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The societal costs of managing vivax malaria episodes, including treatment, G6PD screening, and a clinical review in Cambodia, Ethiopia, Indonesia, and Pakistan

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Abstract

Background

Plasmodium vivax imposes a substantial health and economic burden, largely due to relapsing infections from the parasite's dormant liver stages. Radical cure prevents relapses, but its implementation is constrained by the need for glucose-6-phosphate dehydrogenase (G6PD) testing and safety monitoring. Evidence on the societal costs of *P. vivax* case management is limited. This study estimates the societal cost of the management of uncomplicated *P. vivax* episodes in adults in Cambodia, Ethiopia, Indonesia, and Pakistan.

Methods

The societal costs of the management of an uncomplicated *P. vivax* episode were estimated in 2024 United States dollars ($), using prospective data collected alongside the EFFORT trial. This trial evaluated the effectiveness of 14-day low-dose primaquine (3.5mg/kg total dose), 7-day high-dose primaquine (7.0mg/kg total dose), and tafenoquine (300mg). Provider costs were estimated using bottom-up, activity-based costing for malaria diagnosis, G6PD screening, blood- and liver-stage treatment, and a medical review visit. Household costs included direct medical and non-medical costs, and productivity losses collected from patient surveys on days 0, 3, and 21.

Results

A total of 960 participants were included across the four countries. The mean household costs per episode ranged from $4.15 in Ethiopia to $100.94 in Indonesia, with productivity losses accounting for 24–90% of total household costs. Provider costs without G6PD screening and liver-stage treatment ranged from $6.38 in Ethiopia to $11.81 in Indonesia, driven primarily by malaria diagnosis and blood-stage treatment. Liver-stage medication costs varied by regimen, with low-dose primaquine being consistently the lowest cost treatment option in all settings, while tafenoquine was the most expensive treatment. The total societal costs per episode varied by country and treatment strategy from $10.53 (Ethiopia, low-dose 14-day primaquine without G6PD screening) to $124.74 (Indonesia, tafenoquine with day 3 follow up).

Conclusions

Uncomplicated episodes of *P. vivax* impose substantial societal costs across endemic settings, driven primarily by household productivity losses. G6PD screening and medical review visits increase provider costs, however, increases were small relative to the overall economic burden, highlighting the potential economic value of preventing future *P. vivax* episodes through the strengthening the delivery of safe and effective radical cure.

Trial registration

The trial was registered at ClinicalTrials.gov (NCT04411836). Funding for this study was obtained from the National Health and Medical Research Council (NHMRC; grant number 1182950) and the Bill and Melinda Gates Foundation (BMGF; INV-024389).

INTRODUCTION

In 2024 an estimated 282 million malaria cases occurred in 80 countries, highlighting the persistent burden of the disease despite ongoing control efforts.[1] While significant progress has been made in reducing malaria transmission, several challenges continue to hinder its elimination. *Plasmodium vivax* malaria presents challenges to malaria elimination efforts, largely due to its ability to form dormant liver-stage hypnozoites that can cause multiple relapses after a single infectious bite.[2, 3] These relapses contribute not only to continued transmission, but also to prolonged illness and substantial economic burden, especially among populations with limited access to healthcare.[4–6]

Radical cure is needed to clear both the blood-stages of the parasite that cause acute illness and the liver-stages that cause relapsing infections. Liver-stage drugs include primaquine, administered either as a low-dose regimen (3.5mg/kg total dose) or a high-dose regimen (7.0mg/kg total dose) usually administered over 14 days[7] and tafenoquine, which is given as a single-dose (300mg).[8] Higher doses of primaquine are more efficacious and shorter 7-day regimens have been used to improve adherence.[9]

Both primaquine and tafenoquine can cause haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[10](REF). The World Health Organization (WHO) recommends that high-dose 7-day primaquine (1mg/kg/day) and tafenoquine should only be prescribed in patients who are G6PD normal confirmed by a semi-quantitative test,[11] such as the SD Biosensor's STANDARD™ G6PD Test.[12, 13] Since errors in diagnosis of G6PD and primaquine or tafenoquine prescription can still occur, a medical review visit on day 3 has been suggested to detect early signs of severe haemolysis so that primaquine can be ceased or patients closely monitored.[12, 13] Qualitative studies suggests that implementation of an early review visit is highly context-specific and should be adapted for different settings. Accordingly, approaches to who would conduct such a visit, at what level of the health care system, what procedures it would include, and what support mechanisms are required would likely vary.[14] The additional requirements for testing and follow-up have important implications for provider costs and potentially the overall economic burden of radical cure implementation.

