Cost–effectiveness of artemisinin combination therapy for uncomplicated malaria in children: data from Papua New Guinea

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Objective To compare the cost–effectiveness of conventional antimalarial therapy with that of three artemisinin combination treatment regimens in children from Papua New Guinea aged 6 to 60 months.

Methods An incremental cost–effectiveness analysis was performed using data from 656 children with *Plasmodium falciparum* and/or *P. vivax* malaria who participated in a large intervention trial in two clinics in northern Papua New Guinea. The children were randomized to one of the following groups: (i) conventional treatment with chloroquine plus sulfadoxine plus pyrimethamine (CQ+S+P); (ii) artesunate plus S plus P; (iii) dihydroartemisinin plus piperaquine (DHA+PQ); and (iv) artemether plus lumefantrine (A+L). For treatment outcomes, World Health Organization definitions were used. The cost of transport between home and the clinic plus direct health-care costs served as a basis for determining each regimen's incremental cost per incremental treatment success relative to CQ+S+P by day 42 and its cost per life year saved.

Findings A+L proved to be the most effective regimen against *P. falciparum* malaria and was highly cost-effective at 6.97 United States dollars (US$) per treatment success (about US$ 58 per life year saved). DHA+PQ was the most effective regimen against *P. vivax* malaria and was more cost-effective than CQ+S+P.

Conclusion A+L and DHA+PQ are highly cost-effective regimens for the treatment of paediatric *P. falciparum* and *P. vivax* malaria, respectively, in parts of Papua New Guinea. Future research will be required to determine if these findings hold true for other territories in Asia and Oceania with similar malaria epidemiology.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Recent estimates show that *Plasmodium falciparum* causes 225 to 500 million cases of malaria and nearly one million malaria-related deaths worldwide each year.[1–3] Of these deaths, 96% take place in low-income countries and 87% in children younger than 5 years of age. An additional 70 to 390 million people develop *P. vivax* malaria annually.[3] Although *P. vivax* is generally thought to cause benign disease, it can lead to severe illness and even death.[4] Malaria generates an annual loss of about 34 million disability-adjusted-life-years, is the twelfth leading cause of morbidity in the world,[2] and undermines society and the economy in many ways.[5] In places with intense disease transmission, its long-term detrimental repercussions on economic growth and development transcend the additive costs of individual cases.[5]

Fortunately, the burden of malaria can be reduced through effective case management and vector control measures, including the use of insecticide-treated bed nets and indoor residual insecticide spraying.[5] Although choosing the right antimalarial treatment is crucial for effective management of uncomplicated infections, cost–effectiveness studies have been few. All the studies performed since the 1990s, when artemisinin combination therapy (ACT) became available, have focused on sub-Saharan Africa and India and on *P. falciparum* malaria[6–10] despite increasing recognition of the pathogenic importance of *P. vivax*.[11] Wide differences in the cost and efficacy of ACT regimens make comparative cost–effectiveness studies indispensable.

Both *P. vivax* and *P. falciparum* exist in Oceania and parts of Asia, where malaria is hyper- or holoendemic. A particularly complex epidemiological situation exists in low-lying areas of Papua New Guinea,[12,13] where we recently conducted a trial comparing three ACTs with conventional therapy for uncomplicated paediatric malaria.[14] In this paper we assess the relative cost–effectiveness of these four treatment regimens.

Methods

An open-label, randomized, parallel-group study (Australian New Zealand Clinical Trials Registry ACTRN12605000550606) was conducted between April 2005 and July 2007 in two northern coastal provinces of Papua New Guinea (Madang and East Sepik) among children 6 to 60 months of age with uncomplicated *P. falciparum* or *P. vivax* malaria who presented to two rural clinics. All children were randomly allocated to one of the following: (i) conventional treatment with chloroquine (CQ) plus sulfadoxine (S) plus pyrimethamine (P), henceforth referred to as CQ+S+P; (ii) artesunate (ARTS) plus S plus P, henceforth ARTS+S+P; (iii) dihydroartemisinin (DHA) plus piperaquine (PQ), henceforth DHA+PQ; and (iv) artemether (A) plus lumefantrine (L), henceforth A+L. Recruitment, informed con-

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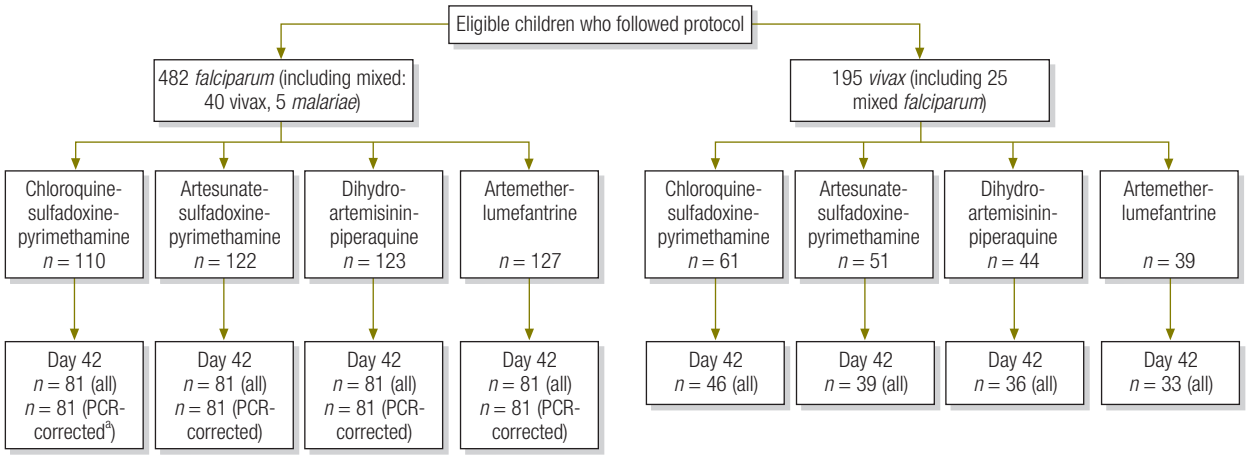
Fig. 1. **Number of patients in trial of antimalarial treatment regimens conducted in 2005-2007 in Papua New Guinea who were eligible for participation and were followed from randomization through day 42. Cost-effectiveness analyses were done using 2007–2008 cost data**



PCR, polymerase *chain* reaction.

