SPAS1 vs. SP alone at day 14.**

The pooled odds ratio for the comparison between SPAS1 and SP alone was 1.35 at day 14. This finding was not, however, statistically significant (95% CI 1.00 to 1.83). Neither was there heterogeneity (H chi-squared = 5.50, p = 0.06).



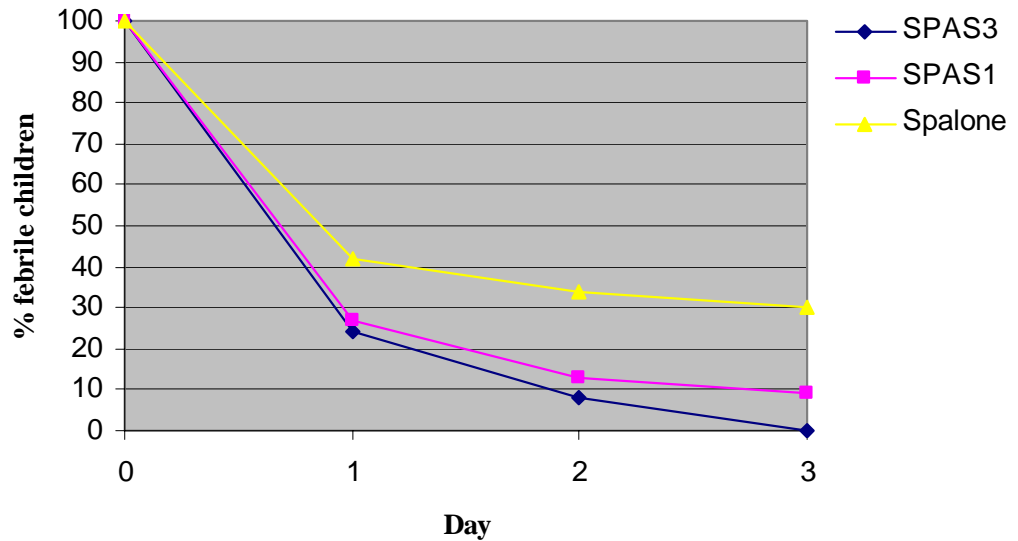
**Figure 3.9 Cure rate at day 14 of SPAS1 vs. SP alone**

**iii. Fever clearance time**

Figure 3.10 shows the trend in the time taken by SPAS3, SPAS1 and SP alone to clear the fever. From the trend lines, it can be seen that the clearance time falls rapidly for both SPAS3 and SPAS1 (though more so for SPAS3) than it did for SP alone.

The chi-squared and p values for SPAS3 vs. SP alone are chi-squared=160.96 p-value <0.001 while they are chi-squared=58.60, p value < 0.001 for SPAS1 vs. SP alone.

Similar pattern was found for parasite clearance time (Figure 3.11).

