Original

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A systematic review of randomized clinical trials published in *Malaria Journal* between 2008 and 2013

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ABSTRACT

Background. Randomized controlled trials (RCT) are a key component in clinical research and they provide the highest quality clinical results. The objective of this study was to describe the main characteristics of RCTs published in *Malaria Journal*, including research topics, study population and design, funding sources and collaboration between institutions. This may help researchers and funders define future research priorities in this field.

Methods. A retrospective analysis was performed on the RCTs published in *Malaria Journal* between January 1, 2008 and December 31, 2013. A key-word search by "Randomized controlled trial" or "Random*" was carried out in PubMed. RCT indexed to MEDLINE were selected for the analysis.

Results. A total of 108 published articles containing RCTs were analysed. Treatment of uncomplicated *Plasmodium falciparum* malaria (n=45, 41.6%), especially the efficacy and safety of antimalarial drugs, and malaria prevention (n=34, 31.5%) were the two main research topics. The majority of trials were conducted in Africa (62.2%) and Asia (27%) and received external funding (private, 42.3% and/or public, 38.6%). Paediatric population was the primary study group (n=63, 58.3%), followed by adults (n=29, 26.9%). Pregnant women (n=7) and geriatric population (n=1) remain underrepresented. Nearly 75% of trials were conducted in individual subjects and 25% in groups of subjects (cluster RCTs). A considerable collaboration between researchers and institutions is noteworthy.

Conclusions. RCTs published in *Malaria Journal* address a wide range of research topics. Paediatric trials conducted in Africa and Asia are frequently performed, and a significant worldwide collaboration to fight against malaria has been identified.

Keywords: Randomized controlled trial, malaria, funding.

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Revisión sistemática de ensayos clínicos aleatorizados publicados en *Malaria Journal* entre 2008 y 2013

RESUMEN

Introducción. Los ensayos clínicos aleatorizados (ECA) y controlados son un componente clave en la investigación clínica y proporcionan la mejor calidad de la evidencia científica. El objetivo de este estudio fue describir las características principales de los ECAs publicados en *Malaria Journal*, incluyendo temas de investigación, diseño del estudio, población, financiación y colaboración entre instituciones. Esto puede ayudar a definir prioridades en la investigación clínica en este campo.

Material y métodos. Se llevó a cabo un análisis sobre los ECAs publicados en *Malaria Journal* entre 2008 y 2013. Se realizó una búsqueda en PubMed mediante las palabras clave "Randomized controlled trial" o "Random*".

Resultados. Se analizaron un total de 108 artículos que contenían ECAs. El tratamiento de malaria no complicada por *Plasmodium falciparum* (n=45; 41,6%) y la prevención de malaria (n=34; 31,5%) fueron los temas de mayor interés. La mayoría de los estudios fueron realizados en África (62,2%) y Asia (27%) y recibieron financiación externa (privada, 42,3% y/o pública, 38,6%). La población pediátrica fue el grupo más estudiado (58,3%), seguido de los adultos (26,9%). Las mujeres embarazadas (n=7) y la población geriátrica (n=1) permanecen infrarrepresentados. Aproximadamente un 75% de los ensayos fueron llevados a cabo en individuos y un 25% en grupos de sujetos. Se observó una colaboración considerable entre los investigadores y las instituciones.

Conclusiones. Los ECAs identificados contienen una amplia variedad de temas de investigación. Los ensayos en pediatría realizados en África y Asia son los más frecuentes y se observa una colaboración global significativa para luchar contra la malaria.

Palabras clave: Ensayo clínico aleatorizado y controlado, malaria, financiación.

INTRODUCTION

Clinical research is crucial for fighting against diseases and for life quality improvement and health promotion. Clinical trials provide the best scientific evidence to make decisions about treatments, preventive measures and global health. However, the low interest of pharmaceutical companies on clinical research for neglected diseases limits the potential improvements in this field[1]. As a result, access to universal health such as the right to use effective, safe and affordable medicines is compromised in low-income countries, which contributes to the poverty cycle. Hence, international support (i.e. economic and technical) in public health and multisectoral collaboration between low and high-income countries is needed in order to implement strategies for reduction of morbidity and mortality caused by malaria disease[2].

Malaria is a tropical disease caused by parasites belonging to the genus *Plasmodium* and transmitted by *Anopheles* mosquito bite. This disease may be potentially fatal if untreated. As a result of the availability of new effective treatments and the strengthening of malaria prevention and control measures, death rate has been reduced 47% globally and 54% in the World Health Organisation (WHO) Africa Region from 2000 to 2013[3] . However, further global efforts towards malaria control and elimination are necessary.