[a] "PCR-corrected" denotes correction for re-infections identified by means of polymerase chain reaction genotyping of polymorphic *Plasmodium falciparum* loci.

sent and other study procedures have been described in detail elsewhere.[14] The present comparative assessment of cost–effectiveness is based on data from 656 children (482 with *P. falciparum* malaria and 195 with *P. vivax* malaria, since 21 children had both pathogens) who were recruited based on eligibility and followed according to the study protocol (Fig. 1).

Drugs and dosage

The drugs used in the trial were from the following laboratories and were administered in the following combinations and doses:

i) CQ+S+P: CQ (Aspen Health, St Leonards, Australia), 10 milligrams (mg) of base per kilogram (kg) of body weight daily for 3 days, plus S and P (Roche, Basel, Switzerland) as 25 mg per kg of S plus 1.25 mg per kg of P with the first dose of CQ;
ii) ARTS+S+P: ARTS (Sanofi-Aventis, Paris, France), 4 mg per kg daily for 3 days, plus S and P as 25 mg per kg of S plus 1.25 mg per kg of P with the first dose of ARTS;
iii) DHA+PQ (Beijing Holley-Cotec, Beijing, China): DHA, 2.5 mg per kg, plus PQ phosphate, 20 mg per kg, daily for 3 days;
iv) A+L (Novartis Pharma AG, Basel, Switzerland): A, 1.7 mg per kg, plus L, 10 mg per kg, twice daily for 3 days.

All drugs were administered with water except for A+L, which was given with milk, as instructed by the manufacturer, to increase bioavailability. All doses were supervised except for the evening doses of A+L, which were taken at home.

Clinical follow-up

Axillary temperature measurements and blood film microscopy were scheduled on days 1, 2, 3, 7, 14, 28 and 42. Asymptomatic children who developed uncomplicated or severe malaria during follow-up were given rescue antimalarial therapy consisting of quinine (7–20 mg of base per kg twice daily for 7 days) intramuscularly if unable to tolerate oral therapy, or otherwise orally plus a single dose of S+P. Efficacy was assessed in accordance with World Health Organization (WHO) definitions,[15] namely, (i) early treatment failure: signs of severe disease[16] or an inadequate parasitological response by day 3; (ii) late parasitological failure: parasitaemia between days 4 and 42 (after a favourable response on days 1–3); (iii) late clinical failure: late parasitological failure plus an axillary temperature > 37.5 °C, and (iv) adequate parasitological and clinical response: none of the conditions in i–iii. In cases of *P. falciparum* malaria, these outcomes were corrected for re-infection by genotyping the disease pathogen through polymerase chain reaction (PCR).[14] Since no equivalent protocols have been established for re-emergent *P. vivax*,[11] treatment outcomes among patients with *P. vivax* malaria were not corrected.

Economic analyses

Our economic analyses focused primarily on societal costs. We estimated the cost of travelling between home and the health clinic plus the direct costs of health care (i.e. conventional treatment and ACTs, visits to health clinics, clinical tests and rescue antimalarial therapy, when indicated). We compared the net costs and net effectiveness of the three ACTs with those of conventional therapy with CQ+S+P and expressed the results as cost–effectiveness ratios. All analyses and comparisons were performed separately for *P. falciparum* and *P. vivax* on both a per protocol and a modified intention-to-treat basis.[14] Per protocol analyses included children with complete follow-up or confirmed treatment failure and excluded those who were treated for malaria without confirmatory microscopy or who defaulted from follow-up. These excluded patients were retained in the modified intention-to-treat group, to which we applied: (i) a worst-case approach (early treatment failure assumed for those excluded on or before day 3 and late parasitological failure or late clinical failure assumed for all others) and (ii) a best-case approach (all missing follow-up blood films were assumed to be parasite-negative). In a secondary analysis, we extrapolated outcomes to estimate the increase in life expectancy obtained with the most effective treatment based on the estimated mortality associated with *P. falciparum* and the remaining life expectancy.

For each patient, standardized data were collected at each scheduled clinic visit and at any extra unscheduled visits on days when fever or other symptoms

were present (sick days). These data included the doses of all the drugs being used to treat the malaria and its symptoms or complications (e.g. trial medication, rescue quinine, paracetamol, iron and folate supplements, etc.). Unit costs were obtained from the Papua New Guinea National Department of Health under the Medium-Term Expenditure Framework,[17] participating clinics, Novartis Pharma AG and local suppliers (Table 1) and were combined with resource volumes to obtain a net cost per patient during follow-up. Mean net costs and associated 95% confidence intervals (CIs) were calculated for each treatment arm. Costs are reported in 2007–2008 United States dollars (US$) and undiscounted due to the relative brevity of the trial.

All study participants were scheduled for eight clinic visits (including day 0 and excluding sick days). However, since usual-care (non-trial) visits are different and less frequent, we conducted a complementary analysis with the costs of conventional therapy or ACT treatment based on a single clinic visit comprising both diagnosis and treatment. We assumed the same number of subsequent sick-day visits for all children except those with early treatment failure, whose clinic visit scheduled for day 1–3 was replaced by a sick-day visit. For each patient, the actual cost of trial visits was replaced by the estimated cost of standard practice, which depended on treatment allocation. We assumed that no-cost forms of fat, such as in breast milk or fat-containing foods, were always consumed with A+L except during the initial clinic visit (day 0).

The primary endpoint of the trial was treatment failure by day 42.[14] A secondary analysis of the lifetime benefits of using A+L to treat *P. falciparum* malaria was performed by using lifetables to estimate the potential life years saved. All results are reported as means and standard deviations (SDs) or mean differences and 95% CIs. The CIs for the key cost–effectiveness ratios were calculated by Fieller's method.[18] The effect of assumptions on the main results was examined by sensitivity analyses involving a cost–effectiveness analysis using best- and worst-case scenarios and modified intention-to-treat assumptions. All data were analysed with SPSS 15.0 (SPSS Inc., Chicago, United States of America) and Microsoft Excel 97 (Redmond, USA).

