Prereferral rectal artesunate for treatment of severe childhood malaria: a cost-effectiveness analysis

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Summary

Background **Severely ill patients with malaria with vomiting, prostration, and altered consciousness cannot be treated orally and need injections. In rural areas, access to health facilities that provide parenteral antimalarial treatment is poor. Safe and effective treatment of most severe malaria cases is delayed or not achieved. Rectal artesunate interrupts disease progression by rapidly reducing parasite density, but should be followed by further antimalarial treatment. We estimated the cost-effectiveness of community-based prereferral artesunate treatment of children suspected to have severe malaria in areas with poor access to formal health care.**

Methods **We assessed the cost-effectiveness (in international dollars) of the intervention from the provider perspective. We studied a cohort of 1000 newborn babies until 5 years of age. The analysis assessed how the cost-effectiveness results changed with low (25%), moderate (50%), high (75%), and full (100%) referral compliance and intervention uptake.**

Findings **At low intervention uptake and referral compliance (25%), the intervention was estimated to avert 19 disability-adjusted life-years (DALYs; 95% CI 16–21) and to cost I$1173 (95% CI 1050–1297) per DALY averted. Under the full uptake and compliance scenario (100%), the intervention could avert 967 DALYs (884–1050) at a cost of I$77 (73–81) per DALY averted.**

Interpretation **Prereferral artesunate treatment is a cost-effective, life-saving intervention, which can substantially improve the management of severe childhood malaria in rural African settings in which programmes for community health workers are in place.**

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Introduction

Malaria caused an estimated 243 million clinical episodes in 2008, 90% of which were due to *Plasmodium falciparum* and 863 000 resulted in deaths;[1] these WHO figures underestimate the malaria burden. Most of these clinical cases and deaths occurred in children in rural areas of Africa.[1,2] If not treated early with an adequate dose of an effective antimalarial medicine, acute infections of *P falciparum* can progress rapidly to life-threatening disease and death.[3] In addition to the increased risk of mortality, a range of developmental deficits have been reported in children who had been infected with *P falciparum*. The community prevalence and characteristics of these deficits are, however, poorly defined,[4] preventing an accurate estimation of the full burden of *P falciparum* malaria.

Severely ill patients with vomiting, prostration, and altered consciousness cannot tolerate oral treatment and need parenteral antimalarial drugs, adjunctive therapy, and supportive care.[3] In rural areas, access to health facilities that provide parenteral treatment is poor, laboratory diagnosis is not available, and quality of inpatient care is variable. Hence, safe and effective treatment of most cases of severe malaria is greatly delayed or not achieved. Rates of malaria mortality after the introduction of quinine treatment have changed very little.[4] In settings in which referral substantially delays the start of parenteral antimalarial treatment, the 2010 WHO guidelines for the treatment of malaria[5] recommend the use of artesunate or artemisinin suppositories for emergency treatment of patients with suspected severe malaria before transfer to a health facility. The use of this intervention in endemic countries remains low, pending evidence about efficacy, effectiveness, costs, and cost-effectiveness.

A community-based, placebo-controlled, randomised trial[6] established the survival benefit of one dose of rectal artesunate in African patients with suspected severe malaria who had a referral delay of more than 6 h. No adverse drug reactions were reported, apart from sciatic nerve damage, which was not attributed to treatment. Village recruiters with little or no previous medical background underwent training and under supervision gave the drug to severely ill children with referral advice to caregivers based on the clinical symptoms of severe malaria. Qualitative studies showed that familiarity of caregivers with artesunate suppositories led to their acceptance and use as a treatment.[7,8]

In view of the established efficacy, safety, and acceptability of rectal artesunate, we undertook a cost-effectiveness analysis of community-based prereferral treatment of patients with rectal artesunate for the management of severe childhood malaria.

Methods

Study design

This cost-effectiveness analysis followed standard guidelines of economic analyses,[9] with the present uptake of treatment services available for severe malaria (ie, parenteral antimalarial treatment to patients who seek care at health facilities) as the comparator. We considered rural settings in which care-seeking at health facilities was low because of poor access, and was substantially delayed. The intervention was the administration of one dose of rectal artesunate by a community health worker to a child with suspected severe malaria alongside referral advice to caregivers. We assumed that community health workers would deliver prereferral artesunate as part of an intervention package within an existing community-based treatment programme. The outcome of this analysis was expressed as a ratio of incremental costs to incremental health outcomes of the intervention. The incremental cost-effectiveness ratios were calculated in international dollars (I$) for 2008.

