Comment on "A. annua and A. afra infusions vs. Artesunate-amodiaquine (ASAQ) in treating Plasmodium falciparum malaria in a large scale, double blind, randomized clinical trial" Munyangi et al., 2019

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Dear Editor,

Introduction

We read with great interest the article entitled "*A. annua* and *A. afra* infusions *vs.* Artesunate-amodiaquine (ASAQ) in treating *Plasmodium falciparum* malaria in a large scale, double blind, randomized clinical trial" (Munyangi et al., 2019).

This study seems to be designed as a phase III double-blind randomized clinical trial demonstrating the superiority of *A. annua* and *A. afra* infusions over ASAQ for the treatment of uncomplicated *P. falciparum* malaria in Africa.

However, we have noticed some issues and inconsistencies in the background, methods and results, and would like to provide the readers of your journal with a critical analysis of this study. Indeed, we believe that the scientific validity of the results is affected as well as the ethical integrity given the lethal risk of malaria for infected patients.

Critical review of the article

Background

The clinical efficacy of *Artemisia* is not fully supported by the references provided. The report of 18 malaria cases treated by dried leaf of *A. annua* is biased as all patients received artesunate before *A. annua* (Daddy et al., 2017). Consequently the attribution of recovery to *A. annua* cannot be asserted. Of the four trials on *Artemisia* that are cited the first one reports a 4-day parasitemia clearance rate of 44 / 48 (92%) for *A. annua* infusion (Mueller et al., 2000). The second reference, is not a clinical trial but rather a survey with retrospective declarative reports of efficacy by patients themselves (Tiruneh et al., 2010). The third reference (Chougouo-Kengne et al., 2012) describes a poorly reported 4-group randomized controlled trial with many inconsistent results showing 18 successes in 18 patients after 7 days of treatment with *A. annua* tea infusions but an average parasitemia equal to 500 trophozoites/µl at 7 days and 100 trophozoites/µl at 14 days in this group. The fourth reference (Zime-Diawara et al., 2015) describes a non-controlled trial of 12 g/day infusions of *A. annua* with a high cure rate (100% parasite clearance in 108 patients after 28 days). Such a miraculous clearance rate has never been observed even with the most efficient drugs. Also there are strange results with 100% of patients with a body temperature exactly equal to 37 °C from D3 to D28 which is unlikely to occur in real life.

Better trials have been performed but none have supported the efficacy of *Artemisia* infusions. Mueller et al. (2004) tested the *in vivo* efficacy of *A. annua* infusions *vs. Quinine* in a randomized controlled trial, including 45 patients assigned to three groups: 5 g herb/day, 9 g herb/day and Quinine 1500 mg/day. The 7-day cure rates were respectively 77%, 70% and 91% while the 30-day cure rates were 34%, 28% and 79%. Therefore, the authors raised concerns about the poor efficacy of *A. annua* infusions and the risk of resistance due to the insufficient dose of Artemisinin contained in *A. annua*. A randomized controlled trial was conducted in Tanzania by Blanke et al. (2008) between September 2002 and October 2003 but was discontinued early because of the poor efficacy of *A. annua* infusions with a 28-day efficacy rate of 10% (1/10) probably due to recrudescences.

Ethics

There are some ethical concerns. First a large-scale randomized controlled trial for *Artemisia* (phase III) should not have been conducted without prior evidence of efficacy in smaller randomized trials (*e.g.,* phase IIb). Mueller et al. (2004) showed that 10 g/day of dried leaf of *A. annua* was not enough to control the disease (recrudescence); the current study protocol uses half the dose (5 g/day).

All treatments were started from D1, as specified in the Methods section. Since the baseline is D0, as seen in tables, figures and text, this implies that patients had to wait until the next day to receive their first Malaria medication even though malaria is a life-threatening disease. Indeed, malaria treatment should have been started as soon as possible, just after randomization. In addition, patients were reportedly diagnosed with fever and parasitemia repeatedly over the duration of follow-up (at D7, D14 and D28) but no rescue treatment was provided to these persons.