Results

Costs

Table 2 shows the mean cost per patient for CQ+S+P and the three ACTs and the mean cost difference between these regimens over the duration of the study, by type of cost and allocation for *P. falciparum* and *P. vivax* in both trial and usual care settings. For *P. falciparum* malaria, ARTS+S+P, DHA+PQ and A+L cost between US$ 0.26 and US$ 0.48 more per patient, on average, than CQ+S+P. The A+L group had the additional cost of milk. Transportation costs made clinic visits the most expensive component. Other costs – quinine rescue treatment, treatment for anaemia, paracetamol or clinic visits – did not differ significantly between conventional therapy and ACT regimens. The total costs of usual care were significantly higher in the ARTS+S+P and A+L groups than in the conventional therapy group.

For *P. vivax* malaria, ARTS+S+P, DHA+PQ and A+L cost between US$ 0.22 and US$ 0.36 more per patient, on average, than CQ+S+P (Table 2). Again, the A+L group had the additional cost of milk. Other costs did not differ significantly between conventional therapy and ACT regimens. The total costs of usual care were significantly higher in the A+L group than in the group that received CQ+S+P.

Outcomes

In the per protocol analysis of the 388 children with *P. falciparum* malaria who completed the trial, 341 (87.9%) had an adequate parasitological and clinical response, with the highest rate of success (95.2%) in the A+L group, followed by the DHA+PQ group (88.0%), the ARTS+S+P group (85.4%) and the CQ+S+P group (81.5%).[14] Among the 154 children with *P. vivax* who attended the clinic on day 42, 69.4% had an adequate parasitological and clinical response in the DHA+PQ group compared with 13.0%, 33.3% and 30.3% in the CQ+S+P, ARTS+S+P and A+L groups, respectively.[14] Table 3 documents the proportion of treatment successes and costs for each pathogen species and type of analysis (per protocol versus modified intention-to-treat) in a usual care setting. The incremental number of successes and costs, together with the incremental cost–effectiveness ratios, are also shown for each ACT compared with CQ+S+P.

Cost–effectiveness

The primary measure of cost–effectiveness was the incremental cost–effectiveness ratio, defined as the incremental cost per incremental treatment success of ACT relative to the comparator, CQ+S+P (see cost–effectiveness planes in Fig. 2). In a usual care setting, DHA+P+Q and A+L are cost-effective alternatives to CQ+S+P. For DHA+PQ the average cost per treatment success was US$ 2.95, with an 87% probability of the cost–effectiveness ratio being < US$ 50.00. For A+L the average cost per treatment success was US$ 6.97, with a 99% probability of this being < US$ 50.00. The incremental cost–effectiveness ratio of A+L relative to DHA+PQ, the next best alternative, was US$ 10.60 per success, with a 92% probability of this ratio being < US$ 50.00. For *P. vivax* (Fig. 2), DHA+PQ was the most effective treatment, with an average cost saving of US$ 0.18 per success in a usual care setting when compared with CQ+S+P, and a > 99% probability of the cost per success being < $1.00.

Cost per life year saved by artemether plus lumefantrine

In 2008, a child aged between 1 and 4 years in Papua New Guinea could expect to live another 64.9 years.[19] Mortality from *P. falciparum* malaria treatment failure has been estimated at 0.185%, or about 1.9 deaths per 1000 patients.[20] In our study, the incremental success of A+L over CQ+S+P in children 6–60 months old was 13.7% (95.2% versus 81.5% success). Thus, for every 1000 patients with *P. falciparum* malaria who are treated with A+L instead of CQ+S+P, an additional 0.253 life is saved ($0.00185 \times 1000 \times 0.137 = 0.253$). The increase in average life expectancy per 1000 cases of *P. falciparum* malaria treated with A+L instead of CQ+S+P is approximately 0.253×64.9 years = 16.4 years (or 12.8 years when discounted at 3%, as recommended by Gold et al.[21]). The extra cost associated with A+L versus CQ+S+P treatment was US$ 955 per 1000 cases treated (per protocol analysis). Therefore, the cost of A+L per life year saved was US$ 955/16.4 = US$ 58.23 (or US$ 74.6 when benefits are discounted at 3%).

Discussion

This is the first economic analysis of a range of contemporary treatment options for children living in an area of

Table 1. **Main unit costs associated with participation in randomized four-arm trial in children aged 6–60 months with uncomplicated malaria, Papua New Guinea, 2007–2008**

Cost item	Unit cost (2007–08 US$)	Price source	Comment
Health clinic visit			
Outpatient	0.517	Alexishafen Health Clinic, Madang	Per treatment course paid for at first visit
Inpatient	3.44	Alexishafen Health Clinic, Madang	One-off admission fee regardless of no. of nights
Transport to health clinic[a]	1.72	Alexishafen Health Clinic, Madang	5 (usual) to 20 (far) PGK[b] round trip
Malaria treatment			–
CQ, 150 mg	0.010	MTEF[c] 2006–07 prices	–
S+P: 500 mg of S, 25 mg of P	0.013	MTEF 2006–07 prices	–
ARTS, 50 mg	0.184	MTEF 2006–07 prices	–
DHA+PQ: 40 mg of DHA, 320 mg of PQ	0.137	Beijing Holley Cotec, China	US$ 0.125 per tablet
A+L: 20 mg of A, 120 mg of L	0.0617	Novartis Pharma AG price to WHO, 2008	–
Quinine sulfate tablets, 300 mg	0.022	MTEF 2006–07 prices	–
Quinine dihydrochloride, 300 mg/ml, 2 ml	0.241	MTEF 2006–07 prices	–
Tests and other medications			–
Hb finger prick test	0.107	MTEF 2006–07 prices	On days 0–42 and sick days
Paracetamol syrup, 120 mg/5 ml	0.00057/ml	MTEF 2006–07 prices	15 mg/kg, if axillary temperature ≥ 37.5 °C
Albendazole, 200 mg tablet	0.007`	MTEF 2006–07 prices	For hookworm, on day 42 if Hb < 10 g/dl
$FeSO_4$, 200 mg; folic acid, 500 µg	0.001	MTEF 2006–07 prices	On day 42 if Hb < 10 g/dl
Amodiaquine, 100 mg tablet	0.005	MTEF 2006–07 prices	On day 42 if Hb < 10 g/dl and splenomegaly ≥ grade 3[d]
Other costs[e]			–
Milk, 250 ml tetra packs full cream (32.15 PGK per 24 packs)	0.462	Wholesale, 2008	–
Malaria microscopy	0.710	MTEF 2006–07 prices	–
Syringe, disposable 10 ml, 21-gauge needle	0.046	MTEF 2006–07 prices	–
Gloves, disposable	0.004 a pair	MTEF 2006–07 prices	–
Blood lancet, disposable	0.043	MTEF 2006–07 prices	–
Alcohol wipe, 1 per blood sample (9.30 PGK per box of 200 sealed wipes)	0.016	Retail pharmacy, 2008	–
Cotton wool swab, 1 per blood sample	0.007	MTEF 2006–07 prices	–

A, artemether; ARTS, artesunate; CQ, chloroquine; DHA, dihydroartemisinin; $FeSO_4$, ferrous sulfate; ; Hb, haemoglobin; L, lumefantrine; MTEF: Medium-Term Expenditure Framework; P, pyrimethamine; PGK, Papua New Guinea kina; PQ, piperaquine; S, sulfadoxine; US$, United States dollars; WHO, World Health Organization.