Consistent with methods developed for the Disease Control Priorities Project, the intervention cost-effectiveness was assessed over a period of 5 years from a provider perspective.[10] The timeframe includes the health benefits of the intervention in terms of averted early mortality and persisting neurological disability in a cohort of 1000 newborn babies until 5 years of age, when the incidence of clinical malaria wanes in high-transmission areas. This approach also takes into account that children are likely to have many infections until that age. In rural areas, the value of time needed for travel, and referral care-seeking, can be substantial because of poor accessibility of health facilities. The assumed provider perspective excluded these indirect costs since prereferral artesunate treatment addressed a treatment gap attributable to the state of the health systems.

Estimation of health outcomes

Children younger than 5 years of age constitute 17·6%[11] of the beneficiary population, and the number of malaria cases in this age group is calculated with a yearly incidence rate of 1682 episodes per 1000 in rural high-transmission areas of Africa.[2] We assumed that 5% of these episodes would progress to severe malaria because of no treatment, or treatment failure with oral antimalarials, and that 3% of survivors would have a persisting neurological disability.[12,13]

Health outcomes were measured in terms of deaths and disability-adjusted life-years (DALYs) averted. DALYs combine years of life lost because of premature death with years of life lived with disability in one outcome measure. The case-fatality rate for severe malaria after inpatient care is 20%, whereas patients who do not seek treatment have a higher mortality rate (50%).[12,13] In young African patients who had a referral delay of more than 6 h, Gomes and colleagues[6] showed an overall 49% reduction (95% CI 19·31–67·76) in mortality and persisting neurological sequelae when prereferral treatment was followed by antimalarial treatment. Although rectal artesunate interrupts disease progression by rapidly reducing parasite density, it is not a cure for severe malaria.[6] Patients who arrive at health facilities might not need parenteral antimalarial treatment because of their favourable course of recovery after prereferral treatment (Gomes M, WHO Special Programme for Research and Training in Tropical Diseases, Geneva, Switzerland, personal communication). We conservatively assumed that patients derived no health benefit from the intervention if not followed by antimalarial treatment (ie, no deaths or DALYs averted) and that all patients who sought referral care for severe malaria after prereferral artesunate treatment would receive inpatient care. The

	Distribution	Distribution parameters
Epidemiology, prevalence, and effectiveness		
Percentage of the population younger than 5 years (%)[12]	Point estimate	17·60
Yearly incidence rate in children younger than 5 years (episodes per 1000)[2]	Triangular	Mode 1682 (min–max 1431–3849)
Proportion of malaria episodes progressing to severe malaria[13,14]	Beta	Mean 0·05 (SD 0·0083)
Proportion of severe malaria survivors having persisting neurological disability[13,14]	Beta	Mean: 0·03 (SD 0·0086)
Efficacy of prereferral artesunate treatment (%)[6]	Triangular	Mode 49 (min–max 19–68)
Case-fatality rate for severe malaria after inpatient care[13,14]	Beta	Mean 0·2 (SD 0·0415)
Case-fatality rate for untreated severe malaria[13,14]	Beta	Mean 0·5 (SD 0·041)
Average length of hospital stay after prereferral treatment (days; assumed)	Triangular	Mode 3 (min–max 1–4·8)
Diagnosis specificity based on clinical symptoms and signs of severe malaria*[6]	Beta	Mean 0·74 (SD 0·0621)
Prereferral artesunate treatment costs for malaria		
Drug cost per child treated† (estimated)	Uniform	Min–max 0·31–0·47
CHW time cost per child treated‡ (estimated)	Uniform	Min–max 0·34–0·51
CHW programme costs		
Programme set-up cost per beneficiary§ (estimated)	Uniform	Min–max 1·25–1·88
Programme recurrent cost per beneficiary¶ (estimated)	Uniform	Min–max 0·38–0·56
Inpatient care costs for malaria		
Drug cost per child treated[15]	Uniform	Min–max 9·23–12·39
Laboratory investigations per child[15]	Uniform	Min–max 17·64–79·15
Cost of hospital bed-day[15]	Point estimate	28·82