One of the main concerns worldwide is the resistance to antimalarial drugs which constitute a global and recurrent setback in malaria control. In 1960, malaria resistance to cloroquine was confirmed in the Greater Mekong subregion and in some South American countries (Venezuela, Colombia and Brazil)[4-6], and became a major obstacle to tackle malaria eradication. Resistance spread rapidly and extended to Africa in late 1970s[4,6] dramatically increasing malaria mortality rate[7]. In the 80s, parasite resistance to sulfadoxine and pyrimethamine emerged in South America[5]. Antimalarial drug resistance became a generalised problem during the 80s and 90s[5]. Since then, new treatments have been developed and nowadays the first-line treatments recommended for malaria disease are the artemisinin-based combination therapies (ACT)[8,9]. The preferred ACTs for the treatment of uncomplicated *P. falciparum* malaria are artemether-lumefantrine (Coartem®) and amodiaquine-artesunate (Coarsucam®)[9]. However, in 2009 artemisinin resistance in *P. falciparum* malaria was initially reported in the Thailand-Cambodia border, and now has been spread to other areas in Southeast Asia[10-12]. Therefore, in 2011 WHO launched a *Global plan for artemisinin resistance containment* including the strengthening of clinical investigation in order to maximize the reduction of the artemisinin resistance and to improve the access to adequate treatments with ACTs[13].

Overall, although a large and significant progress on malaria control has been achieved, further clinical research on new effective treatments is necessary, especially in order to be prepared for a potential widespread failure of ACTs. Clinical investigation on other health interventions such as prevention measures, vector control strategies, and improved diagnosis also plays an important role in the elimination of malaria. For instance, researchers are currently working on the development of a new vaccine against malaria[14]. Furthermore, the benefit of insecticide-treated mosquito nets (ITN) on the incidence and prevalence of malaria have been widely proved[15,16] and continue to be studied[17]. Additional clinical studies related to the effect, durability and community acceptability of long lasting insecticidal treated-nets (LLITN) are also being conducted[18].

Articles published in *Malaria Journal* use different types of clinical investigation methodologies for the data acquisition and analysis. According to the hierarchical pyramid of the scientific evidence that established the quality of evidence, randomized controlled trials are considered the gold standard in clinical research. These trials allow to extract results that provide the highest validity in order to establish a proper relationship between the intervention and the result[19-21]. For this reason, RCTs performed in human subjects have been selected for the analysis.

Research priorities and goals for malaria treatment and prevention are well defined[2,13,22]. The strategic framework developed by WHO includes global efforts to expand research as one of the main points for the elimination of malaria[2]. Therefore, it is relevant to identify the current main areas of interest in malaria research, which is one of the main objectives of this analysis. The principal characteristics of the RCTs including study design, target population and treatments or interventions assessed may be very informative with regards to the present clinical methodology used and research approach. Moreover, relevant data concerning the topics investigated, countries involved in those trials, collaborations among researchers and funding sources may help researchers and funders define future research priorities in this tropical disease considering the current needs in the present setting.

Overall, this evidence-based medicine analysis on malaria disease is particularly designed to describe the current malaria research lines and to highlight the identified research gaps and the possible future priorities on malaria clinical investigation.

The primary goal is to describe the main characteristics of RCTs recently published in *Malaria Journal*, such as research topics, study population and design, funding sources and countries where RCTs were performed. The secondary objective is expected to describe the collaboration among countries, researchers or institutions.

METHODS

Study design, search strategy and selection criteria of articles. A retrospective analysis of randomized controlled trials published in the 6-year-period from January 1, 2008 to

December 30, 2013 in *Malaria Journal* was performed. This period of time is considered sufficiently representative to characterise the current clinical investigation lines on malaria disease.

In order to identify the randomized controlled trials, a wide and sensitive search was carried out in PubMed including a search by "Randomized controlled trials" according to MEDLINE classification and a non-restrictive search by the term "Random*". This search criteria examines titles, keywords and abstracts by words containing "Randomized controlled trial" or beginning by "Random".