[a] Based on cost of travel, by public transport, for the average distance to the clinic in the surrounding area.

[b] One PGK is equivalent to US$ 0.345 (2007–08).

[c] Framework of the Papua New Guinea National Department of Health.

[d] Hackett grade 3: spleen palpable between Grade 2 limit (halfway between left costal margin and level of umbilicus) and level of umbilicus.

[e] Inpatients and their families need to provide their own food and cooking facilities. Patients who are very sick go to hospital; others visit the local health clinic. In this study no child was referred to hospital.

Table 2. **Mean cost of treatment per patient and mean cost difference per patient between conventional antimalarial therapy and artemisinin combination therapy (ACT), by malaria pathogen species and for usual care and trial settings, Papua New Guinea, 2007–2008**

Cost item	Mean cost per patient in US$ (± SD)				Mean cost difference per patient in US$[a] (95% CI)		
	Conventional	ACT regimen					
	CQ+S+P	ARTS+S+P	DHA+PQ	A+L	ARTS+S+P vs CQ+S+P	DHA+PQ vs CQ+S+P	A+L vs CQ+S+P
Plasmodium falciparum							
No. allocated	81	103	100	104	–	–	–
Antimalarial treatment	0.04 (± 0.01)	0.52 (± 0.20)***	0.30 (± 0.06)***	0.37 (± 0.12)***	0.48 (0.43 to 0.52)***	0.26 (0.24 to 0.27)***	0.33 (0.31 to 0.35)***
Milk	–	–	–	0.48 (± 0.08)***	–	–	0.48 (0.46 to 0.49)***
Quinine treatment	0.01 (± 0.05)	0.01 (± 0.05)	0.01 (± 0.03)	0.01 (± 0.05)	0.00 (–0.02 to 0.01)	–0.01 (–0.02 to 0.00)	0.00 (–0.01 to 0.02)
Paracetamol	0.07 (± 0.05)	0.06 (± 0.05)	0.06 (± 0.05)	0.07 (± 0.06)	0.00 (–0.02 to 0.02)	–0.01 (–0.02 to 0.01)	0.00 (–0.01 to 0.02)
Clinic visits	3.39 (± 0.78)	3.30 (± 0.66)	3.34 (± 0.71)	3.53 (± 0.95)	–0.08 (–0.30 to 0.12)	–0.05 (–0.28 to 0.17)	0.14 (–0.11 to 0.39)
Total (usual care)	**3.50 (± 0.81)**	**3.90 (± 0.70)****	**3.69 (± 0.71)**	**4.46 (± 0.98)*****	**0.40 (0.17 to 0.61)****	**0.19 (–0.04 to 0.61)**	**0.96 (0.69 to 1.21)*****
Excess costs for trial	17.98 (± 1.05)	17.83 (± 2.75)	18.08 (± 0.89)	20.47 (± 0.68)***	–0.16 (–0.79 to 0.26)	0.10 (–0.18 to 0.40)	2.49 (2.23 to 2.77)***
Total (trial)	**21.48 (± 0.92)**	**21.73 (± 2.50)**	**21.78 (± 0.99)**	**24.93 (± 1.25)*****	**0.24 (–0.36 to 0.69)**	**0.29 (–0.01 to 0.57)**	**3.44 (3.13 to 3.76)*****
Plasmodium vivax							
No. allocated	46	39	36	33	–	–	–
Antimalarial treatment	0.03 (± 0.01)	0.40 (± 0.16)***	0.25 (± 0.06)***	0.27 (± 0.10)***	0.36 (0.32 to 0.41)***	0.22 (0.20 to 0.23)***	0.23 (0.20 to 0.27)***
Milk	–	–	–	0.46 (± 0.10)***	–	–	0.46 (0.46 to 0.46)***
Quinine treatment	0.04 (± 0.07)	0.04 (± 0.07)	0.01 (± 0.05)	0.04 (± 0.09)	0.00 (–0.03 to 0.03)	–0.03 (–0.05 to 0.00)	0.01 (–0.03 to 0.05)
Paracetamol	0.04 (± 0.05)	0.04 (± 0.05)	0.04 (± 0.05)	0.02 (± 0.04)	0.00 (–0.02 to 0.02)	0.00 (–0.02 to 0.02)	–0.02 (–0.04 to 0.00)
Clinic visits	3.92 (± 1.33)	4.13 (± 1.65)	3.64 (± 1.05)	4.39 (± 1.61)	0.21 (–0.41 to 0.87)	–0.29 (–0.81 to 0.23)	0.47 (–0.19 to 1.13)
Total (usual care)	**4.03 (± 1.33)**	**4.60 (± 1.65)**	**3.93 (± 1.06)**	**5.19 (± 1.62)****	**0.57 (–0.05 to 1.24)**	**–0.10 (–0.61 to 0.42)**	**1.16 (0.50 to 1.82)****
Excess costs for trial	17.98 (± 1.05)	17.35 (± 3.14)	18.15 (± 0.61)	20.40 (± 0.10)***	–0.63 (–1.79 to 0.12)	0.17 (–0.19 to 0.53)	2.42 (1.95 to 2.85)***
Total (trial)	**22.01 (± 1.48)**	**21.95 (± 3.17)**	**22.07 (± 1.12)**	**25.59 (± 1.71)*****	**–0.06 (–1.24 to 0.91)**	**0.07 (–0.51 to 0.64)**	**3.58 (2.86 to 4.31)*****

A, artemether; ARTS, artesunate; CI, confidence interval; CQ, chloroquine; DHA, dihydroartemisinin; L, lumefantrine; P, pyrimethamine; PQ, piperaquine; S, sulfadoxine; SD, standard deviation; US$, United States dollars; *$P < 0.05$;**$P < 0.01$; ***$P < 0.001$ (with adjustment for multiple comparisons following Bonferroni's method).