All costs are expressed in International dollars for the year 2008. CWH=community health worker. Min=minimum. Max=maximum. *The range is plus or minus 20% of the reported diagnosis specificity of 74%.[6] †With a manufacturing drug cost of $0·10–0·156 and assuming a 100% mark-up for international distribution;[16] a 25% mark-up for transport, insurance, and delivery to the point of administration;[17] and a 25% drug wastage rate.[22] ‡With a monthly wage of $95·44–142·38[18] and assuming a 5-h workday, a 7-day workweek, and 30 min care per child. §With the provider set-up costs of $11 277 reported for a pilot CHW programme providing near home malaria treatment to 8500 people living in rural villages of Nigeria,[19] the programme set-up cost is estimated at $1·57 per beneficiary. The range is plus or minus 20% of this estimated value. ¶With the provider recurrent costs of $3383 reported for a pilot CHW programme providing near home malaria treatment to 8500 people living in rural villages of Nigeria,[19] the programme recurrent cost is estimated at $0·47 per beneficiary. The range is plus or minus 20% of this estimated value.

Table 1: **Effectiveness and cost input variables used in the analysis**

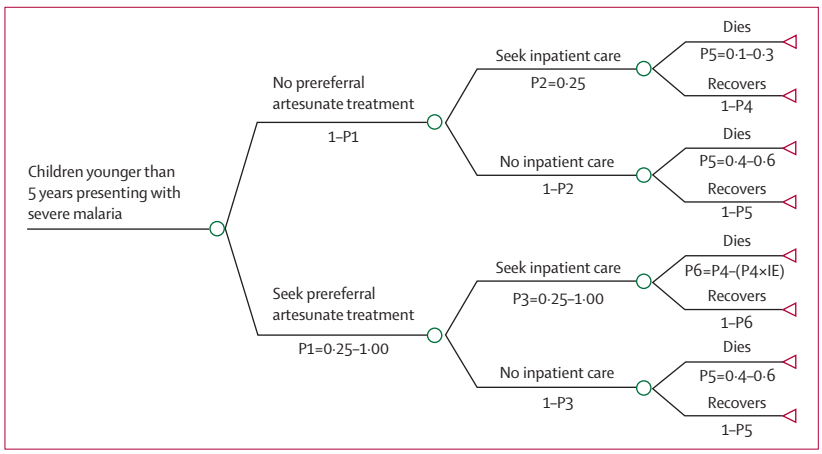

Figure: **Decision tree to assess the cost-effectiveness of prereferral artesunate treatment for management of severe childhood malaria**

P1=intervention uptake. P2=baseline referral compliance. P3=referral compliance after prereferral treatment. P4=inpatient case fatality rate for severe malaria. P5=case-fatality rate for untreated severe malaria. P6=inpatient case-fatality rate for severe malaria after prereferral artesunate treatment. IE=intervention efficacy.

average length of hospital stay for malaria patients is 4·8 days.[14] We assumed that prereferral artesunate treatment reduced the duration of severe illness and hospital stay to 3 days, averting inpatient care costs.

Presumptive treatment based on the clinical symptoms and signs of severe malaria has a diagnosis specificity of 74%[6] (95% CI 73–75) and is assumed to have perfect sensitivity. We used an average life expectancy of 49 years for children aged 0–4 years on the basis of the life tables for men and women in sub-Saharan Africa.[15] In the absence of a disability weight for severe malaria episodes, we used the disability weight for uncomplicated episodes, 0·211,[16] as a conservative estimate. The disability weight for treated neurological sequelae was 0·436.[16] DALYs were discounted at 3%, as recommended by the World Bank.[17] Age weighting was not applied, thus a year of healthy life was valued equally at all ages.

To avoid a potential fatal outcome after prereferral treatment, caregivers have to adhere to referral advice, promptly access a qualified source, and receive proper treatment. Referral compliance and promptness vary widely across communities because of geographical and socioeconomic factors.[18] In Africa, less than half of all fatal malaria illnesses are treated at health facilities.[18–20] Moreover, efficacious interventions are often less effective in real-life settings because of varying uptake by the target population. Uptake was defined as percentage of children with severe malaria who receive community-based prereferral treatment. Evidence from controlled deployment studies suggests that referral compliance is improved after prereferral treatment and caregivers are more likely to adhere to referral advice when their children are severely ill.[8] In this analysis, we assumed a referral compliance of 25% without the intervention. Against this baseline, we explored scenarios of low (25%), moderate (50%), high (75%), and full (100%) referral compliance and intervention uptake to assess the intervention cost-effectiveness.