Numerous studies have attempted to quantify the economic burden of malaria, including *P. vivax*.[5, 15, 16] These studies have demonstrated that productivity losses were the dominant component of household costs for *P. vivax* as well as other species of malaria.[5, 15, 16] Few studies have simultaneously evaluated provider and household costs of *P. vivax* malaria using prospective data,[15, 16] and none have reported the additional costs of an early clinical review visit. This study addresses these gaps by estimating the societal cost of an uncomplicated *P. vivax* episode across Cambodia, Ethiopia, Indonesia, and Pakistan, drawing on primary data collected through a clinical trial,[17] including healthcare provider costs (G6PD screening, treatment, and medical review visit), household out-of-pocket costs, and productivity losses.

METHODS

Study setting

Data were collected alongside the EFFORT clinical trial (NCT04411836), a multi-country effectiveness study of radical cure strategies for adult *P. vivax* patients conducted in Cambodia, Ethiopia, Indonesia, and Pakistan.[17] The EFFORT clinical trial was approved by the Human Research Ethics Committee of Northern Territory Health and Menzies School of Health Research (#20-3694) and country-specific institutional, national and regulatory authorities.

Country context

Routine *P. vivax* case management varies in the study countries. At the time of the study, Ethiopia and Pakistan both used chloroquine and 14-day low-dose primaquine (0.25 mg/kg/day) without routine G6PD screening (Table 1). In Ethiopia antimalarial policy has been influenced by the relatively low prevalence of G6PD deficiency.[13] In both Ethiopia and Pakistan, programmatic adherence to 14-day low-dose primaquine is tenuous. As a result, in 2024, Pakistan changed its guidelines to recommend 7-day low-dose primaquine (0.5mg/kg/day). Due to high levels of chloroquine-resistant *P. vivax*, Indonesia adopted dihydroartemisinin-piperaquine (DHP) in 2006 and combines this with a low-dose primaquine regimen; Indonesia is currently piloting the prescription of high-dose primaquine (1mg/kg/day) for G6PD normal individuals in selected areas.[14, 15] In Cambodia, at the time of the study, artesunate-mefloquine (ASMQ) - was used as the schizonticidal treatment, and 14-day low-dose primaquine (0.25 mg/kg/day) was provided after G6PD screening with SD Biosensor STANDARD™ G6PD Test (SD Biosensor).[16] Routine care in Cambodia also included a follow up visit by village malaria workers on day 3,7, and 14 to ensure safety and improve adherence. These follow up visits entailed checking treatment adherence, the recording of symptoms or side effects, and a real-time urine check; however, operationalisation of the guidelines varies.[17] The policy has now been revised to a shorter 7-day low-dose primaquine regimen (0.5mg/kg/day) with follow up visits on day 3 and 7.[18]

Table 1
National blood and liver stage treatment guidelines during and after trial

Country	During the study				Policy changes since study
	Blood-stage treatment	Radical cure policy	G6PD screening	Follow-up policy	
Cambodia	Artesunate-mefloquine	14-day low-dose PQ (0.25 mg/kg/day)	Routine screening with SD Biosensor STANDARD™ G6PD Test	Village malaria worker follow-up on days 3, 7, and 14. Visit includes checking treatment adherence, the recording of symptoms or side effects, and a real-time urine check; however, operationalisation of the guidelines varies [19]	Revised in 2022 to artesunate-pyronaridine (implemented 2025) and 7-day low-dose PQ (0.5 mg/kg/day) with follow-up on days 3 and 7 (implemented 2023)
Ethiopia	Chloroquine	14-day low-dose PQ (0.25 mg/kg/day)	No routine screening	No formal follow-up visits since 2022, but counselling patients on how to self-monitor for side effects	No major policy change
Indonesia	Dihydroartemisinin-piperaquine	14-day low-dose PQ (0.25 mg/kg/day)	G6PD screening with SD Biosensor STANDARD™ G6PD Test in pilot areas for high-dose PQ implementation	Clinical examination at health facility on day 3, 7, 14, 21, 28 and provided with counselling while their urine colour is monitored	Continued piloting of high-dose PQ approaches
Pakistan	Chloroquine	14-day low-dose PQ (0.25 mg/kg/day)	No routine screening	Close medical supervision when G6PD testing is not possible. Monitoring only implemented among populations with known higher G6PD deficiency	Revised in 2024 to 7-day low-dose PQ (0.5 mg/kg/day)

G6PD – glucose–6–phosphate dehydrogenase; PQ – primaquine

Cost adjustments

All costs were collected in local currencies and adjusted into 2024 United States dollars ($) using standard methods [20, 21] and exchange rates and gross domestic product (GDP) deflators from the World Bank.[22,

23] Costs from Cambodia and Indonesia were inflated to 2024 costs before conversion to United States dollars. Since Ethiopia and Pakistan had high inflation rates during the study period (2021–2024), all costs collected in these currencies were converted into United States dollars before adjusting to 2024 costs.[20, 21]

Household costs

Information related to treatment-seeking behaviour and costs prior to enrolment, direct costs during enrolment, and time losses due to illness for patients and their households were collected through surveys on the day of enrolment (day 0), three days after enrolment (day 3), and 21 days after enrolment (day 21) of the initial recruitment episode. These included any activities related to seeking care for illness such as visits to drug shops, traditional healers, and health facilities. Patient-level data were analysed using Stata, version 18 (StataCorp, College Station, USA).