[a] Negative cost differences indicate the cost savings associated with ACT.

Table 3. **Comparative costs, treatment successes and cost–effectiveness for conventional therapy and three artemisinin combination therapy (ACT) regimens for paediatric uncomplicated malaria, by pathogen species, including worst-case and best-case scenarios under modified intention-to-treat analysis, Papua New Guinea, 2007–2008**

Cost or effectiveness parameter	*Plasmodium falciparum*				*Plasmodium vivax*			
	Conventional	ACT			Conventional	ACT		
	CQ+S+P	ARTS+S+P	DHA+PQ	A+L	CQ+S+P	ARTS+S+P	DHA+PQ	A+L
Per protocol								
No. of patients	81	103	100	104	46	39	36	33
Successes (%)	82	85	88	95	13	33	69	30
Mean cost (US$) per patient	3.50	3.90	3.69	4.46	4.03	4.60	3.93	5.19
Incremental successes	–	0.04	0.07	0.14	–	0.20	0.56	0.17
Incremental costs (US$)	–	0.40	0.19	0.96	–	0.57	–0.10	1.16
Incremental cost–effectiveness ratio[a]	–	10.21	2.95	6.97	–	2.83	–0.18	6.70
Modified intention-to-treat								
No. of patients	110	122	123	127	61	51	44	39
Worst case[b]								
Successes (%)	60	72	72	78	10	26	57	26
Mean cost per patient (US$)	3.48	3.98	3.93	4.48	4.08	4.40	4.03	4.99
Incremental successes	–	0.12	0.12	0.18	–	0.16	0.47	0.16
Incremental costs (US$)	–	0.50	0.46	1.01	–	0.32	–0.06	0.91
Incremental cost–effectiveness ratio[a]	–	4.12	3.97	5.59	–	2.05	–0.12	5.78
Best case[c]								
Successes (%)	86	88	90	96	34	49	75	41
Mean cost per patient (US$)	3.48	3.98	3.93	4.48	4.08	4.40	4.03	4.99
Incremental successes	–	0.01	0.04	0.10	–	0.15	0.41	0.07
Incremental costs (US$)	–	0.50	0.46	1.01	–	0.32	–0.06	0.91
Incremental cost–effectiveness ratio[a]	–	38.31	12.00	10.37	–	2.21	–0.14	13.83

A, artemether; ARTS, artesunate; CQ, chloroquine; DHA, dihydroartemisinin; L, lumefantrine; P, pyrimethamine; PQ, piperaquine; S, sulfadoxine; US$, United States dollars.

[a] Incremental cost per incremental treatment success for each novel ACT regimen versus CQ+S+P.

[b] Worst-case scenario: Early treatment failure assumed for those excluded on or before day 3 and late parasitological failure or late clinical failure assumed for all others.

[c] Best-case scenario: All missing follow-up blood films were assumed to be parasite-negative.

intense malaria transmission caused by several species of *Plasmodium*. According to the findings, in Papua New Guinea the most cost-effective treatment for paediatric *P. falciparum* malaria differs from that for paediatric *P. vivax* malaria for clinical and financial reasons. In a usual care setting, three ACTs proved more effective against *P. falciparum* malaria but also more costly than CQ+S+P. Both A+L and DHA+PQ were found to be cost-effective alternatives to CQ+S+P, with A+L being the more effective of the two drugs but also the most expensive. The availability of donated or subsidized drugs and willingness to pay can determine the choice of regimen. For *P. vivax* malaria, DHA+PQ was found to be the most effective treatment and led to savings in a usual care setting when compared with CQ+S+P. A+L was the least cost-effective ACT regimen against *P. vivax* malaria among children in Papua New Guinea.

Our data for *P. falciparum* malaria are comparable to those from other studies. In a 2005 prospective observational study in Zambia,[6] the incremental cost–effectiveness ratio for A+L versus S+P was estimated at US$ 4.10 per case successfully treated from the health care provider's perspective. This is similar to the US$ 6.97 per success found in the present analyses. In a study from KwaZulu Natal Province in South Africa, A+L proved more cost-effective than S+P at the population level despite its greater cost, mainly owing to a reduction in local transmission.[9] A predictive modelling study concluded that ACTs are extremely likely to be cost-effective under most conditions, unless resistance to S+P is very low.[7] The findings of an Indian study comparing CQ monotherapy with mefloquine and A+L were difficult to interpret because the cost of A+L was unavailable and many patients on CQ experienced early treatment failure.[8] In studies from two sub-Saharan regions, high ACT coverage was found to be the most cost-effective strategy for malaria control (9–12 international dollars per disability-adjusted life year averted) compared with insecticide-treated bed nets, indoor residual spraying and intermittent preventive treatment in pregnancy.[22]

Some population data from Papua New Guinea are detailed enough to estimate the benefits of ACT regimens. In 2004, 1 660 645 malaria patients (28.7% of the total population, assuming no double counting) were treated in Papua New Guinea.[20] Of these patients, 92 956 required further treatment as outpatients and 29 406 as inpatients.[19] These figures suggest a substantial need for secondary treatment or for treatment for severe malaria. Our trial data showed that nearly 70% of uncomplicated malaria cases were caused by *P. falciparum* and 30% by *P. vivax*. If the findings of the trial's per protocol analysis are projected to the

general population of Papua New Guinea (5 789 796), US$ 49 321 per year could be saved and 280 981 more cases could be successfully treated every year by using DHA+PQ instead of CQ+S+P to treat children with *P. vivax* malaria. If A+L were used to treat *P. falciparum* malaria, an extra US$ 1 110 141 would have to be expended to attain an additional 159 256 treatment successes every year. These estimates may have to be revised, however, if in future the use of insecticide-treated bed nets and other integrated malaria control measures increases and the malaria burden decreases in Papua New Guinea.[23]