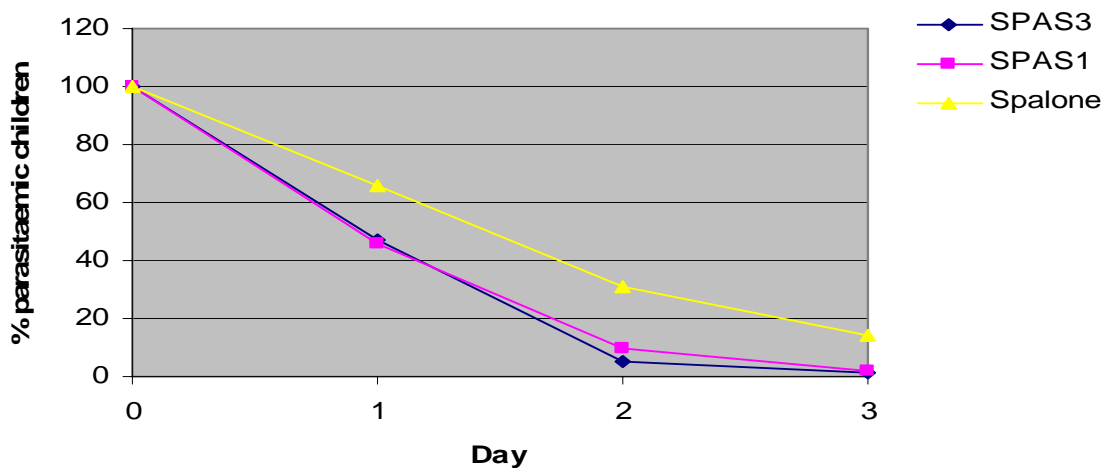


**Figure 3.10 Fever clearance time following treatment.**

**iv. Parasite clearance time**

SPAS3vs. SPalone chi- squared 24.62, p value <0.001

SPAS1 vs. SPalone chi-squared=16.05 p value <0.001



**Figure 3.11 Parasite clearance time following treatment**

## v. Gametocytaemia

At enrollment the proportions of children with gametocytes were 16%, 18% and 19% in SPAS3, SPAS1 and SP alone groups, respectively. By day 7 there was a significant increase in the proportion of children with gametocytes in the group who received SP alone (59%), which followed a downward trend thereafter to a level of 18% by day 28. All the children in the combination groups were however agametocytaemic by day 28.

The chi-squared and p-values between comparison groups are as follows:

SPAS3 vs. SP alone chi-squared=95.25 p value <0.001

SPAS1 vs. SP alone chi-squared=92.52 p value <0.001

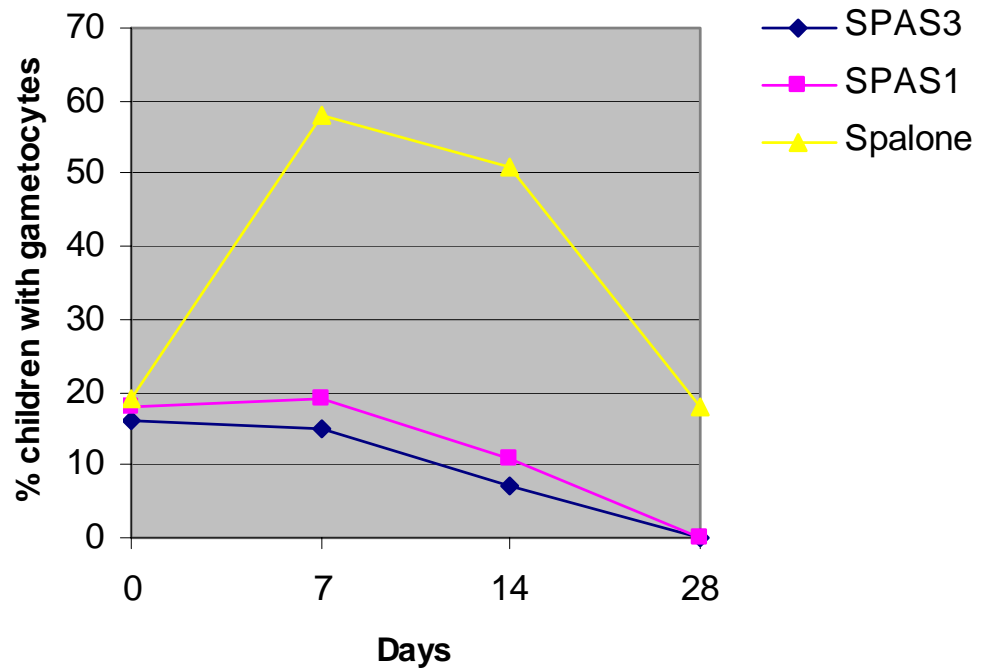


Figure 3.12 Gametocytaemia following treatment.

## **vi. Adverse events**

All the studies reported minor adverse events. These studies did not give enough details on each adverse event, thereby limiting the analysis.

All regimens were safe and well tolerated. Using the available extracted data the 3 most observed minor adverse events were weakness 24% (66/271), anorexia 18% (48/271) and headache 14% (37/271).

## 4.0 DISCUSSION

This study aimed at comparing the combined effect of artesunate and SP with SP alone in areas with different levels of SP resistance and malaria endemicity. According to the WHO protocol for *in vivo* efficacy assessment of antimalarial drugs, patients must be followed-up for a minimum of 14 days.<sup>24</sup> Most clinical trials follow children for at least 28 days. This study included RCT which followed patients for at least 28 days to determine the efficacy of both regimens at day 14 and 28.