The household cost estimation included three main components: (1) direct medical costs, comprising out-of-pocket expenditures for treatment and diagnostics incurred prior to and during the enrolment visit; (2) direct non-medical costs, which cover transportation expenses (including transportation for treatment-seeking before trial enrolment); and (3) productivity losses among patients and caregivers (where applicable). The cost of transportation to the enrolment visit was multiplied by two in order to account for the return journey. While costs related to treatment-seeking between visits were collected at all time points, direct costs related to the day 3 and day 21 visits at the trial facility were not collected.

Pre-enrolment treatment-seeking behaviour was recorded during the trial intake survey. Patients were asked to report any care-seeking actions prior to visiting the study facility, including formal providers (public or private clinics/hospitals) and informal providers (e.g. drug stores) and associated costs. Multiple contacts were allowed. These data help to capture typical patient pathways and potential delays in accessing definitive treatment.

For the productivity losses, information on employment status (paid employment, unpaid housework, unpaid subsistence farming, attending school, or other), both for patients and caregivers, was collected, alongside the amount of time lost from usual activities. Country-specific minimum monthly wage rates from 2024 were used to value productivity losses for all patients,[24] which were divided by 22 working days to get daily rates of $9.27 for Cambodia, $0.23 for Ethiopia, $14.53 for Indonesia, and $6.04 for Pakistan.

Mean and standard deviation were calculated for costs and days lost from usual activities. Since there were low levels of missing cost data and these were only at days 3 and 21, these were assumed to be 0.

Provider costs

Provider costs per episode were estimated using a bottom-up approach with activity-based costing [25] using a structured data collection instrument. Details on staff time, capital, and recurrent costs for each activity were obtained using an observation log for one site in each of the four countries: Siem Pang Health Centre in Cambodia, Arba Minch General Hospital in Ethiopia, Tanjung Leidong Health Centre in Indonesia, and Thatta Health Centre in Pakistan. Unit prices of each cost component were collected from country-specific

procurement sources and trial site expenditure logs. Costs relevant only to the trial setting, such as compensation for staff time to provide informed consent and follow-up visit schedules, were not included. Operational activity costs, such as buildings, were not included.

Direct costs for medical activities included: initial outpatient consultation, finger prick blood draw (used for both malaria diagnosis and G6PD screening at enrolment; and haemoglobin test on day 3), malaria diagnosis (by rapid diagnostic test in Cambodia, Indonesia, and Pakistan; microscopy in Ethiopia), G6PD screening using the SD Biosensor, and medications (blood-stage, liver-stage, and other). In addition, a medical review visit on day 3, subsequently referred to as 'day 3 review', assessed whether the patients had persistent peripheral parasitaemia, ensured clinical recovery, and identified any adverse drug reactions. Costs for this day 3 review included the cost of an outpatient clinical consultation, haemoglobin test, and urine colour assessment (Hillmen score). It was assumed that the cost of clinical consultation for the initial visit and the day 3 review were the same.

The cost for G6PD screening was taken from the recent volume guarantee agreement Ex Works prices: $300 for the analyser, $3.27 for the test strip, and $30 per control kit.[26] The unit costs for malaria diagnosis and blood-stage treatment were estimated from study records, with local unit costs for consumables, equipment, and human resources applied per patient, validated by local study teams. Equipment costs were annualized by the expected life years of the equipment based on expert opinion. Local unit costs for primaquine treatment were also used, with dosage dependent on treatment arm. The cost of tafenoquine for Cambodia, Indonesia, and Pakistan was set uniformly across all countries at $3.74 based on pricing from Thailand, with local taxes applied in Cambodia to align with the current financing structure for primaquine. In Ethiopia, this was set at $1.72 to reflect local availability.[27]

Equipment costs were annualised over their expected useful life using a 3% annuitisation rate in all countries.[28] The annuitisation was used solely to allocate up-front investment costs over time and does not imply projection of future costs or outcomes.

The staff time for each service component was estimated through direct observation. Trained observers recorded the duration required to complete each step of care, including patient admission and anthropometric assessment, malaria diagnosis, G6PD screening, and activities of the day 3 review. Time measurements were taken prospectively using a structured observation log and averaged across multiple patient encounters.

The following assumptions were made regarding the provider costs estimation. One blood draw was done for several purposes, including the diagnosis, the haemoglobin test, as well as the G6PD test. The total number of annual healthcare visits at each facility was used as the throughput for equipment, such as computers, needed for all patients visiting the health facility, with the exception of the G6PD analyser, for which the total number of annual vivax malaria cases was used for the throughput. As the study site in Ethiopia only sees malaria patients, throughputs from a similar facility in the same district were used as the denominator for all equipment used at the Ethiopian site.