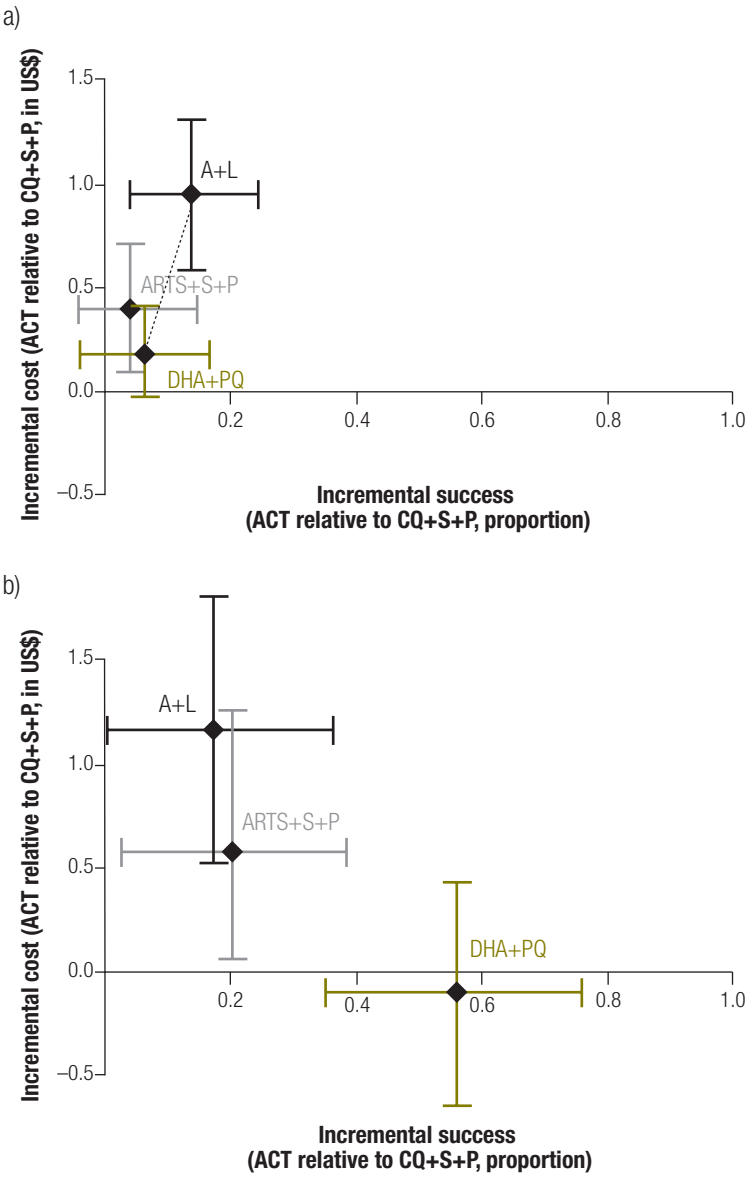
At a cost per life year saved of US$ 58, A+L appears to be a highly cost-effective and affordable regimen for uncomplicated paediatric malaria in Papua New Guinea, where the gross national income per capita in 2008 was US$ 1040.[24] In a large multicentre trial that compared ARTS with quinine for the treatment of severe malaria in south-east Asia, the incremental cost per death averted by the use of ARTS was US$ 140 from the provider's perspective,[25] and it was concluded that substituting quinine with ARTS provided a return on investment that few health interventions could match in terms of immediate health gains and minimal additional cost.

Treatment compliance has not been considered in the present economic analysis. All treatments were given over three days, but A+L requires two doses per day and the medication has to be taken with a fatty meal, so that compliance may be lower than with other therapies. In a cost–effectiveness study of ACTs in sub-Saharan Africa, estimated compliance with ACTs ranged from 30% to 60% compared with 85% to 95% for S+P.[7] Opportunity costs, such as the time parents took off work to look after their sick children and take them to the health clinic, were not factored into our analysis. Prompt recovery after effective treatment might allow parents to return to work more quickly. The intervention trial was not designed to investigate the impact of mixed infections.[14] The fact that the most effective novel treatment for *P. falciparum* malaria proved to be the least effective for *P. vivax* malaria may have implications in terms of cost–effectiveness, but the present data suggest that DHA+PQ would be the regimen of choice for mixed infections.

As conventionally recommended in cost–effectiveness analyses, we based our estimates on the primary trial endpoints. In countries such as Papua New Guinea, PCR is not performed as part of usual care to diagnose malaria and monitor treatment effectiveness. Worth noting in this regard is the absence of between-group differences in adequate clinical and parasitological response rates on day 42, without PCR correction, among children with *P. falciparum* malaria (67.9%, 63.9%, 62.6% and 64.2% for CQ+S+P, ARTS+S+P, DHA+PQ and A+L, respectively).[14] In the absence of PCR correction, CQ+S+P is substantially more cost-effective than the other three regimens because it is the least expensive. However, most early treatment failures in the intervention trial were observed in the CQ+S+P group. Thus, continued use of CQ+S+P in the holoendemic setting where the trial was conducted is likely to result in increased parasite resistance and a greater disease burden.[14] For this reason, WHO has proscribed this type of therapeutic procrastination.[15]

In areas of Papua New Guinea and of other resource-poor tropical countries, microscopy and/or rapid diagnostic tests may not be available or reliable.[1] Empirical treatment may be administered based

Fig. 2. **Planes showing the cost–effectiveness of each intervention relative to conventional treatment with chloroquine (CQ) plus sulfadoxine (S) plus pyrimethamine (P) for children with (a) *Plasmodium falciparum* malaria and (b) *P. vivax* malaria, in a usual care setting, Papua New Guinea, 2007–2008**



ACT, artemisinin combination therapy.

on symptoms and on the most likely infecting *Plasmodium* species. Although an economic analysis of such practices was beyond the scope of the present study, a progressive reduction in the cost of rapid diagnostic tests and a resulting increase in their availability may improve the accuracy of malaria diagnosis in countries such as Papua New Guinea, and this, in turn, would reduce the cost of unnecessary treatment. We did not consider the cost implications of continuing to carry *Plasmodium* gametocytes after treatment. Although this occurred much more often after CQ+S+P than after any of the ACTs,[14] there is emerging evidence that S+P impairs both *P. falciparum* gametocyte infectivity and *Anopheles* mosquito survival.[26]