The parasitological cure rate for the combination of SPAS3 was two times greater than that of SP alone at day 28 (OR=2.06, 95% CI 1.56 to 2.70). However, the cure rate for the combination of SPAS1 was not statistically significantly different from giving SP alone (OR=0.97 95% CI 0.73 to 1.28). These findings are consistent and comparable with those reported by authors in the field.<sup>7, 25</sup>

The efficacy of antimalarial drugs at day 28 usually consists of assessing both the crude cure rate and the cure rate corrected by PCR. PCR involves genotyping *P. falciparum* proteins namely merozoite surface protein 1 and 2 (msp1 and msp2) and glutamate rich protein (glurp). This molecular technique is used as part of the assessment of efficacy of antimalarial drugs to distinguish recrudescence from re-infection. In malaria endemic areas this distinction is of importance. It helps in avoiding misclassification of the parasitological cure or failure rate. Parasitaemia is classified as reinfection if the results of PCR on the day of admission are different from the PCR results of parasitaemia

reappearance at day 28. If they are the same, the recurrent parasitaemia is classified as recrudescence or failure.

The estimated pooled effect in the meta-analysis did not change when the cure rate was corrected by PCR. The efficacy of the combination of SPAS3 remained statistically significantly higher compared to SP alone (OR=2.55, 95% CI 1.93 to 3.37). The efficacy of the combination of SPAS1 was comparable to that of SP alone (OR= 1.06, 95% CI 0.98 to 1.15). In a meta-analysis of artesunate based-combination therapy recently published, Garner and colleagues reported a significant improvement in cure rate when three doses of artesunate was added to a standard antimalarial drug, irrespective of the standard antimalarial drug used.<sup>25</sup>

Management of uncomplicated *P. falciparum* malaria includes the reduction of clinical symptoms such as fever and parasitaemia clearance. In children, the rapid increase of temperature can lead to convulsions, coma and several other complications. Studies have shown that artesunate is effective in clearing fever and parasitaemia rapidly.<sup>7,8,9</sup> In this meta-analysis there was rapid fever clearance in the combination of SPAS1 or SPAS3 compared to SP alone. At day 3, the proportion of afebrile children was 1 and 2 % in SPAS3 and SPAS1 groups, respectively. The corresponding proportion was statistically significantly higher in children who received SP alone 14% (p<0.001).

In the studies there were debates regarding the benefits of using the combination of SPAS for one day as compared to three days.<sup>6,22,23</sup> This meta-analysis found no difference between the one day and three day options as far as parasite clearance at day

one, two and three were concerned. Besides, the single day therapy would be more cost effective since instead of using 3 doses of artesunate in one patient, two to three patients could be treated on the same dose. The single day regimen would also be more convenient for patients. There are several limitations with this argument.

Firstly, it only looks at one secondary endpoint (parasite clearance) and ignores fever clearance at day 2 and 3 (the other secondary endpoint) and cure rate at day 28 (the primary endpoint) in which case the three day options is clearly superior to the one day option. Due to the low cure rate at day 28 in the one day treatment option SPAS1 there are higher chances of recrudescence of malaria. These episodes might be more severe and may require more expensive treatment. There are also high chances of an emergence of resistance to the drug combination.

The rationale for combining artesunate with existing antimalarial drugs is to delay the emergence of resistant strains, improve the cure rate and decrease malaria transmission. In areas with no SP resistance, combination therapy may prevent the emergence of resistant strains compared to delaying resistance in areas with existing SP resistance.

Gametocyte carriage is used as a measure of the transmission potential of *P. falciparum*. The greater the number of children with gametocytes after treatment, the higher the risk of malaria transmission. An antimalarial drug that has an anti-gametocidal property may decrease the reservoir and therefore malaria transmission.

In this meta-analysis, there was a statistically significant reduction in gametocytaemia at day 28 in children who received the combination of SPAS1 or SPAS3 as compared to those who received SP alone (Figure 3.12). Similar findings are reported by Price, Target and colleagues.<sup>16, 26</sup> They went further to examine how artemisinin derivatives may reduce the reservoir and infectivity by lowering gametocytaemia. A positive association was found between infection of mosquitoes and gametocyte density. The probability of transmission was lowest in children who received the combination of SPAS3, and it was 8-fold higher in the group that received SP alone.

Ascertainment of publication bias in the study was based on the Egger test and a Begg's funnel plot. The results of both methods provide strong evidence against the null hypothesis of the existence of bias. The potential confounders that could have affected the results of the study were also investigated using meta-regression. The pooled effect remained the same after adjusting for the effect of potential confounders. This provided strong evidence that: i) the combination of SPAS3 is more effective than SP alone in areas with SP resistance, ii) There is no difference in the efficacy between the combination of SPAS1 and SP alone. The combination of SPAS3 may therefore be suggested for use in areas with or without SP resistance. In areas with resistance, the combination may delay SP resistance while in areas without resistance it will prevent the emergence of resistance to both SP and artesunate.