We would like to point out that the same authors recently published in your journal (Munyangi et al., 2018) another large-scale double blind randomized controlled trial on *Artemisia vs.* praziquantel for the treatment of schistosomiasis. We also found scientific and ethical issues, in this previous article and sent a comment to your journal (Argemi et al., 2019). We noticed that the article on schistosomiasis referred to the same ethics committee registration number as the malaria article: MIN.RST/SG/180/001/2016. Since the two protocols are very different and cannot be applied to the same patients, it is hardly conceivable that the same registration number could apply to both studies. Moreover both studies were conducted in 2015 while the registration number suggests that approval was obtained in 2016.

Methods

The study design has several issues. The randomization procedure is unclear or inadequate. Envelope randomization assumes that envelopes are given in the order patients are included but authors specify that patients randomly selected an envelope. This makes stratified randomization impossible and envelope tracking harder. The authors specify

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that the drugs were contained in an envelope. This is strange, but not impossible when drugs provided for 7 days do not have a large volume. However, since the *Artemisia* placebos were infusions of 0.2 g/day of the plant, the number or size of *Artemisia* leaves would have been very different between arms and the physician looking at the size of the envelope would have been able to identify the group as well as the patient. There are also concerns about the similarity of presentation between the ASAQ placebo (purchased in "a pharmacy") and the real ASAQ Winthrop, Sanofi-Aventis. Obtaining visually identical placebo usually requires a specific pharmaceutical preparation.

The study protocol mentions that all patients, with non-severe malaria, were hospitalized for 7 days in order to ensure therapeutic compliance. The list of hospital centers was not specified. Direct delivery of drugs to the patient in envelopes seems to be useless when nurses could have provided the treatment during hospitalization. In the ASAQ group, the active drug was given for 3 days, followed by 4 days of placebo, without any clear reason for giving a placebo. Patients with persistent vomiting were excluded; this may have caused an attrition bias.

Neither a primary outcome nor a primary analysis was mentioned in the Methods section. In the results section it was stated that "The primary outcome of the trial was that, based on microscopic analyses, both *Artemisia* sp. cured malaria faster and more effectively than ASAQ", but no numeric results and no ***P***-values were given. The analyses supporting the statement "faster and more effectively" are not specified in the methods. Since there are two *Artemisia* arms, multiple comparisons should have been performed, with a multiple testing procedure adjustment to control the family-wise error rate. There is no sample size calculation mentioned. Hypothesis test statistics are mandatory for a clinical trial but descriptive results alone are provided by authors for major outcomes such as parasitemia.

Results

Frequencies

Results are strange and inconsistent. Why was the number of screened patients exactly equal to 2000? Why were the numbers of included patients, at the same time, multiples of hundred in all centers but one? If each center had been given instructions to stop screening when a given number of patients was screened, that could explain why the number of screened patients was a multiple of hundred, but would not explain why numbers of included patients were multiples of hundred and *vice versa*.

Sample sizes are inconsistent. The flow chart shows 957 randomized patients at baseline but supplementary Table S1 shows 1000 randomized patients. The flow chart shows 229 patients randomized in the *A. afra* group but Table 5 shows 249 patients at D28 which means that 20 patients were gained during follow-up, a rather unusual situation.

Loss to follow-up shown in Fig. 1 (flow-chart) was 1.7% in pooled *Artemisia* groups and 1.3% in the ASAQ group, but in Fig. 2 it was 10.3%, 26.7% and 0.0% in the *A. annua, A. afra* and ASAQ groups, respectively.

Fever

In the summary, fever clearance was evaluated at 48 h for ASAQ and 24 h for *Artemisia* groups. Conversely, in the results section, the lower panel of Fig. 2 shows that, at 7 days, fever persisted for 50% of patients in the ASAQ and *A. afra* groups. The upper panel of Fig. 2 shows an average temperature below 37 °C in the *A. afra* group at 7 days, which is hardly compatible with 50% of patients having fever as shown in the lower panel.