Our intervention trial[14] has led to changes in the national malaria treatment guidelines; A+L has replaced CQ+S+P as the recommended first-line therapy for uncomplicated malaria and is being distributed throughout the country with the help of the Global Fund to Fight AIDS, Tuberculosis and Malaria, and other entities.[1] DHA+PQ has been recommended as an alternative regimen because it is more effective than A+L against *P. vivax*. Our cost–effectiveness data support these recommendations, but further research is needed to determine if they are broadly applicable to parts of Oceania and Asia where CQ+S+P is losing its effectiveness and ACTs are available. ■

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الملخص:

النظام العلاجي بتوليفة الأرتيميسينين لمعالجة الملاريا غير المصحوبة بمضاعفات في الأطفال

جدوى تكلفة العلاج بتوليفية الأرتيميسينين لمكافحة الملاريا غير المصحوبة بمضاعفات في الأطفال: معطيات من من بابوا غينيا الجديدة

الهدف: مقارنة جدوى تكلفة العلاج التقليدي المضاد للملاريا مع النظم العلاجية بتوليفة الأرتيميسينين الثلاثية في أطفال بابوا غينيا الجديدة الذين تتراوح أعمارهم ما بين 6 و 60 شهراً.

الطرائق: تم إجراء تحاليل تزايدية لقياس مدى الجدوى والمردودية باستخدام معطيات جمعت من 656 طفلاً مصاباً بالمتصورة المنجلية أو ملاريا المتصورات النشيطة، الذين شاركوا في تجربة لمداخلة كبيرة في عيادتين في شمال بابوا غينيا الجديدة. ولقد تم تقسيم الأطفال بصورة عشوائية بين المجموعات التالية: (1) وسائل العلاج التقليدية بالكلوروكين وسلفادوكسين وبيريميثامين (CQ+S+P); (2) والمعالجة بالأرتيسونات وسلفادوكسين وبيريميثامين، (3) المعالجة بديهايدروأرتميسينين وبايبراكوين (DHA+PQ) و(4) المعالجة بأرتيميثير واللوميفانترين (A+L). ولقد استخدمت تعاريف منظمة الصحة العالمية لتوحيد مصطلحات نتائج المعالجة. ولقد كانت تكلفة الانتقال من المنزل إلى العايدة إضافة إلى تكلفة الرعاية الصحية المباشرة هما أساس تحديد التكلفة المتزايدة لكل نظام لكل من نظم المعالجة التزايدية الناجعة والتي تتعلق بالكلوروكين وسلفادوكسين وبيريميثامين (CQ+S+P)، وذلك في اليوم الثاني والأربعين، وتكلفة هذه المعالجة بالنسبة لكل سنة يتم إنقاذها من حياة الإنسان.

النتائج: أثبتت النتائج أن توليفة الأرتيميثير واللوميفانترين (A+L) هي التوليفة الأكثر فعالية لمعالجة المتصورة المنجلية، والأعلى مردودية لقاء التكلفة، حيث بلغت تكلفة المعالجة الناجحة 6.97 دولاراً أمريكياً (حوالي 58 دولار أمريكي لكل سنة يتم إنقاذها من حياة الإنسان). كما كان النظام العلاجي بالديهايدروأرتميسينين وبايبراكوين (DHA+PQ) هو الأكثر فعالية ضد ملاريا المتصورات النشيطة، وكان أكثر مردودية لقاء التكلفة من النظام العلاجي بالكلوروكين والسلفادوكسين والبيريميثامين (CQ+S+P).

الخاتمة: يعتبر النظام العلاجي بالأرتيميثير واللوميفانترين (A+L) والنظام العلاجي بالدديهايدروأرتميسينين وبايبراكوين (DHA+PQ) من الأنظمة عالية الفاعلية من حيث مردودية التكلفة لعلاج الأطفال المصابين بالمتصورة المنجلية وملاريا المتصورات النشيطة على التوالي، في أجزاء من بابوا غينيا الجديدة. ويتطلب الأمر إجراء المزيد من البحوث المستقبلية لتحديد ما إذا كانت هذه النتائج تنطبق على المناطق الأخرى في آسيا وأوقيانيا مع وباء مثل وراء الملاريا .

摘要

儿童非重症疟疾青蒿素联合疗法的成本效益：来自巴布亚新几内亚的数据

目的 旨在比较6到60个月巴布亚新几内亚儿童中传统的抗疟疾疗法与三种青蒿素联合疗法的成本效益。

方法 我们运用从巴布亚新几内亚北部海岸参与一个大型干预试验的患恶性疟原虫疟疾和/或间日疟的656名儿童处所得的数据，进行了增量成本效益分析。在两家诊所问诊的儿童被随机分配，接受下述四种治疗方案中的一种：（1）使用氯喹、磺胺多辛和息疟定的传统疗法；（2）青蒿琥酯，磺胺多辛和息疟定；（3）二氢青蒿素加哌喹（DHA+PQ）和（4）青蒿醚加苯芴醇（A+L）。治疗结果根据世界卫生组织的标准定义进行界定。住所与诊所间的交通费加上就医的直接成本作为计算每种疗法42天成功治疗增量成本以及每寿命年所节省的成本的基础。

结果 青蒿醚加苯芴醇被证明是治疗恶性疟原虫疟疾最有效的临床治疗方案，具有极高的成本效益，每一成功疗程可节省6.97美金（每寿命年可节省58美金）。二氢青蒿素加哌喹是治疗间日疟的最有效治疗组合，比传统的疟疾治疗法更具成本效益。

结论 在巴布亚新几内亚部分地区，青蒿醚加苯芴醇和二氢青蒿素加哌喹分别是治疗小儿恶性疟原虫疟疾和间日疟的最具成本效益的治疗方案。然而，还需做进一步研究以确定该发现是否适用于有类似疟疾流行病的亚洲和大洋洲。

Résumé

Rapport coût-efficacité de l'association thérapeutique à base d'artémisinine chez les enfants souffrant de paludisme non compliqué: les données de la Papouasie-Nouvelle-Guinée

Objectif Comparer le rapport coût -efficacité de la thérapie antipaludéenne conventionnelle avec le rapport respectif de trois régimes de traitement associé à base d'artémisinine chez des enfants de Papouasie-Nouvelle-Guinée âgés de 6 à 60 mois.