Each component of the initial provider visit was presented separately, including initial consultation, blood draw, malaria diagnosis, G6PD screening, blood-stage, liver-stage, and other medication. The same was done for the consultation, haemoglobin test, and urine assessment for the day 3 review. These components were

then combined to estimate the total cost of current practice and a range of alternative strategies, including 14-day low dose primaquine with and without G6PD screening, 7-day high dose primaquine with and without day 3 review (both with G6PD screening), and single-dose tafenoquine with and without day 3 review (both with G6PD screening)

RESULTS

Patient characteristics

Trial results have been presented previously.[17] Briefly, a total of 960 participants were recruited from Cambodia, Ethiopia, Indonesia, and Pakistan, with 320 participants in each arm. At the day 3 review, 96% (917/960) patients completed the cost survey, and 87% (838/960) completed the cost survey at day 21. The baseline characteristics are presented in Table 2. The mean age was 30 years, and the majority of participants were male (70%; 672/960), ranging from 56% in Ethiopia to 90% in Cambodia. Overall, 31% of study participants reported missing unpaid work due to illness (294/960), 43% (421/960) reported missing out on paid work, 17% (161/960) reported missing school, and a further 9% (84/960) reported other activities that could not be classified into these categories. By country, the percentage of patients in paid employment ranged from 35% (78/220) in Cambodia to 56% (134/240) in Pakistan (Table 2). Overall, 47% (455/960) of patients reported requiring a caregiver while ill, ranging from 15% (36/240) in Pakistan to 79% (118/150) in Indonesia. For those who required a caregiver, they reported that 57% (259/455) would have been in unpaid work, 27% (121/455) reported missing out on paid work, and 12% (53/455) reported missing school. A further 5% (22/455) reported other activities that could not be classified into the aforementioned categories.

Table 2
Baseline patient characteristics of those included in the trial by country.

Age – mean (SD)	**Cambodia (n = 220)**	**Ethiopia (n = 350)**	**Indonesia (n = 150)**	**Pakistan (n = 240)**	**Total (N = 960)**
	28.8 (9.6)	**26.4 (9.9)**	**30.6 (13.2)**	**33.9 (13.0)**	**29.5 (11.6)**
Male – n (%)	198 (90%)	197 (56%)	100 (67%)	177 (74%)	672 (70%)
What the patient would be doing today if not unwell – n (%)					
Unpaid housework	19 (9%)	61 (17%)	40 (27%)	60 (25%)	180 (19%)
Unpaid subsistence farming	70 (32%)	20 (6%)	6 (4%)	18 (8%)	114 (12%)
Attending school	0 (0%)	119 (34%)	23 (15%)	19 (8%)	161 (17%)
Paid employment	78 (35%)	138 (39%)	71 (47%)	134 (56%)	421 (44%)
Other	53 (24%)	12 (3%)	10 (7%)	9 (4%)	84 (9%)
Patients reporting a caregiver – n (%)	120 (55%)	181 (52%)	118 (79%)	36 (15%)	455 (47%)
What the caregiver would be doing today if the patient wasn't unwell – n (%)[†]					
Unpaid housework	36 (30%)	47 (26%)	83 (70%)	27 (75%)	193 (42%)
Unpaid subsistence farming	41 (34%)	21 (12%)	2 (2%)	2 (6%)	66 (15%)
Attending school	2 (2%)	49 (27%)	0 (0%)	2 (6%)	53 (12%)
Paid employment	27 (23%)	63 (35%)	26 (22%)	5 (14%)	121 (27%)
Other	14 (12%)	1 (1%)	7 (6%)	0 (0%)	22 (5%)

[†] The denominator is the number of patients reporting that they had a caregiver.

SD – standard deviation.

Treatment-seeking behaviour

The treatment-seeking behaviour prior to trial enrolment revealed distinct patterns across the four countries, reflecting variations in health system structure, access, and community preferences (Table 3). In Cambodia, the majority of patients (96%, 212/220) actively sought care before enrolment, often consulting multiple

providers, with formal and informal sources both playing a role. In Pakistan nearly half of the participants (49%, 118/240) had not sought any prior care. Only 23 of the 960 patients (3%) sought additional treatment between recruitment in the trial, and 24 patients (3%) between the day 3 and day 21 follow up (Table 3).

Table 3
Treatment-seeking behaviour by country. Some patients reported visiting multiple locations before enrolling in the trial; accordingly, the percentages of those who sought care could be more than 100%.