Estimation of costs

We considered the direct costs of the intervention, which included patient-related costs and programme-related costs, over 5 years. Patient-related costs included the cost of rectal artesunate and time of community health worker. The manufacturing cost of a 100 mg rectal artesunate capsule was estimated at $0·10–0·15.[6] The warehouse cost was estimated with a mark-up rate of 100% and included costs of international distribution from the manufacturer to countries.[21] Transport, insurance, and delivery to the point of administration added an additional 25% to the cost, and we assumed a drug wastage rate of 25%.[22] The cost of time of community health worker per child was calculated with the assumption of a 5-h workday, a 7-day workweek, and a monthly salary range of $95·44–142·38, which corresponded to the amount paid to community health workers at the time of the rectal artesunate trial in Tanzania (Warsame M, WHO, Geneva, Switzerland, personal communication) and the present minimum monthly wage, respectively.[23] We assumed that every patient needed 30 min of care, and that community health workers resided within the communities.

A study[24] documented the implementation costs (recruitment and training, advocacy, treatment provision, community mobilisation and monitoring) of a pilot programme providing malaria treatment near the home through community health workers in rural Nigerian villages. On the basis of the study results, the initial cost of incorporating prereferral treatment into the existing programme, including all costs but excluding treatment provision, was estimated at $1·57 per beneficiary. The recurrent cost per beneficiary was estimated at $0·47 per year, including only community mobilisation and monitoring costs.

We took into account variable costs of inpatient care for malaria, but excluded fixed costs (buildings, equipment, supervision, and staff costs), which would not change because of the intervention. In a Kenyan costing study,[13] the cost of inpatient care per child was reported to range between $166·32 and $226·80 at primary referral hospitals, with bed occupancy rates of 120% and 80%, respectively. Costs for hospital stay per patient were calculated per day per hospital bed. Most deaths from severe malaria occurred within 24–48 h of hospital admission.[3] We assumed an average hospital stay of 2 days if the patient died, irrespective of prereferral treatment status, and we calculated foregone inpatient care costs attributable to deaths in the cohort. Lastly, we included the costs of incorrect prereferral treatment of non-malarial severe episodes due to imperfect diagnosis. The cost of prereferral treatment per child included the cost of rectal artesunate and the community-health-worker time.

	Low referral compliance (25%)	Moderate referral compliance (50%)	High referral compliance (75%)	Full referral compliance (100%)
Low intervention uptake (25%)				
Deaths averted	1 (1–1)	10 (9–11)	19 (18–21)	29 (26–31)
DALYs averted	19 (16–21)	260 (239–281)	501 (461–541)	743 (683–802)
Incremental costs	17 466 (17 023–17 908)	40 416 (38 614–42 217)	63 366 (59 834–66 898)	86 316 (81 036–91 597)
Cost per DALY averted	1173 (1050–1297)	166 (157–175)	133 (127–139)	122 (116–127)
Moderate intervention uptake (50%)				
Deaths averted	1 (1–2)	11 (10–12)	21 (20–23)	31 (29–34)
DALYs averted	37 (32–43)	297 (273–322)	557 (512–603)	817 (751–884)
Incremental costs	16 311 (15 747–16 875)	37 957 (36 126–39 788)	59 603 (56 083–63 124)	81 250 (76 011–86 488)
Cost per DALY averted	550 (489–610)	136 (129–144)	112 (107–118)	104 (99–109)
High intervention uptake (75%)				
Deaths averted	2 (2–2)	13 (12–14)	23 (22–25)	34 (31–37)
DALYs averted	56 (48–64)	335 (306–364)	614 (562–665)	892 (818–967)
Incremental costs	15 156 (14 446–15 866)	35 498 (33 570–37 427)	55 841 (52 250–59 432)	76 183 (70 888–81 478)
Cost per DALY averted	342 (302–382)	114 (107–120)	96 (91–101)	89 (85–93)
Full intervention uptake (100%) *vs* no treatment				
Deaths averted	3 (2–3)	14 (13–15)	26 (23–28)	37 (34–40)
DALYs averted	75 (64–85)	372 (338–406)	670 (611–728)	967 (884–1050)
Incremental costs	14 001 (13 133–14 870)	33 040 (30 956–35 124)	52 078 (48 338–55 818)	71 116 (65 668–76 564)
Cost per DALY averted	238 (208–268)	96 (89–102)	82 (77–87)	77 (73–81)

All costs in international dollars (95% CI) for the year 2008. DALY=disability-adjusted life-years.