Méthodes Une analyse différentielle de coût-efficacité a été réalisée à l'aide des données de 656 enfants souffrant de *Plasmodium falciparum* et/ou de paludisme à *P. vivax* ayant participé à un vaste essai d'intervention sur le littoral nord-occidental de la Papouasie-Nouvelle-Guinée. Les enfants, qui ont été présentés dans deux cliniques, ont fait l'objet d'une randomisation vers l'un des régimes thérapeutiques suivants : (i) traitement conventionnel avec chloroquine et sulfadoxine-pyriméthamine; (ii) artésunate plus sulfadoxine-pyriméthamine; (iii) dihydroartémisinine-pipéraquine (DHA+PQ); et (iv) artéméther-luméfantrine (A+L). Les résultats des traitements ont été établis conformément aux définitions standard de l'Organisation mondiale de la Santé. Le coût du transport entre le domicile et la clinique, ainsi que les frais directs liés aux soins de santé dispensés, ont été calculés comme base déterminante du coût différentiel de chaque régime par traitement réussi au jour 42, et son coût par année de vie sauvée.

Résultats A+L s'est révélé comme le régime le plus efficace du point de vue clinique dans le traitement du paludisme à *P. falciparum* et représentait un excellent rapport coût-efficacité à 6,97 dollars par traitement réussi (environ 58 dollars par année de vie sauvée). DHA+PQ représentait l'association de traitement la plus efficace dans la lutte contre le paludisme à *P. vivax*, et était d'un meilleur rapport coût-efficacité que le traitement conventionnel contre le paludisme.

Conclusion A+L et DHA+PQ sont des régimes très rentables pour traiter, respectivement, le paludisme pédiatrique à *P. falciparum* et à *P. vivax*, dans les régions de la Papouasie-Nouvelle-Guinée. Des recherches futures seront nécessaires afin de déterminer si ces résultats se confirment dans d'autres territoires d'Asie et d'Océanie présentant une épidémiologie de paludisme similaire.

Резюме

Соотношение «затраты–эффективность» для артемизин-комбинированной терапии неосложненной формы малярии у детей: данные по Папуа–Новой Гвинее

Цель Сравнить соотношение «затраты–эффективность» для традиционной антималярийной терапии и трех схем артемизин-содержащего комбинированного лечения детей из Папуа – Новой Гвинеи в возрасте от шести до 60 месяцев.

Методы Был проведен маржинальный анализ соотношения «затраты–эффективность» с использованием данных по 656 детям с малярией *Plasmodium falciparum* и/или *Plasmodium vivax* , участвовавшим в крупном интервенционном испытании в двух лечебных учреждениях в северной Папуа – Новой Гвинее. Дети были рандомизированно распределены в одну из следующих групп: (i) традиционное лечение хлорохином плюс сульфадоксин плюс пириметамин (CQ+S+P); (ii) артесунат плюс S плюс P; (iii) дигидроартемизинин плюс пиперахин (DHA+PQ) и (iv) артеметер плюс люмефантрин (A+L). Для исходов лечения использовались определения Всемирной организации здравоохранения. Стоимость транспорта между домом и лечебным учреждением плюс прямые затраты на медицинскую помощь служили основой для определения приростных издержек каждой схемы на приростной успех лечения по отношению к CQ+S+P по состоянию на 42-ой день и ее издержек на один продленный год жизни.

Результаты A+L оказалась наиболее эффективной схемой по отношению к малярии *Plasmodium falciparum* и была высокорентабельной; соотношение «затраты – эффективность» для нее составляло 6,97 долл. США на один успешный исход лечения (около 58 долл. США на один продленный год жизни). DHA+PQ была наиболее высокоэффективной схемой по отношению к малярии *Plasmodium vivax* , а соотношение «затраты–эффективность» для нее было выше, чем для CQ+S+P.

Вывод A+L и DHA+PQ являются высокорентабельными схемами лечения малярии *Plasmodium falciparum* и *Plasmodium vivax* (соответственно) у детей в некоторых районах Папуа – Новой Гвинеи. В будущем потребуются научные исследования, чтобы определить, верны ли эти результаты по отношению к другим районам Азии и Океании с аналогичной эпидемиологией малярии.

Resumen

Rentabilidad del tratamiento combinado con artemisinina contra la malaria infantil sin complicaciones: datos de Papua Nueva Guinea

Objetivo Comparar la rentabilidad del tratamiento antipalúdico convencional respecto a la de los tres tratamientos combinados con artemisinina en niños de entre 6 y 60 meses de Papua Nueva Guinea.

Métodos Se realizó un análisis incremental de la rentabilidad con los datos procedentes de 656 niños con malaria por *Plasmodium falciparum* y/o por *P. vivax* que participaron en un ensayo intervencionista a gran escala en la costa Norte de Papua Nueva Guinea. A los niños que acudieron a dos consultorios, se les asignó aleatoriamente uno de los siguientes tratamientos: (a) tratamiento tradicional con cloroquina, sulfadoxina y pirimetamina; (b) artesunato, sulfadoxina y pirimetamina; (c) dihidroartemisinina y piperaquina (DHA+PQ); y (d) arteméter y lumefantrina (A+L). Se definieron los resultados terapéuticos siguiendo las definiciones normalizadas de la Organización Mundial de la Salud. Como base para la determinación de los costes incrementales por cada logro terapéutico alcanzado a los 42 días y su coste por año de vida salvado, se calculó el coste del transporte entre el hogar y el centro de salud, junto con los gastos directos ocasionados por la asistencia sanitaria proporcionada.

Resultados Desde el punto de vista clínico, el tratamiento más eficaz contra la malaria por *P. falciparum* fue el A+L, con una rentabilidad muy elevada de 6,97 dólares norteamericanos (US$) por logro terapéutico (unos 58 US$ por año de vida salvado). La combinación terapéutica más

eficaz contra la malaria producida por *P. vivax* fue la DHA+PQ y resultó ser más rentable que el tratamiento antipalúdico habitual.
Conclusión En algunas zonas de Papua Nueva Guinea, los tratamientos A+L y DHA+PQ resultan muy rentables en el tratamiento pediátrico contra la malaria por *P. falciparum* y *P. vivax*, respectivamente. Es preciso que se investigue más en profundidad para determinar si estos resultados también son válidos para otras regiones de Asia y Oceanía que presenten una epidemiología de malaria similar.

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