Sought treatment before enrolment	**Cambodia (n = 220)**	**Ethiopia (n = 350)**	**Indonesia (n = 150)**	**Pakistan (n = 240)**	**Total (N = 960)**
	212 (96%)	**349 (100%)**	**121 (81%)**	**122 (51%)**	**804 (83%)**
Visited a drug shop	6 (3%)	1 (0.3%)	30 (25%)	13 (11%)	50 (6%)
Visited this health facility	2 (1%)	0 (0%)	0 (0%)	9 (7%)	11 (1%)
Visited a private clinic	16 (8%)	2 (1%)	89 (74%)	42 (34%)	149 (19%)
Visited a public clinic	25 (12%)	148 (42%)	21 (17%)	32 (26%)	226 (28%)
Visited a hospital	35 (17%)	200 (57%)	3 (2%)	34 (28%)	272 (34%)
Visited a traditional healer	0 (0%)	0 (0%)	2 (2%)	0 (0%)	2 (0.3%)
Visited a village malaria worker	144 (68%)	0 (0%)	0 (0%)	0 (0%)	144 (18%)
Visited other location	2 (1%)	0 (0%)	3 (2%)	4 (13%)	9 (2%)
Sought treatment between day 0 and day 3 visits	3 (1%)	0 (0%)	8 (6%)	12 (5%)	23 (3%)
Sought treatment between day 3 and day 21 visits	6 (4%)	0 (0%)	14 (12%)	4 (2%)	24 (3%)

The hours spent, treatment cost, and transportation cost associated with seeking treatment at each type of facility for each country are reported in Supplementary Table 1. Across all countries, seeking treatment at a hospital took longer than doing so at other types of facilities (Supplementary Table 1). In Indonesia, this was particularly high due to one patient reporting spending 10 days in hospital before enrolment in the study; this patient also reported 50 days of illness prior to enrolment, likely skewing the days of illness presented in Table 3.

Indonesian patients showed reliance on private clinics (74%, 89/150) as one of the initial sources of care (Table 3). In contrast, Ethiopian patients showed a stronger preference toward the formal public sector, with most patients accessing either hospital (57%, 200/350) or public clinics (42%, 148/350) prior to enrolment. Patients in Pakistan chose a mix of facilities, with private clinics (34%, 42/240), hospitals (28%, 34/240), and

private clinics (26%, 32/240) being used the most frequently. In Cambodia, 68% of patients (144/220) went to village malaria workers first.

Household costs

Across all countries, patients reported a longer mean amount of time feeling unwell (4.1 days) as compared to time unable to do usual activities at enrolment into the study (2.0 days; Table 4). The total time away from usual activities for patients (3.8 days) were also much higher than those for any caregivers (0.5 days; Table 4). Patients in Indonesia experienced higher patient time off usual activities (3.9 days) as compared to the other three countries, which ranged from 1.4 to 1.9 days. Conversely, the time that caregivers were unable to do usual activities was higher for Cambodia (1.5 days) than what was reported in Ethiopia (0.4 days), Indonesia (0.2 days), and Pakistan (0.1 days; Table 4). While most patients reported taking 30–59 minutes to travel from their homes to the health facility (44%, 420/960), this varied by location with 81% (122/150) in Indonesia reporting less than 30 minutes and 68% (164/240) in Pakistan reporting it took between one hour and less than half a day (Supplementary Table 2).

Table 4
Mean days and standard deviation (SD) that patient was ill and that the patient and any caregiver needed to take away from usual activities.

Days patient were sick before day 0	**Cambodia (n = 220)**	**Ethiopia (n = 350)**	**Indonesia (n = 150)**	**Pakistan (n = 240)**	**Total (N = 960)**
	2.9 (1.1)	**2.5 (1.4)**	**8.7 (8.3)**	**4.7 (3.1)**	**4.1 (4.3)**
Days patient was unable to do usual activities before day 0	1.7 (1.2)	1.4 (1.1)	3.9 (4.8)	1.9 (2.3)	2.0 (2.5)
Total days patient unable to do usual activities	3.3 (2.0)	3.9 (2.2)	6.1 (7.0)	2.7 (2.9)	3.8 (3.7)
Total days caregiver unable to do usual activities	1.5 (1.9)	0.4 (0.6)	0.2 (0.7)	0.1 (0.6)	0.5 (1.2)

Household costs related to having an episode of malaria varied across countries, with the highest total costs observed in Indonesia at $100.94 (SD = 105.66) then Cambodia $58.82 (SD = 35.35), followed by Pakistan $19.85 (SD = 22.05) and Ethiopia $4.15 (SD = 1.64); (Table 5). The dominant cost driver was productivity losses due to patient and caregiver time away from usual activities, comprising 24–90% of the total costs across settings. The costs of productivity losses were highest in Indonesia, where patients experienced substantial time losses due to missed work (Table 5).

Direct medical costs were also highest in Indonesia ($8.39), while direct non-medical costs were highest in Cambodia ($11.58). In all settings except Cambodia, most of the direct expenses were incurred due to treatment-seeking prior to enrolment (Table 5). One patient in Cambodia reported a private clinic treatment cost of $118, resulting in a mean cost of $27 for private clinics as compared to $0.20–4.08 for other types of visits. This resulted in a mean overall treatment cost during treatment-seeking of $2.83 (SD = 11.78), despite

the majority of treatment-seeking locations being reported as the village malaria worker where there was no treatment cost.