Trophozoite clearance

In the summary, trophozoites were cleared within 24 h in *Artemisia* groups and 14 days in the ASAQ group. This contradicts the lower panel of Fig. 3, showing more than 80% of patients with parasites at D7 in all groups. The upper panel of Fig. 3 shows an average number of trophozoites / µl equal or very close to 0 at 24 h in the *A. annua* group, in contradiction with the lower panel showing fewer than 20% of negative patients at that time.

The low response rate (34%) and the delayed response (14 days) shown in Fig. 3 for ASAQ does not match the literature on this treatment. In a recent (2013–2014) study conducted in South Kivu, a region near to Kalima health district, the absolute parasitological cure rate of ASAQ was about 91.6% (109 / 119) at D28 without Polymerase Chain Reaction (PCR) correction for reinfections and 97.5% (116 / 119) with PCR correction (Wit et al., 2016). With ASAQ, parasite clearance is expected in less than three days (Dorkenoo et al., 2016)

World Health Organization (WHO) guidelines (*Methods for Surveillance of Antimalarial Drug Efficacy*, 2009) recommend the evaluation of the PCR adjusted cure rate, which requires collecting genotype evidence to estimate if an infection identified post-treatment is a recrudescence (an infection caused by the same parasite as identified before treatment) interpreted as a failure or a reinfection (caused by a parasite with a different genotype). Surprisingly, the authors report that no sample could be exploited out of several thousand filter paper samples that should have been collected.

Microscopy results suggest that detection of trophozoites might have been insufficiently sensitive across the study. In the ASAQ arm, 161 patients displayed no parasites at D14. The same number of patients displayed no parasites at D28. This shows that no patient had any reinfection or recrudescence between D14 and D28 or that an equal number of patients had reinfection/recrudescence and delayed cure. A similar absence or very low rate of reinfection is reported in the other two arms. In high malaria transmission areas such as the Democratic Republic of Congo, these results are highly unusual and contrast with the study in South Kivu (Wit et al., 2016), showing a PCR-unadjusted cure rate equal to 91.6% with ASAQ at D28 and 97.5% after PCR-adjustment, indicating that the majority of parasitemias observed after treatment were caused by reinfections.

The authors stated that "By the log-rank test at D28, three of the four compared groups were significantly different, but there was no significant difference between *A. annua* and *A. afra* ($p = 0.505$)". First, log-rank test is not appropriate to compare rates at one time point, here D28. Second, in the methodology, only three groups are presented, not four.

There is also considerable heterogeneity in efficacy of treatments between study sites, ranging from 0% (Kamundala) to 100% (Lubile) negative parasitemia at D28 for ASAQ and from 0% (Kinkungwa, $n = 7$) to 100% (Kakutya) for *A. afra*.

Hemoglobin levels

Hemoglobin levels are said to be non-significantly different at D0, D1, D3 and D4 between *A. annua* and ASAQ groups. This contradicts the data in Fig. 5. Indeed, Fig. 5 shows whiskers that may either be confidence intervals or standard errors (not specified by authors). Even in case of standard errors, the difference at D0 between ASAQ and *A. annua* would have been statistically significant. Indeed, doubling width of whiskers could provide confidence intervals that do not overlap at all. A statistically significant difference at D0 (baseline) suggests that the randomization protocol was not properly conducted.

Adverse effects

Table 4 shows adverse effects. Both *Artemisia* arms were pooled. The very low level of adverse effects in the *Artemisia* arms suggests a differential declaration bias, since non-specific symptoms such as asthenia should have been found in more than four hundred patients followed for 28 days (more than eleven thousand patient-days). This is only possible if the blinding was broken. The difference between adverse effects (attributed to treatment) and adverse events (not necessarily attributed to treatment) was not made. Strangely, numbers of adverse effects were mostly multiples of five, as 10 in 13 frequencies of non-zero