Nonrandomized trials, studies not using humans subjects or groups of humans as the unit of randomization and observation (i.e. malaria vector studies), observational studies (i.e. case and control study, cross-sectional studies, cohort study, longitudinal study), meta-analysis, systematic reviews, surveys, parasitological analysis, epidemiological and genetic studies, risk factors studies, economic studies, etc., were excluded from the analysis. Abstracts and, when necessary, articles were examined for all articles identified by the MEDLINE search to assess exclusion criteria.

This systematic review has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[23].

The quality of studies was evaluated using the Jadad Scale, which assesses the methodological quality of reports of randomized clinical trials with a score ranging from 0 (worst quality of the publication) to 5 (best quality of the publication)[24].

Data collection. Nine variables of interest were measured during the analysis including the total number of authors involved, country of the institution of the first author, number and origin of researchers, countries where the clinical trials were conducted, study design, target population, research topic, clinical intervention or treatment and funding source.

The origin of researchers was categorized as Americans (North America and Canada), Europeans (Europe region) and

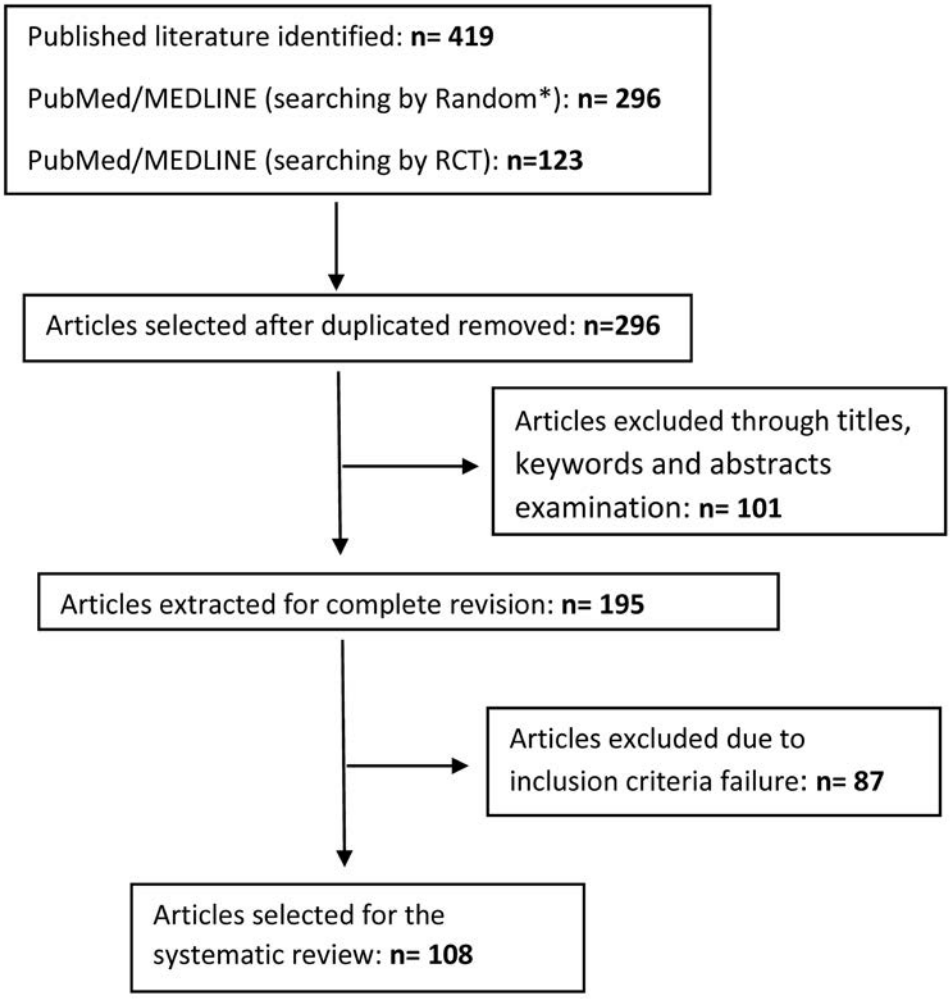

Figure 1 | **Flow diagram. Procedure followed for selecting articles.**

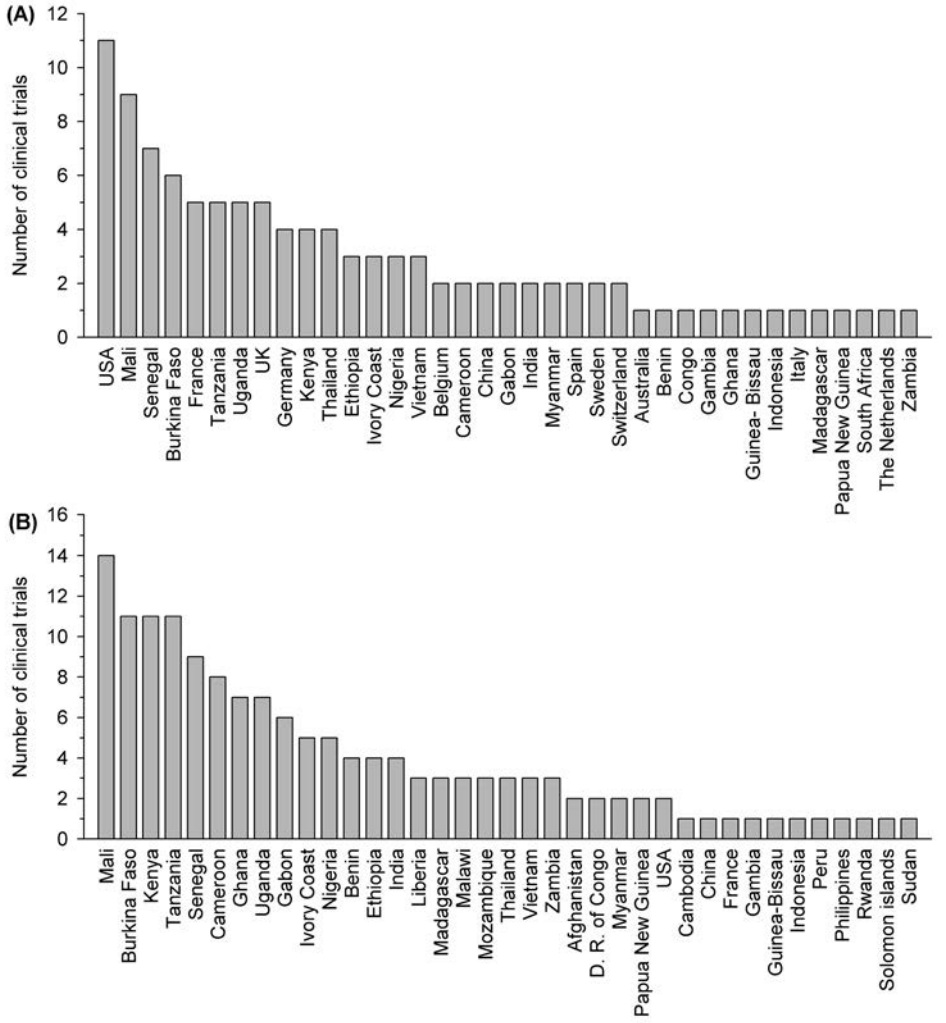