Table 5
Mean and standard deviation (SD) household costs per vivax malaria episode in 2024 United States dollars. Treatment-seeking costs include all reported visits outside of the trial between days 0 and 21.

Cost component	Cambodia		Ethiopia		Indonesia		Pakistan		Overall	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total treatment-seeking outside of enrolment	**4.17**	**12.61**	**1.59**	**1.04**	**8.83**	**13.28**	**2.52**	**8.71**	**3.55**	**9.44**
Treatment costs	2.83	11.78	0.95	0.82	8.39	13.18	2.24	8.17	2.87	9.04
Transport costs	1.35	2.88	0.64	0.41	0.44	0.99	0.28	1.03	0.68	1.59
Total direct costs at enrolment	**10.23**	**13.48**	**1.57**	**0.73**	**1.06**	**1.66**	**0.03**	**0.47**	**3.09**	**7.60**
Medical costs	0.00	0.00	0.18	0.37	0.00	0.00	0.00	0.00	0.07	0.24
Transport costs	10.23	13.48	1.39	0.69	1.06	1.66	0.03	0.47	3.03	7.61
Total productivity costs	**44.41**	**29.40**	**0.99**	**0.55**	**91.05**	**102.14**	**17.30**	**17.55**	**29.09**	**53.60**
Patients	30.38	18.80	0.90	0.50	88.54	102.23	16.53	17.32	25.26	51.45
Caregivers	14.03	18.04	0.09	0.13	2.52	9.82	0.77	3.52	3.83	11.14
Total household costs	**58.82**	**35.35**	**4.15**	**1.64**	**100.94**	**105.66**	**19.85**	**22.05**	**35.73**	**57.93**

Provider costs

The total provider cost of current case management of *P. vivax* varied between $6.38 in Ethiopia and $13.99 in Cambodia (Table 6). This included the cost of the initial consultation, blood draw, malaria diagnosis, G6PD screening (in Cambodia only), blood stage treatment, and 14-day low-dose primaquine.

Table 6
Healthcare provider costs per vivax malaria episode in 2024 United States dollars.

Total initial visit cost for current practice	**Cambodia**	**Ethiopia**	**Indonesia**	**Pakistan**
	13.99	**6.38**	**11.14**	**8.92**
Initial consultation	2.20	1.04	1.26	1.29
Blood draw (finger prick)	0.76	1.56	1.79	1.95
Malaria diagnosis[†]	2.10	1.62	3.69	4.27
G6PD screening	6.05	n/a	n/a	n/a
Blood-stage treatment	1.18	1.19	3.59	0.72
Other medications	0.30	0.47	0.82	n/a
PQ14	1.40	0.50	0.67	0.70
Alternative intervention costs				
G6PD screening	(as above)	4.02	6.15	3.88
PQ7	2.80	1.01	1.34	1.40
Tafenoquine	4.49	1.72	3.74	3.74
Day 3 review total cost	**3.68**	**4.48**	**2.77**	**4.09**
Consultation	2.20	1.04	1.26	1.29
Haemoglobin test	0.96	2.89	1.20	0.65
Urine test	0.52	0.55	0.31	2.15

[†] While microscopy was used in routine practice in Ethiopia, rapid diagnostic tests were used in Cambodia, Indonesia, and Pakistan.

G6PD – glucose–6–phosphate dehydrogenase; n/a – not applicable; PQ14 – low-dose primaquine (3.5mg/kg total dose) over 14 days; PQ7 – high-dose primaquine (7mg/kg total dose) over 7 days

The per-patient cost of G6PD screening ranged from $3.88 in Pakistan to $6.15 in Indonesia. These costs were higher in Indonesia and Cambodia compared to Pakistan and Ethiopia. Full details of the assumptions used, including throughputs and quality control costs, which impact the per person screening cost, are presented in Supplementary Table 3. The costs for treating patients with high-dose primaquine ranged from $1.01 in Ethiopia to $2.80 in Cambodia. Tafenoquine was the highest cost treatment across all settings. The cost of the day 3 review ranged from $2.77 in Indonesia to $4.48 in Ethiopia. The costs for the day 3 review were predominantly driven by haemoglobin testing. Excluding urine and haemoglobin tests, the day 3 review cost was reduced to $1.04 - $2.20.

Total costs

When the household costs were combined with the provider costs, the total cost of *P. vivax* malaria episodes ranged from $10.53 for 14-day low-dose primaquine (without G6PD screening) in Ethiopia to $124.74 for tafenoquine (with a day 3 review) in Indonesia, demonstrating substantial variability across locations (Table 7). In all settings 14-day low-dose primaquine consistently had the lowest average episode costs, while 7-day high-dose primaquine incurred slightly higher total costs, and tafenoquine incurring the largest costs. Using 14-day low-dose primaquine without G6PD screening, total societal costs ranged from $10.53 in Ethiopia to $112.75 in Indonesia, demonstrating substantial variation across settings. Comparatively, the tafenoquine strategy without day 3 review resulted in higher societal costs in all countries, from $15.77 in Ethiopia to $121.97 in Indonesia.