Studies across the world have documented the safety and tolerability of artesunate in combination with other antimalarial drugs.<sup>6,7,8,9,10</sup> The combination of artesunate with

other antimalarial drugs is found to be safe and well tolerated. The 2 regimens used in this meta-analysis were safe and well tolerated.

While the meta-analysis has shown strong evidence in support of the combination of SPAS3 and would recommend its adoption in the malaria endemic countries, the issue of cost has to be considered. Changing an antimalarial drug policy usually has huge cost implications. The combination of SPAS is estimated to cost US\$ 1.0 per patient per day compared to US\$ 0.25 for SP alone. However the cost issues must not constitute an argument for not adopting a new, safe and effective therapy such as the combination SPAS3. The impact of the continued use of CQ in areas with CQ resistance has been studied and shown to be associated with an increased malaria related morbidity and mortality in children.<sup>3, 11</sup>

This study had a number of limitations. Firstly, while it is best to conduct a meta-analysis on Individual Patient Data (IPD), this study did not have the benefit of analysing such data because of the difficulty of accessing them. Secondly, there could have been some publication and or language biases. The other major constraint was time; this study was conducted within three months. It was not, therefore, possible to do an exhaustive search for both published and unpublished literature, secure expert input from peers in the field of meta-analysis, especially in malaria and get adequate input on the study details from the authors. For example, information on each adverse event and biological parameters (e.g. hemoglobin, creatinine) was not made available to the researcher even after contacting the authors of the original papers.

The strictness of inclusion and exclusion criteria could also have had an effect on the number of studies included. The following inclusion criteria used were: the study must have been an RCT comparing SP to either SPAS1 or SPAS3, and focused on only children aged six months to ten years. This rigor was partly responsible for the small number of studies included, which may have limited the external validity of the conclusions to only children.

However, by pooling four studies from different settings with different levels of endemicity and SP resistance, coupled with the advantage of a robust sample size, this study provided more generalizable evidence in support of the use of the combination of SPAS3 over SP alone in children.

## 5.0 CONCLUSION AND RECOMMENDATIONS

The combination of SPAS3 is more effective than SP alone. There is no statistical difference between using the combination of SPAS1 and SP alone. The combination of SPAS3 significantly improves the cure rate at both day 14 and 28, results in rapid parasite and fever clearance times. In addition the combination of SPAS3 is more effective in clearing gametocytaemia at day 28, which property adds to its effectiveness as a potent antimalarial drug. This property has not, however, been well documented. All regimens are safe and well tolerated. No serious adverse events were recorded.

The combination of SPAS3 is, therefore, recommended for use or adoption as a replacement to SP alone in both areas with and without SP resistance. Further studies are needed to assess the impact of the combination on malaria transmission and the pattern of *P. falciparum* resistance to SP.

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**Table 3.3 Baseline characteristics of included studies**

Trial	Trial name	Treatment	Randomised	Male	Female	Age	Weight	Temperature	Parasites	Gametocytes
1	Gambia-D	spalone	20	12	8	4.7	16.5	38.3	58974	1
1	Gambia-D	spas3	20	11	9	5.9	18.4	38.3	74641	1
2	Gambia-S	spalone	200	96	104	4.7	14.8	37.7	16000	40
2	Gambia-S	spas1	200	106	94	4.71	15	37.7	23000	34
2	Gambia-S	spas3	200	110	90	4.83	15.3	37.8	19000	34
3	Kenya	spalone	200	97	103	1.4	9.4	38	19172	29
3	Kenya	spas1	200	105	95	1.5	9.6	37.8	19858	33
3	Kenya	spas3	200	104	96	1.3	9.2	37.8	20429	24
4	Uganda	spalone	168	84	84	2.2	11.1	37.8	16143	43
4	Uganda	spas1	126	60	66	2.1	10.9	37.8	17078	28
4	Uganda	spas3	126	52	74	2.4	11.7	37.8	21373	30

Data used in the analysis are the averages of the variables: age (in years), weight (in Kg), temperature (in °C) and parasites (in µl). For gametocytes data represent the number of children with gametocytes (at enrollment).