Figure 2 | **Countries of trials and first author. (A) Number of studies per country of the institution of the first author. (B) Number of studies per country where trials were performed.**

other origins (Africa, Asia and South America and Oceania) based on the country of the institution.

The studied population was defined as paediatric population (< 18 years), adults (≥18 - < 65 years), elderly (≥ 65 years), pregnant women and general population (when all age ranges were included or if the different groups of age were not specified).

The topic studied in each clinical trial was classified in 4 categories covering treatment (i.e. treatment of uncomplicated *Plasmodium falciparum* malaria, *P. vivax* malaria, malaria in pregnancy, complicated malaria, resistant and multiresistant *P. falciparum* malaria, *P. falciparum* malaria in patients with G-6PDH deficiency, severe malarial anaemia, uncomplicated *P. falciparum*, *P. vivax* or mixed malaria and treatment of fever in uncomplicated *P. falciparum* malaria patients), malaria prevention/public health intervention (i.e. insecticide-treated bed nets, intermittent preventive treatment or IPT, vaccine, IPT with home management, malaria chemoprophylaxis, treatment of asymptomatic carriers, frequency of *P. falciparum* infection, interruption of malaria transmission, resistance to sulphadoxine-pyrimethamine), malaria diagnosis and others (i.e. pharmacokinetic of antimalarial combinations, bioequivalence study, frequency of G6PD deficiency in malaria patients, impact of vaccination in malarial anaemia, malaria and pneumonia)