Table 7
Total costs of a vivax malaria episode in 2024 United States dollars from different perspectives. Provider costs for 14-day low-dose primaquine regimen (total dose 3.5mg/kg; PQ14) strategy are presented with and without G6PD screening; the day 3 review was not included. Provider costs for both the high-dose 7-day primaquine regimen (total dose 7mg/kg; PQ7) and tafenoquine (300mg) strategies are presented with and without the day 3 review; all include the cost of G6PD screening. Note that the household costs of seeking treatment for the day 3 review are not included here.

Household perspective	**Cambodia**	**Ethiopia**	**Indonesia**	**Pakistan**
	58.82	**4.15**	**100.94**	**19.85**
Provider perspective				
PQ14	7.94	6.38	11.81	8.92
PQ14 with G6PD screening	13.99	10.40	17.96	12.80
PQ7	15.39	10.90	18.63	13.50
PQ7 with day 3 review	19.07	11.36	21.40	17.60
Tafenoquine	17.08	11.62	21.03	16.06
Tafenoquine with day 3 review	20.76	16.09	23.80	19.94
Societal perspective				
PQ14	66.76	10.53	112.75	28.77
PQ14 with G6PD screening	72.81	14.55	118.90	32.65
PQ7	74.21	15.05	119.57	33.35
PQ7 with day 3 review	77.89	15.51	122.34	37.45
Tafenoquine	75.90	15.77	121.97	35.91
Tafenoquine with day 3 review	79.58	20.24	124.74	39.79

G6PD – glucose–6–phosphate dehydrogenase; PQ14 – low-dose primaquine (3.5mg/kg total dose) over 14 days; PQ7 – high-dose primaquine (7mg/kg total dose) over 7 days

DISCUSSION

Our study provides a comprehensive, multi-country estimate of the societal costs of uncomplicated *P. vivax* malaria episodes in Cambodia, Ethiopia, Indonesia, and Pakistan, incorporating both provider and household perspectives and the potential additional costs of G6PD screening and a day 3 review to support a change to more effective radical cure regimens. Across all four settings, substantial heterogeneity in associated costs were observed, driven largely by differences in treatment-seeking behaviour and productivity loss estimates. Consistent with prior evidence,[5, 15, 29] productivity losses were the dominant contributor to household costs, accounting for 24–90% of total household expenditures and underscoring the economic vulnerability associated with *P. vivax* even in ostensibly uncomplicated cases. Provider costs were more homogeneous across countries, with G6PD testing representing the largest cost component beyond routine malaria care.

The magnitude and composition of costs observed in this study are broadly consistent with previous single and multi-country evaluations of malaria-related economic burden.[15, 16, 30, 31] Earlier analyses have similarly identified lost productivity as the principal cost driver for *P. vivax* episodes, often exceeding direct medical and non-medical costs combined.[15, 31] Few prior studies, however, have explicitly included the provider-side costs of routine G6PD testing,[32] and none have included the costs of structured follow-up visits.

Drawing on the full range of interventions, the total provider costs per episode ranged from $6.38 In Ethiopia to $23.80 in Indonesia. The largest contributors to provider costs were G6PD screening and the day 3 follow-up review, while the costs of blood-stage and liver-stage treatments were comparatively low. The inclusion of day 3 review visits designed to improve safety and adherence to radical cure regimens, added only modestly to provider costs, with haemoglobin testing representing the largest component. The costs presented here assume the visit was conducted at same facility as that for the enrolment visit. Currently, no clear consensus exists regarding which activities should be included as part of the day 3 visit, whether haemoglobin testing is required for every patient, or at which level of the health system and by whom these reviews should be conducted. Recent qualitative work from Cambodia and Ethiopia demonstrated substantial variation in stakeholder preferences regarding the location, implementer, procedures, and support mechanisms for day 3 review visits.[14] Consequently, the costs associated with day 3 follow-up are likely to vary considerably depending on the delivery model adopted. If different models are chosen (e.g., follow up by a village malaria worker or haemoglobin testing based on clinical signs and symptoms only), these costs would likely be lower. The costs of each of these additional measures will need to be weighed up against the future benefits of cases averted in a cost-effectiveness analysis to ascertain their value.

Prior estimates from individual-level claim data within the National Health Insurance system in Indonesia indicated that the mean cost for an outpatient consultation ($16.2 [33] versus $11.1 in the current study) likely reflected both differences due to the level of care and methodological differences. While National Health Insurance data relied on top-down administrative claims, providing broader population-level estimates at the hospital level that are subject to higher tariffs, the current study's facility-level observations offer a more detailed bottom-up assessment of resource use at a primary care facility (Puskesmas), where over 50% of malaria cases in Indonesia are managed.