**Table 3.5 Data used to assess the efficacy of the drug regimens**

<b>Trial</b>	<b>Trial name</b>	<b>Year</b>	<b>Treatment</b>	<b>Randomised</b>	<b>cured at day 28</b>	<b>cured at day28 corrected by PCR</b>	<b>cured at day14</b>	<b>endemicity</b>	<b>SP resistance</b>
1	Gambia-D	1999	spalone	20	11	11	13	mesoendemic	10
1	Gambia-D	1999	spas3	20	16	17	18	mesoendemic	10
2	Gambia-S	2000	spalone	200	178	180	188	mesoendemic	10
2	Gambia-S	2000	spas1	200	173	178	182	mesoendemic	10
2	Gambia-S	2000	spas3	200	183	184	185	mesoendemic	10
3	Kenya	2003	spalone	200	66	102	143	holoendemic	27
3	Kenya	2003	spas1	200	77	118	165	holoendemic	27
3	Kenya	2003	spas3	200	102	142	174	holoendemic	27
4	Uganda	2003	spas3	126	68	87	99	mesoendemic	25
4	Uganda	2003	spalone	168	56	62	86	mesoendemic	25
4	Uganda	2003	spas1	126	34	52	73	mesoendemic	25

**Sample eligibility form**

Study ID: \_\_\_\_\_ Date \_\_\_\_\_ Extractor (initials): \_\_\_\_\_  
 Journal: \_\_\_\_\_ Year publication: \_\_\_\_\_  
 Trial name: \_\_\_\_\_

**(1) DESIGN**

(a) Described as randomized? **Yes** **No** **Unclear**

If No Exclude. If YES go to question 2.

**(2) PARTICIPANTS**

(a) Did the participants have confirmed falciparum malaria? **Yes** **No**  
**Unclear**  
*NB Confirmed by blood slide*

(b) Did the participants have uncomplicated malaria? **Yes** **No**  
**Unclear**

If No Exclude. Otherwise go to question 3.

**(3) INTERVENTIONS**

(a) Was one group given oral Artesunate and SP **Yes** **No**  
**Unclear**  
 as treatment?

b. Did another group receive SP and the same care? **Yes** **No**  
**Unclear**

If No to (a) or (b) then Exclude

FINAL DECISION	Include	Exclude
<b>Unclear</b>	(If all <b>YES</b> )	(If any <b>NO</b> )

Excluded / Unclear because (delete as appropriate): \_\_\_\_\_

If unclear, action taken: \_\_\_\_\_

## Appendix 2

### Displaying the assessment of methodological quality

Study	Concealed allocation	Generation of allocation	Blinding	Loss to follow up

## Description of quality components

The following definitions are from the Cochrane Library guidelines available at [www.cochrane.org](http://www.cochrane.org)

### Allocation concealment

Process used to prevent foreknowledge of group assignment in a randomized controlled trial.

**Adequate:** If participants and the investigators enrolling participants cannot foresee assignment

**Unclear:** method is not described.

**Inadequate:** If participants and investigators enrolling participants can foresee upcoming.

### Generation of allocation sequence

Process used to generate the randomization list.

**Adequate:** If the method used is described and the resulting sequences are unpredictable.

**Unclear:** stated that the trial is randomized, but the method is not described.

**Inadequate:** If sequence could be related to prognosis according to record number, date of birth, date of admission, or alternation.

### Blinding

Refers to whether the participant or outcome assessor is blind to the treatment group.

**Double-blind:** the trial uses a placebo or a double dummy technique so that neither the participant nor the care provider/assessor knows which treatment has been given.

**Single blind:** the participant or care provider/assessor is aware of the treatment given.

**Open:** all parties aware of treatment.

**Loss to follow up:** all randomized participants should be included in the analysis and kept in their original groups regardless of their adherence to the study protocol; this is called an intention-to-treat analysis.

**Adequate:** more than 90% of all the participants randomized into the trial were included in the analysis.

**Unclear:** It is not clear how many participants were originally randomized into the trial.

**Inadequate:** less than 90% of those randomized into the trial were included in the analysis.

**Data extraction form**

Study identifier: \_\_\_\_\_ Date: \_\_\_\_\_ Extractor (initials): \_\_\_\_\_  
 Journal: \_\_\_\_\_ Year publication: \_\_\_\_\_  
 Trial name: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Study period: \_\_\_\_\_  
 Assessed for eligibility: \_\_\_\_\_  
 Eligible: \_\_\_\_\_  
 Notes: \_\_\_\_\_