According to the study design and unit of randomization, trials were classified as clinical trials in individual subjects or in groups of subjects (i.e. cluster RCT). Treatments or interventions assessed during clinical trials may include drugs, vaccines, insecticide-treated bed nets or other public health intervention. Funding source was classified in the following categories: public (governments, universities and schools), private (private foundations, pharmaceutical and chemical industry), World Health Organisation (WHO) or other International Organisations (e.g. United Nations' Children Fund - UNICEF, Uni-

Table 1 Research areas and specific categories

Areas	Number	Percentage	Specific categories	Number	Percentage
Treatment	60	55.5	Uncomplicated *P. falciparum* malaria	45	41.6
			P. vivax malaria	4	3.7
			Malaria in pregnancy	3	2.7
			Complicated malaria	2	1.8
			Resistant *P. falciparum* malaria (including multiresistant malaria)	2	1.8
			P. falciparum malaria in patients with G-6PDH deficiency	1	0.9
			Severe malarial anaemia	1	0.9
			Treatment of fever in uncomplicated *P. falciparum* malaria patients	1	0.9
			Uncomplicated *P. falciparum*, *P. vivax* or mixed malaria	1	0.9
Prevention/public health intervention	34	31.5	Insecticide-treated bed nets	10	9.3
			Intermittent preventive treatment (IPT)	9	8.3
			Vaccine	5	4.6
			IPT with home management	3	2.7
			Malaria chemoprophylaxis	2	1.8
			Treatment of asymptomatic carriers	2	1.8
			Frequency of *P. falciparum* infection	1	0.9
			Interruption of malaria transmission	1	0.9
			Resistance to sulphadoxine-pyrimethamine	1	0.9
Diagnosis	3	2.8	Malaria diagnosis	3	2.7
Others	11	10.2	Pharmacokinetic of antimalarial medication	5	4.6
			Bioequivalence study	3	2.7
			Frequency of G6PD deficiency in malaria patients	1	0.9
			Impact of vaccination in malarial anaemia	1	0.9
			Malaria and pneumonia	1	0.9

ted Nations Development Programme - UNDP, World Bank), public-private organizations, European Commission or other European Institutions or unfunded. Trials were considered industry sponsored if a company provided any funding or free medicines or nets for the study.

Primary data analysis. The results were analysed using the SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables were codified for the statistical analysis. The description of data collected has been carried out through absolute and relative count using table of frequencies and graphs. Quantitative variables have been described using statistical measures of central tendency (mean and median) and their respective measures of dispersion (standard deviation and interquartile range).

RESULTS

After searching in PubMed, 123 articles with keyword "Randomized controlled trials" and 296 with the term "Random*" were assessed for study inclusion. All articles identified by "Randomized controlled trials" search were also included in the group of articles identified by "Random*". Of these 296 articles, 188 were excluded: 69 were surveys (i.e. cross-sectional surveys, house to house surveys, cluster surveys, entomological surveys), 19 observational studies (i.e. case and control studies, cross-sectional studies, cohort studies, longitudinal studies), 11 reviews and/or meta-analysis, 10 genetic studies, 7 malaria prevention and control studies, 7 vector studies, 6 case reports, 5 health economic studies (i.e. cost-effectiveness, cost analysis and cost benefit studies), 2 non-randomized studies and 52 were included under "others" category. This left a total of 108 articles eligible for the present study analysis (figure 1).

The mean number of authors involved in each article was 10 (standard deviation = 4.2), with a minimum of 3 and a maximum of 29. The origin of the institution of the first author most frequently observed was USA (10.1%), Mali (8.3%), Sene-