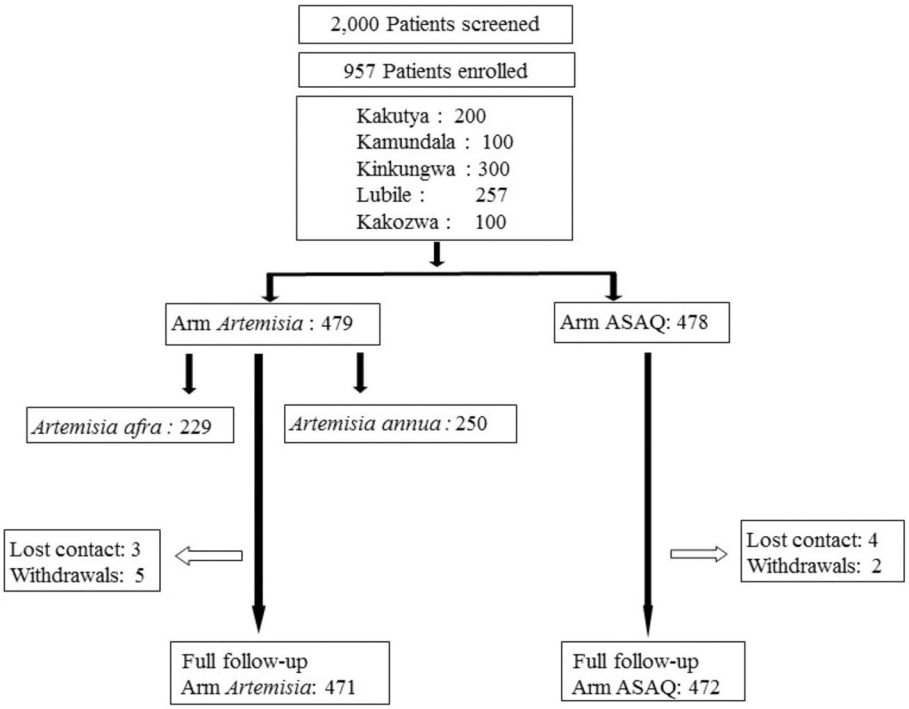

Fig. 1. Trial design.

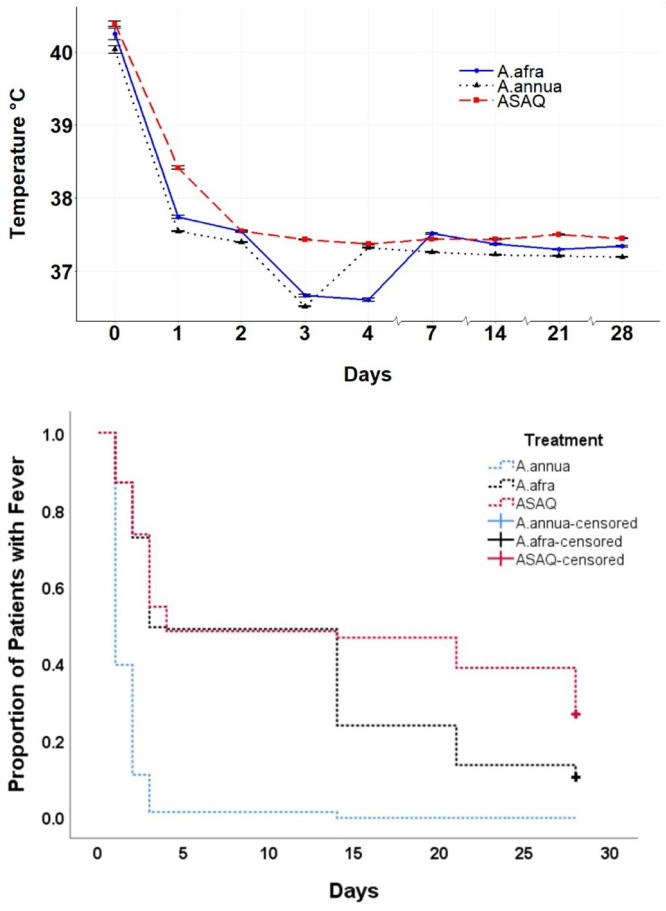

Fig. 2. Average fever progression among the three treatment arms. Top, graphical representation. Bottom, Kaplan–Meier; survival time of fever started when a patient was included in the study (D0). Patients were followed until D28. For patients withdrawing from the study before D28 or still having fever until D28, survival time is said to be censored. The survival probability was calculated using the Kaplan–Meier method. The censored rates of A. annua, A. afra, and ASAQ are 0.0%, 10.3%, and 26.7%, respectively, with p-value of log-rank still near to zero and statistically significant.