Most of the direct costs experienced by participants occurred during treatment seeking, prior to study enrolment. Across all study sites, more than half of direct costs were experienced prior to enrolment, with

large variation between sites. These differences can be explained by variations in health systems and treatment-seeking pathways. In Cambodia, most patients sought care from village malaria workers reflecting a focus community-based malaria services and on treating remaining cases. In contrast patients in Indonesia and Pakistan commonly sought care at private clinics,[15, 34, 35] which may not be prescribing appropriate treatment for *P. vivax*.[15, 35] Ethiopian patients showed a stronger preference toward the formal public sector, with most patients accessing either public clinics or hospitals prior to enrolment, though this may reflect the trial set-up where patients were screened at health facilities and referred to the trial centre only when malaria positive. These findings demonstrate how fragmented care pathways can contribute substantial to patient cost.

Household cost differences were driven primarily by variation in time lost from usual activities and differences in the minimum wages that were used to value productivity losses. In Indonesia, the duration of illness was longer and was associated with a greater time away from usual activities; this translated into the highest productivity losses. Conversely in Cambodia, non-medical costs such as transportation contributed a larger share of direct household expenditures, with some patients having to travel almost 100 kilometres to receive care. In contrast, the overall household costs in Ethiopia and Pakistan were substantially lower, reflecting shorter reported illness duration and lower wage estimates used to value time losses. Household costs were higher than provider costs for each vivax malaria episode in Cambodia, Indonesia, and Pakistan, indicating the substantial economic burden borne by these populations.

Despite only including adults, our study reveals a large caregiving burden with 47% of patients overall reported requiring a caregiver while ill, potentially indicating the degree of febrile illness and incapacity associated with acute vivax malaria episodes. It is interesting to note that this varied by country, ranging from 15% in Pakistan to 79% in Indonesia.

The Ethiopian study site showed the largest proportion of patients who were unable to attend school (34%) and included a large proportion of caregivers (27%) of who took time off school to attend the health facility with the patients. This is particularly concerning given the relationship between malaria and educational attainment,[36] and the importance of school attendance.[37] For this analysis, we valued all participants time equally using local wage estimates from each setting, which may overestimate the costs of school attendees. While we did not collect the ages of caregivers, all Ethiopian patients within this study were over the age of 16 years. Of the 119 patients who reported attending school 86% (102/119) were aged 17–22 with the oldest respondent 33 years old. Given the importance of educational attainment on longer term cognitive and socioeconomic development, valuing productivity losses for patients and caregivers could be viewed as necessary, especially in the context of inequities. Whether missed schooling should be included within productivity loss estimates is inconsistently reported in the wider literature.[38]

This study has several limitations. First, provider costs were estimated using detailed data from a single health facility in each country, which may not capture variation across different facility types or geographic settings. Nevertheless, the use of standardised activity-based costing methods improves internal validity and comparability across countries. Second, household costs were self-reported and may be subject to recall bias, although the prospective design with multiple follow-up interviews at days 3 and 21 likely reduced this risk. Third, productivity losses were valued using minimum wage rates by country, which may overestimate the

opportunity costs for individuals engaged in informal employment;[38] however, this approach was consistent for all countries, enabling comparability across settings.

CONCLUSIONS

Uncomplicated *P. vivax* malaria imposes considerable societal costs across Cambodia, Ethiopia, Indonesia, and Pakistan, with household productivity losses constituting the largest component of the overall economic burden. Provider costs varied modestly across settings and increased with the inclusion of G6PD screening and day 3 follow-up reviews, however, these additional expenditures were relatively small compared to the total societal costs. Our findings underscore the importance of strengthening timely access to appropriate diagnosis and radical cure, as reducing recurrent illness has the potential to alleviate both household financial strain and broader economic losses in endemic settings. Future research should evaluate whether the higher upfront provider costs associated with G6PD screening and shorter-course regimens are offset by reductions in recurrent episodes, productivity losses, and onward transmission. As countries progress toward *P. vivax* elimination, understanding the long-term economic implications of different radical cure delivery strategies will be critical for informing sustainable policy decisions.

Abbreviations

G6PD
glucose–6–phosphate dehydrogenase
PQ
primaquine
SD
standard deviation

Declarations

Ethics approval and consent to participate

The EFFORT clinical trial was approved by the Human Research Ethics Committee of Northern Territory Health and Menzies School of Health Research (#20-3694) and country-specific institutional, national and regulatory authorities. Written informed consent was obtained from all patients before enrolment.

Consent for publication

Not applicable.

Availability of data and materials

Data available upon request to corresponding author.

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Authors' contributions

KT and RNP conceived the clinical trial. AD conceived the health economics components of the trial. ES, RT, BA, SO, MYPS, TT, DT, FJ, SC-S, HM, GL, RSH, AP, NG, MAB, LD and LvS oversaw all field data collection activities, data entry and processing. AD, ES, and PA analysed the data and interpreted the results with support from all co-authors. ES and AD led the writing of the manuscript with input from all co-authors. All co-authors read and approved the final manuscript.

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