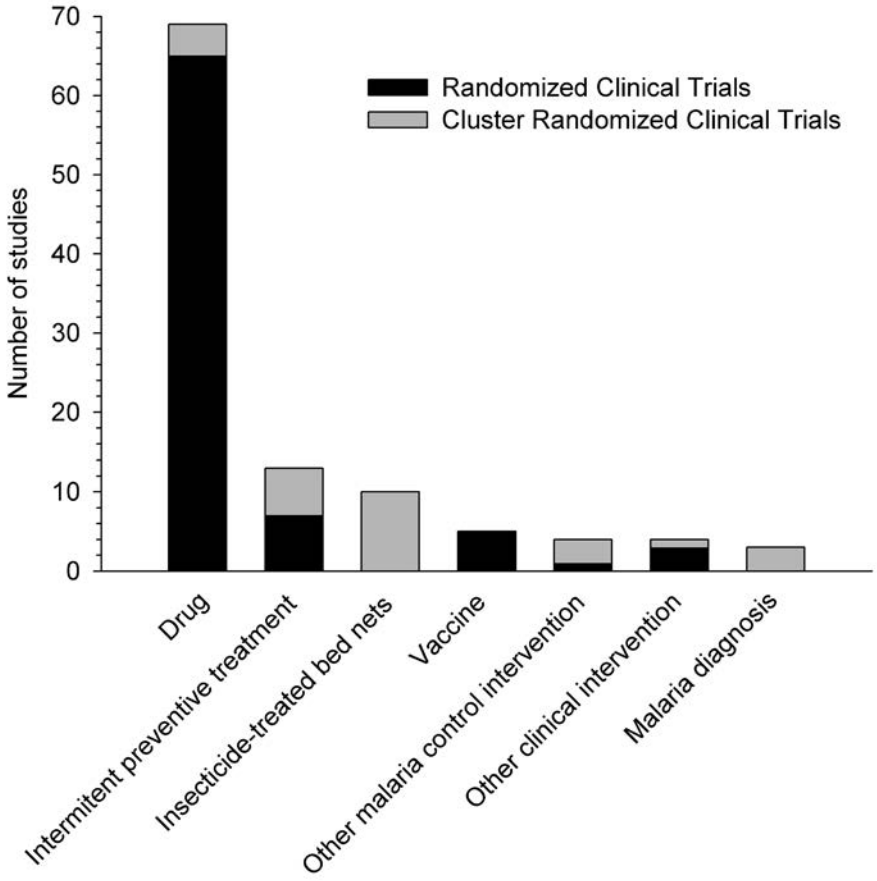

Figure 3 | **Clinical trial design and type of malaria intervention. Frequency of trials in relation to clinical trial design and type of malaria intervention.**

gal (6.5%) and Burkina Faso (5.6%), among a total of 37 countries (figure 2A). By geographic area these institutions belonged mainly to Africa with 57 articles (52.8%), followed by Europe (15.7%), Asia (13%), North America (10.2%), and Australia (1.9%). Furthermore, 70 European researchers, 25 American researchers and 105 researchers from other countries (generally African and Asiatic countries) collaborated in the development of the 108 selected studies.

Clinical trials were conducted in 37 different countries. These were mainly from Africa (62.2%) and Asia (27%), although a 10.8% were also distributed between North America, South America, Europe and Oceania. The countries with higher number of RCTs performed were Mali, Burkina Faso, Kenya and Tanzania (figure 2B). In general, among the 108 studies evaluated, 95 (87.9%) were performed in one country. The rest of studies (n=13) were performed in more than one country (2 to 7 countries).

The target study group was mainly paediatric population (63 studies, 58.3%). Yet, 26.9% of studies included adults and 18.5% of trials covered all age groups or do not specify the age. Only 7 studies included pregnant women (6.5%) and elderly patients (≥65 years) were only studied in one RCT.

Uncomplicated *P. falciparum* malaria treatment and malaria prevention were the two main research topics of the clinical trials (41.7% and 20.4%, respectively) (table 1).

The most common clinical intervention was the use of drugs in order to determine their efficacy and safety in patients suffering from malaria (63.9%). Other frequent clinical interventions included prevention and control measures such as intermittent preventive treatment (12%), insecticide treated bed nets (9.3%), and vaccines (4.6%) (figure 3).

Considering clinical trial design and unit of randomization, approximately 75% of trials were categorized as clinical trials in individual subjects and 25% as cluster RCTs in which groups of subjects were assigned at random to an intervention group. It is to be noted that the majority of cluster RCTs (70%) were focused on malaria control. Of them, more than half investigated the effect of using insecticide-treated bed net on the reduction of malaria illness. The rest were intended to study intermittent preventive treatment, malaria diagnosis and other malaria control interventions (figure 3).

The great majority of RCTs published in the selected articles (98.4%) were sponsored. A total of 89 different institutions funded these investigations. Only three studies (1.6%) were