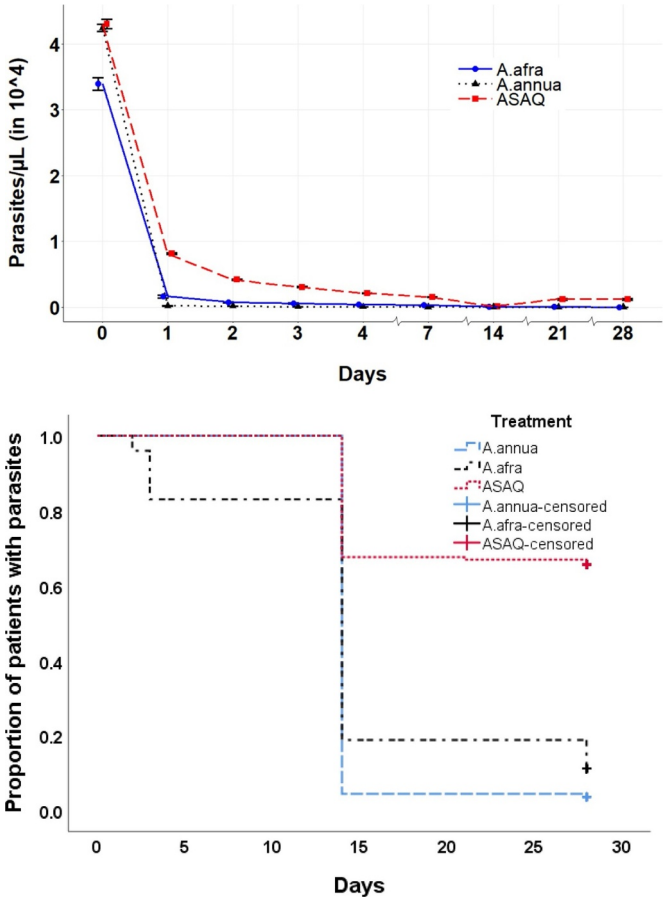

Fig. 3. Average parasitemia progression among the three treatment arms. Top, graphical representation. Bottom, Kaplan–Meier; survival time of parasites started when a patient was included in the study (D0). Patients were followed until D28. For patients withdrawing from the study before D28 or still having parasites until D28, survival time is said to be censored. The censored survival rates of A. annua, A. afra, and ASAQ are 3.6%, 11.2%, and 65.7%, respectively.

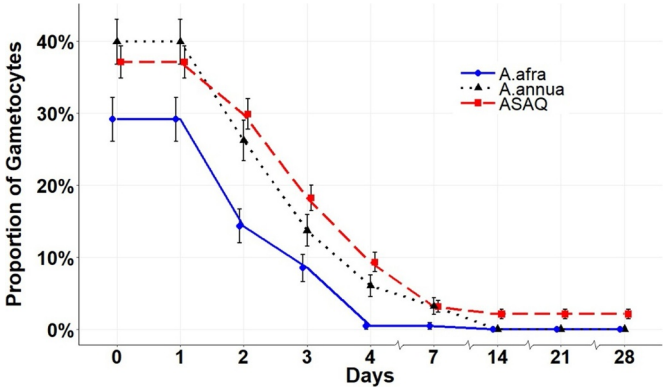

Fig. 4. Microscopically determined proportion of patients with gametocytes (carriers) throughout the trial period.

side effects were multiples of five. Comparison with the theoretical value of 20% yields a *P*-value of 1.6×10^{-5}, showing that this cannot be explained by random fluctuations.