**1. PARTICIPANTS**

	SP alone	SPAS1day	SPAS3day
Number randomized			
Male/Female			
Age ( years ) <sup>a</sup>			
Weight (Kg) <sup>a</sup>			
Temperature <sup>a</sup>			
Parasites (µl) <sup>b</sup>			
Day 0			
Day 14			
Day 28			

<sup>a</sup>Mean (SD)    <sup>b</sup>Geometric Mean (range)

Local endemicity: \_\_\_\_\_  
 Local SP resistance: \_\_\_\_\_

Inclusion criteria	Exclusion criteria

Were intervention and control groups comparable at baseline? **Yes** **No** **Unclear**

## 2. INTERVENTIONS

Regime used:

<b>Drug</b>	<b>Total dose (mg/kg)</b>
SP alone	
SPAS 1 day	
SPAS 3 days	

## 3. Follow-up

<b>N</b>	<b>SP alone</b>	<b>SPAS 1day</b>	<b>SPAS 3days</b>
Day 0			
14 days			
28 days			
Lost to follow up			

#### 4. Outcomes

	Outcome	n	Rate (%)	OR <sup>a</sup> (95%CI)	P
Efficacy at day 14					
<b>SP alone</b>	Cure				
	Failure				
<b>SPAS 1 day</b>	Cure				
	Failure				
<b>SPAS 3 days</b>	Cure				
	Failure				
Efficacy at day 28					
<b>SP alone</b>	Cure				
	Failure				
<b>SPAS 1 day</b>	Cure				
	Failure				
<b>SPAS 3 days</b>	Cure				
	Failure				
Efficacy at day 28, corrected by PCR (excluding new infections)					
<b>SP alone</b>	Cure				
	Failure				
<b>SPAS 1 day</b>	Cure				
	Failure				
<b>SPAS 3 days</b>	Cure				
	Failure				
Efficacy at day 28, corrected by PCR (including new infections)					
<b>SP alone</b>	Cure				
	Failure				
<b>SPAS 1 day</b>	Cure				
	Failure				
<b>SPAS 3 days</b>	Cure				
	Failure				

<sup>a</sup>Odds ratio (SPAS3 vs. SP alone and SPAS1 vs. SP alone)

	SP alone	SPAS1day	SPAS3day	OR <sup>a,b</sup> (95% CI)	P value
<b>FCT (days)<sup>a</sup></b>					
Day 1					
Day 2					
Day 3					
<b>PCT (days)<sup>a</sup></b>					
Day 1					
Day 2					
Day 3					
<b>Gametocytes</b>					
<b>No with G.</b>					
Day 0					
Day 7					
Day 14					
Day 28					
<b>No without G.</b>					
Day 0					
G.Day 7					
G.Day 14					
G. Day 28					
<b>Hemoglobin (g/dl)<sup>c</sup></b>					
Day 0					
Day 14					
Day 28					
Day 28					
<b>ALT (IU/L, mean)</b>					
Day 0					
Day 14					
Day 28					
<b>Creatinin ( umol/L, mean)</b>					
Day 0					
Day 14					
Day 28					
<b>Bilirubin (g/dl)</b>					
Day 0					
Day 14					
Day 28					
<b>Albumin (g/dl)</b>					
Day 0					
Day 14					
Day 28					

<sup>a</sup>Mean (SD)    <sup>b</sup>Geometric Mean (range)    <sup>c</sup>Mean (range)  
<sup>a</sup>Odds ratio: SPAS3 vs. SP alone and SPAS1 vs. SP alone

## 5. Adverse events

Adverse events	SP alone	SPAS 1 day	SPAS 3 days
Vomiting			
Nausea			
Diarrhoea			
Pruritus			
Headache			
Abdominal pain			
Dizziness			
Anorexia			
Weakness			
Coughing			
Insomnia			
Rash			
Chills			
Epistaxis			
Myalgia			
Palpitation			
Hepatomegaly			
Hypotension			
Splenomegaly			
Tinnitus			
Sore throat			
Others			
<b>Total</b>			

Notes: \_\_\_\_\_

Source of data: \_\_\_\_\_

Notes: \_\_\_\_\_

**Investigator(s) contacted for more information:** Yes \_\_\_\_\_ No \_\_\_\_\_

Name of person contacted: \_\_\_\_\_

Address: \_\_\_\_\_

Telephone: \_\_\_\_\_ E-mail: \_\_\_\_\_

**Data:** Available \_\_\_\_\_ Requested \_\_\_\_\_ Obtained \_\_\_\_\_

Comments: \_\_\_\_\_