Table 2 **Funding sources and type of institutions supporting malaria trials**

Funding source	Number	Percentage	Main institutions	Number	Percentage
Private	80	42.3	**Private foundations and other institutions:**	43	22.7
			- Bill and Melinda Gate Foundation	8	
			- The Wellcome Trust	7	
			- Drugs for Neglected Diseases Initiative (DNDi)	5	
			- Médecins Sans Frontières	5	
			- Gates Malaria Partnership at the London School of Hygiene and Tropical Medicine	3	
			- Global Fund for AIDS, Tuberculosis and Malaria	3	
			- PATH Malaria Vaccine Initiative	3	
			- Others	9	
			Pharmaceutical and chemical industries (excluding medicines or nets donation):	24	12.7
			- Novartis S A	5	
			- Sanofi	4	
			- DafraP harma Belgium	3	
			- GlaxoSmithKline (GSK)	3	
			- Kunming Pharmaceutical Corp	3	
			- Pfizer	2	
			- Others	4	
			Companies that donate medicines or nets:	13	6.9
			- Sanofi	4	
			- Kunming Pharmaceutical Corp	3	
			- Novartis S A	2	
			- Others	4	
Public	73	38.6	Government (national institutes or agencies, ministries of health)	55	29.1
			Universities and Schools	18	9.5
International	17	9	WHO (including UNICEF/UNDP/World Bank/WHO and MIM/TDR)	14	7.4
			International Atomic Energy, Agency (IAEA)	3	1.6
European	11	5.8	**European institutions:**	11	5.8
			- European Commission	10	
			- European Developing Countries Clinical Trials Partnership (EDCTP)	1	
Public-private	5	2.6	Medicines for Malaria Venture (MMV)	5	2.6
Unfunded	3	1.6	No funding institutions	3	1.6

*** UNICEF (United Nations's Children Fund), UNDP (United Nations Development Programme), MIM/TDR (Multilateral Initiative of Malaria/Tropical Disease Research)**

not supported by any institution. Private organizations funded 42.3% of the studies, covering private foundations (22.7%) and pharmaceutical or chemical companies (19.6%). It should be highlighted that 13 studies (6.9%) were supported by the deployment of drugs or nets free of charge from pharmaceutical or chemical companies. Approximately 39% of manuscripts received funding from public institutions including governments (29.1%) and universities (9.5%). The rest of trials' funding came from European (i.e. European Commission) or International institutions (i.e. WHO). Most of the trials were sponsored by one (99 studies) or two institutions (48 studies) although in some cases 4 to 5 institutions took part in the trial funding. The financial institutions most commonly involved in the funding of the malaria trials selected were government institutions (55 studies), universities and schools (18 studies), World Health Organization (WHO) or other international organizations (14 studies), European Commission (10 studies), Bill and Melinda Gates Foundation (8 studies), Sanofi Aventis (8 studies), The Wellcome Trust (7 studies) and Novartis S.A (7 studies) (table 2).

The mean quality of the studies selected was 1.83 using the Jadad Scale. Seventy two out of 108 studies had ≥ 2 points (7 with a score of 5). The reports of RCTs with less than 2 points were considered of low methodological quality.

DISCUSSION

The primary analysis is based on a descriptive assessment of the principal characteristics of RCTs published in *Malaria*

Journal and the capacity of collaboration among countries, researchers or institutions. This information may provide interesting data concerning the current lines of investigation in malaria disease as well as the potential research gaps considering the current needs in this field. Consequently, this RCT analysis may offer an opportunity to strengthen certain malaria research areas in the future.

The results indicate that RCTs identified in *Malaria Journal* addressed a wide range of malaria research topics, which are in line with the global malaria elimination goals[2]. Treatment of uncomplicated *P. falciparum* malaria and malaria prevention are the two topics most represented.

The principal strategic priority in the fight against malaria seems to be related to therapeutic innovation. The study of the efficacy and safety of new combinations of antimalarials, new routes of administrations or new dose regimens are mainly investigated in most of the studies. In addition, the already authorised malaria treatments are also being studied in order to guarantee their positive benefit-risk balance in the clinical practice. Drug-resistance to artemisinin drugs and sulphadoxine-pyrimethamine is also considered a major problem and some studies related to these topics have been identified. The majority of the above mentioned studies were designed as RCT in individuals.

The second and relevant milestone is related to malaria prevention. Different interventions to control malaria are being investigated, especially the efficacy of using insecticide-treated bed nets in endemic areas. Moreover, chemoprophylaxis including intermittent preventive treatment and other management strategies, prophylactic vaccines, treatment of carriers, and so on are also important areas of research. Currently, RTS,S vaccine is being studied in order to obtain a marketing authorization.

Following WHO recommendations[2], malaria diagnosis is also a key point in the elimination of malaria. However, low quantity of RCTs related to malaria diagnosis was identified in this analysis.