Randomization

In the appendix, table S1 shows baseline clinical symptoms in two groups. Although there are actually three groups, both *Artemisia* groups were pooled. Table S1 shows more patients than were randomized according to Fig. 1 in the main body of the article. Moreover, the differences between groups were smaller than expected by random fluctuations. A chi-square test on this table yields a *P*-value equal to 0.958, meaning that randomization had a less than 5% chance of providing a difference as small as or smaller than the actual difference observed between groups. Unless minimization randomization was used on symptoms, this excellent balance cannot be explained; but minimization randomization cannot be performed in envelopes. Table 1 shows an unbalanced distribution of age that is incompatible with a proper randomization procedure. Indeed there are 102 (41.1%) children 6–15 years old in the *A. annua* group, compared to 51 (22.9%) in the *A. afra* group and 105 (22.3%) in the ASAQ group which is highly significant ($p = 10^{-7}$ for a chi-square test). Out of 300 patients randomized on the Kinkungwa site only seven were randomized in the *A. afra* arm according to the footnote of Table 2, while 75 were expected. This cannot be explained by random fluctuations (binomial test $p < 10^{-26}$).

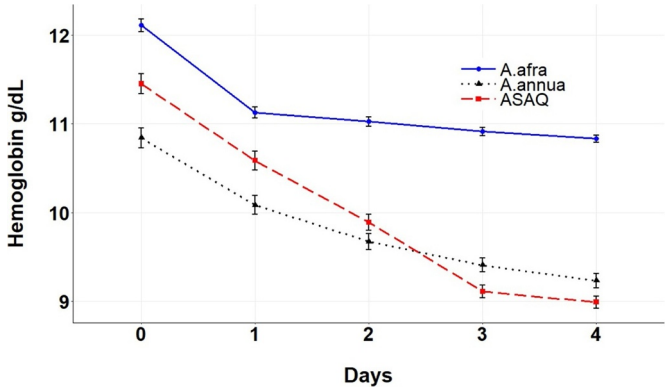

Fig. 5. Hemoglobin levels during the first four days of treatment.

Table 1
Demographics of the Artemisia and ASAQ trial arms at time of enrollment (D0).

Treatment arm	Gender		Age		
	Male (%)	Female (%)	≤ 5 y	6–15 y (%)	> 15 y (%)
A. annua	168 (67.7%)	80 (32.3%)	0	102 (41.1%)	146 (58.9%)
A. afra	158 (70.9%)	65 (29.1%)	0	51 (22.9%)	172 (77.1%)
ASAQ	308 (65.3%)	164 (34.7%)	0	105 (22.3%)	367 (77.7%)

Baseline data by study site

Table 2 shows the characteristics of patients at baseline and D28 in the five study sites. Some data are not shown as some variables were "not measured" (nm) according to authors. Age was not measured in Kamundala in the *A. afra* group but was measured in the *A. annua* and ASAQ groups. How can some core baseline variables be collected in some randomization arms but not in others in a double blind randomized controlled trial? Age must be collected before randomization. The same problem applies to parasitemia (trophozoites/μl) at D0 and D28. The handling of these missing data on a major outcome is never described: were these patients excluded for parasitemia analyses)?

Summary

In summary the critical analysis of this clinical trial shows important ethical issues, major concerns about methodology and highly

Table 3
Cure rates by age group within each trial arm at D14 and 28.

Age (y)	D14			D28		
	A. annua n/N[a] (%)[b]	*A. afra* n/N (%)	ASAQ n/N (%)	*A. annua* n/N (%)	*A. afra* n/N (%)	ASAQ n/N (%)
5–15	93/102 (91.2%)	36/51 (70.6%)	51/105 (48.6%)	93/102 (91.2%)	42/51 (82.4%)	52/105 (49.5%)
16–65	146/146 (100.0%)	145/172 (84.3%)	110/367 (30.0%)	146/146 (100.0%)	156/172 (90.7%)	110/367 (30.0%)
Overall	239/248 (96.4%)	181/223 (81.2%)	161/472 (34.1%)	239/248 (96.4%)	198/223 (88.8%)	162/472 (34.3%)

[a] N, total number within age group less any who left the trial; n, number with 0 parasitemia.
[b] (%), n/N × 100.

Table 2
Average and median patient age and parasite levels at the five study sites at D0 and D28.