Studies related to malaria prevention and malaria diagnosis were principally performed in groups of subjects (i.e. cluster RCTs), which is not unexpected. These type of trials are noted to be very useful in the field of public health to study the effectiveness of community interventions[25,26]. Moreover, these studies are very practical in low-income countries where the belief and cultural differences limit the performance of clinical trials in individual subjects.

Trials received support from one or more public or private institutions, being government institutions, universities, WHO, European Commission, Bill and Melinda Gates Foundation, The Wellcome Trust, Drugs for Neglected Diseases initiative - DNDi, Médecins Sans Frontière and Novartis S.A the ones that most contributed to funding. Pharmaceutical or Chemical companies sponsored a low number of studies and some of them provided medicines or nets for free. Only 3 trials did not receive external funding. Overall, this information reflects the relevance of external funding sources in the development of clinical trials for malaria.

Paediatric patients, one of the most vulnerable groups to malaria disease in endemic countries[27], were the primary study population followed by adults. Pregnant women and elderly were underrepresented, which is not unexpected. Pregnant women are generally less studied due to ethical considerations concerning the potential foetal risks. However, given that malaria in pregnancy increases the risk of maternal and foetal problems[24], the development of clinical trials in this population would need to be strengthened. Elderly are less likely to be enrolled in clinical trials given that the incidence of malaria is lower compared to other age groups and the life expectancy at birth in low-income countries is limited to approximately 60 years[28].

Centres conducting clinical trials were primarily situated in Africa and Asia, which is reasonable regarding the epidemiological profile of malaria. Collaboration between countries and institutions is highly notable, being African, Asiatic and European researchers the most involved in these trials, followed by North American researchers. These findings may reflect that a global cooperation is essential and is currently being a benchmark in the fight against malaria.

In relation to the assessment risk of bias in each article, it is remarkable that all RCTs included in the articles selected were reported to be randomized as it was established in the search criteria using PubMed. However, several RCTs were not blinded to the study arms after allocation due to the nature of the malaria interventions (e.g. cluster randomized trials). This may justify the identification of some reports with less than 2 points (low methodological quality) using the Jadad scale.

This study has several important limitations. Firstly, only RCTs in *Malaria Journal* were evaluated. RCTs related to malaria published in other general medicine journals such as *The Lancet* or *The Nature Medicine* were not included in this analysis. Therefore, although this analysis provides a general view about the predominant trends in malaria research, its results should be interpreted with caution. Nevertheless, the topics studied in this analysis seem to be well-represented given that *Malaria Journal* is considered the main reference in malaria field. Secondly, it is likely that the search strategy performed failed in the identification of some RCTs published in *Malaria Journal* during the time period analysed. This may affect to the final number of selected studies for the analysis. Finally, the results of the clinical trials evaluated are based on the information reported by the authors. Data included in the abstract regarding the characteristics of the study depends on a single author and may be reported in a different manner by another author. This may lead to a misclassification of the clinical study. Moreover, funding source data may be underreported in the published articles and therefore the percentage of external funding will be underestimated. Therefore, information bias cannot be ruled out in this malaria RCTs' revision.

In conclusion, RCTs identified in *Malaria Journal* provide an insight into the main activity areas on malaria research, the principal study population, the current patterns of randomized trials funding and the collaboration between countries and

institutions. Malaria disease is a global health challenge that requires further efforts to be controlled and reduced. Therefore, it is expected that this analysis may be useful for malaria researchers and funders.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTIONS

JMR conceived this study. JMR and EMA formulated the study protocol, extracted data, analysed the data and prepared the manuscript. All authors have read and approved the final manuscript.

Additional information

Appendix 1. Articles selected for this analysis. This file contains the 108 references of the articles from *Malaria Journal* evaluated in this study.

Appendix 2. Search strategy for the identification of reports of randomized controlled trials using PubMed.

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Appendix 1

Articles selected for this analysis. This appendix contains the 108 references of the articles from *Malaria Journal* evaluated in this study

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Appendix 2

	Search strategy for the identification of reports of randomized controlled trials using PubMed

(("Malaria journal"[Journal]) AND ("2008/01/01"[Date - Publication] : "2013/31/12"[Date - Publication])): 2278 results

(("Malaria journal"[Journal]) AND ("2008/01/01"[Date - Publication] : "2013/31/12"[Date - Publication])) AND Random*: 296 results

Search (("Malaria journal"[Journal]) AND ("2008/01/01"[Date - Publication] : "2013/31/12"[Date - Publication])) Filters: Randomized Controlled Trial: 123 results.