Arm	Median (y)	Site average patient age (y)				
		Kakutya	Kinkungwa	Kamundala	Lubile	Kakozwa
A. annua	19	22	25	24	nm	20
A. afra	25	28	27.5	nm	26.5	13.5
ASAQ	29	33	29.5	32	23	21
Overall	26	26	28.5	28	25	19.5
Median parasites D0 mean/site (trophozoites/μl)						
A. annua	42,426	40,632	36,120	≥ 50,000[a]	nm	≥ 50,000[a]
A. afra	33,911	39,860	39,150	nm	29,617	≥ 50,000[a]
ASAQ	43,018	38,702	42,106	≥ 50,000[a]	39,915	≥ 50,000[a]
% parasites D28 mean/site (trophozoites/μl)						
A. annua	na	91% = 0 9% ≤ 10	100% = 0	100% = 0	nm	100% = 0
A. afra	na	100% = 0	100% ≤ 10[b]	nm	100% = 0	92% = 0 8% ≤ 10
ASAQ	na	93% = 0 7% ≤ 10	6% = 0 84% ≤ 10 10% ≥ 10,000	100% ≤ 10	100% = 0	38% ≤ 10 62% ≥ 10,000

Not all test sites included both *Artemisias*; na, not applicable; nm, not measured at that site.
[a] Parasites were not enumerated beyond 50,000.
[b] There were only 7 *A. afra* patients in this arm at this site.

Table 4
Distribution among patients of adverse effects from treatment.

Observed adverse effects	Number of subjects in the *Artemisia* arms	Number of subjects in the ASAQ arm
Abdominal pain	0	25
Asthenia	0	30
Diarrhea	0	5
Drowsiness	0	3
Fatty cough	0	1
Hypoglycemia	0	20
Insomnia	0	10
Nausea	10	30
Pruritis	0	35
Vertigo	0	1
Vomiting	15	50
Total	25	210
% of total	5.0%	42.8%

Table 5
Level of microscopically determined gametocyte carriage decrease D14–28 within age groups.

Age (y)	*A. annua* n/N (%)	*A. afra* n/N (%)	ASAQ n/N (%)
Children (5–15)	43/43 (100%)	102/102 (100%)	111/114 (97.4%)
Adults (16–65)	205/205 (100%)	147/147 (100%)	369/376 (98.1%)
Total	248/248 (100%)	249/249 (100%)	480/490 (98.0%)

N, total within age group; n, number of patients with microscopically undetectable gametocytes.

discordant results. No large-scale clinical randomized trial should have been performed with *A. afra* infusions, which have not shown consistent *in vivo* efficacy against *P. falciparum*. Moreover cases of severe malaria have already been reported in travelers receiving *A. annua* as chemoprophylaxis (Lagarce et al., 2016). Failure of chemoprophylaxis does not support the use of the same drug in the treatment of malaria. Inconsistencies and methodology issues call into question the results of this trial. In light of these discordant results, ACT should remain the first treatment of uncomplicated *P. falciparum* malaria.

Conflict of interest

Prof. Jean Gaudart declares he is a volunteer in the non-profit association “Prospective et coopération”.

Dr Stéphane Jauréguiberry declares he has worked on Malaria projects funded by Guilin, has received personal fees (expert board) from Alfasigma S.p.A. and has presented unfunded scientific oral communications for Pfizer.

Other authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2019.152981.

References

Argemi, X., Hansmann, Y., Gaudart, J., Gillibert, A., Caumes, E., Jaureguibérry, S., Meyer, N., 2019. Comment on “Effect of artemisia annua and artemisia afra tea infusions on schistosomiasis in a large clinical trial.”. Phytomedicine 62, 1–3 Article 152804.

Blanke, C.H., Naisabha, G.B., Balema, M.B., Mbaruku, G.M., Heide, L., Müller, M.S., 2008. Herba Artemisiae annuae tea preparation compared to sulfadoxine-pyrimethamine in the treatment of uncomplicated falciparum malaria in adults: a randomized double-blind clinical trial. Trop. Doct. 38, 113–116.

Chougouo-Kengne, R., Kouamouo, J., Moyou-Somo, R., Penge On'Okoko, A., 2012. Étude comparative de l'efficacité thérapeutique de l'artésunate seule ou en association avec l'amiodaquine et de la tisane de Artemisia annua cultivée à l'Ouest du cameroun. Ann. Pharm. 4, 127–148.

Daddy, N.B., Kalisya, L.M., Bagire, P.G., Watt, R.L., Towler, M.J., Weathers, P.J., 2017. Artemisia annua dried leaf tablets treated malaria resistant to ACT and i.v. artesunate: case reports. Phytomed. Int. J. Phytother. Phytopharm 32, 37–40.

Dorkenoo, A.M., Yehadji, D., Agbo, Y.M., Layibo, Y., Agbeko, F., Adjeloh, P., Yakpa, K., Sossou, E., Awokou, F., Ringwald, P., 2016. Therapeutic efficacy trial of artemisinin-based combination therapy for the treatment of uncomplicated malaria and investigation of mutations in k13 propeller domain in Togo, 2012–2013. Malar. J. 15, 1–9.

Lagarce, L., Lerolle, N., Asfar, P., Le Govic, Y., Lainé-Cessac, P., de Gentile, L., 2016. A non-pharmaceutical form of Artemisia annua is not effective in preventing Plasmodium falciparum malaria. J. Travel Med. 23, 1–3.

Methods for Surveillance of Antimalarial Drug Efficacy, 2009. World Health Organization.

Mueller, M.S., Karhagomba, I.B., Hirt, H.M., Wemakor, E., 2000. The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects. J. Ethnopharmacol 73, 487–493.

Mueller, M.S., Runyambo, N., Wagner, I., Borrmann, S., Dietz, K., Heide, L., 2004. Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria. Trans. R. Soc. Trop. Med. Hyg. 98, 318–321.

Munyangi, J., Cornet-Vernet, L., Idumbo, M., Lu, C., Lutgen, P., Perronne, C., Ngombe, N., Bianga, J., Mupenda, B., Lalukala, P., Mergeai, G., Mumba, D., Towler, M., Weathers, P., 2019. Artemisia annua and Artemisia afra tea infusions *vs.* artesunate-amodiaquine (ASAQ) in treating Plasmodium falciparum malaria in a large scale, double blind, randomized clinical trial. Phytomedicine 57, 49–56.

Munyangi, J., Cornet-Vernet, L., Idumbo, M., Lu, C., Lutgen, P., Perronne, C., Ngombe, N., Bianga, J., Mupenda, B., Lalukala, P., Mergeai, G., Mumba, D., Towler, M., Weathers, P., 2018. Effect of Artemisia annua and Artemisia afra tea infusions on schistosomiasis in a large clinical trial. Phytomedicine 51, 233–240.

Tiruneh, G., Kebede, Y., Yigzaw, T., 2010. Use of the plant Artemisia annua as a natural anti-malarial herb in Arbaminch town. Ethiop. J. Health Biomed. Sci. 2, 76–82.

Wit, M., Funk, A.L., Moussally, K., Nkuba, D.A., Siddiqui, R., Bil, K., Piriou, E., Bart, A., Bizoza, P.B., Bousema, T., 2016. *In vivo* efficacy of artesunate–amodiaquine and artemether–lumefantrine for the treatment of uncomplicated falciparum malaria: an open-randomized, non-inferiority clinical trial in South Kivu, Democratic Republic of Congo. Malar. J. 15, 455.

Zime-Diawara, H., Tove, Y.S.-S.de, Akogbeto, O.E., Ogouyemi-Hounto, A., Gbaguidi, F.A., Kinde-Gazard, D., Massougbodji, A., Bigot, A., Sinsin, B., Quetin-Leclercq, J., Evrard, B., Moudachirou, M., 2015. Etude de l'efficacité et de la tolérance d'une tisane à base de Artemisia annua L. (Asteraceae) cultivée au Bénin pour la prise en charge du paludisme simple. Int. J. Biol. Chem. Sci. 9, 692–702 –702.

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