Table 2: **Incremental health outcomes, costs, and cost-effectiveness of prereferral artesunate treatment for a cohort of 1000 children younger than 5 years living in a stable endemic area during 5 years**

Sensitivity analysis

To assess the uncertainty in the model and the robustness of our results, we used a Monte Carlo sampling method[25] (webappendix p 1). Because the intervention uptake and referral compliance had the greatest effect on the results, we assessed the effect of uncertainty in other variables across varying values of uptake and compliance. Input variables were varied over their full range (table 1) to produce confidence intervals.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. YT and co-authors had full access to all the data in the study. YT had final responsibility to submit for publication.

Results

Table 1 shows all variables for effectiveness and cost input and their ranges derived from the peer-reviewed literature. The figure shows the cost-effectiveness framework represented as a decision tree. Table 2 shows the incremental health outcomes attributable to the intervention compared with a low (25%) baseline level of referral compliance for 5 years. The full (100%) uptake and compliance scenario shows the maximum potential benefit of the intervention, resulting in 37 deaths (95% CI 34–40) averted in a cohort of 1000 children younger than 5 years of age.

Incremental intervention costs over the 5 years ranged between $14 001 (95% CI 13 133–14 870) and $86 316 (81 036–91 597; table 2). In the scenarios in which the intervention had no effect on baseline referral compliance, inpatient care costs driven by reduced hospital stay were averted, increasing proportionally with intervention uptake from $1194 (95% CI 1014–1373) to $4775 (4056–5493). In scenarios in which prereferral treatment improved baseline referral compliance, no such savings occurred because of increased inpatient care provided to patients (data not shown). Costs of incorrect prereferral treatment of non-malarial severe cases increased proportionally with intervention uptake, ranging between $39 (95% CI 35–43) and $156 (141–171).

See Online for webappendix

Incremental cost-effectiveness ratios were calculated for all assumed levels of intervention uptake and referral compliance. When the uptake and compliance were both low (25%), the intervention was estimated to avert 19 DALYs (95% CI 16–21) at a cost of $1173 (1050–1297) per DALY averted. Under the full (100%) uptake and compliance assumption, we estimated that the intervention could avert 967 DALYs (95% CI 884–1050) at a cost of $77 (73–81) per DALY averted. To assess the relative importance of the input parameters on our cost-effectiveness results, we estimated the partial rank correlation coefficients of the input variables. These estimates suggested that our results were mainly sensitive to effectiveness input variables, which directly affected the avertable disease burden, modulating the incremental costs (webappendix p 3–4).

Discussion

Under the scenarios in which referral compliance and intervention uptake is moderate or higher, prereferral artesunate is a cost-effective intervention for treatment of severe childhood malaria in rural African settings in which programmes for community health workers exist. The Commission on Macroeconomics and Health classified interventions as highly cost effective if the cost per DALY averted was less than the gross domestic product (GDP) per head, and as cost effective if this cost was less than one-to-three times the GDP per head. The per head GDP corresponds to each citizen's fair share of national economic output, which could be devoted to health care. With the 2008 per head GDP for the sub-Saharan African region (excluding South Africa) adjusted for purchasing power parity of $1546 as a threshold,[26] prereferral artesunate treatment was highly cost effective under all scenarios. This analysis presents a broad indication of the cost-effectiveness of the intervention based on the regional pattern of clinical malaria in high-transmission areas and the available cost data from the African region. The cost-effectiveness results should be interpreted as a range of best estimates; decision makers should contextualise intervention costs and assess intervention uptake, referral compliance, pattern of clinical malaria, and other key parameters in their own settings to arrive at more locally representative incremental cost-effectiveness ratios.

Compared with the interventions that target key childhood illnesses in sub-Saharan Africa, prereferral artesunate treatment is among the most cost effective, especially if the intervention uptake is moderate or higher. The assumption of no health benefit from prereferral treatment if not followed by antimalarial treatment sets a lower bound on the estimated incremental health outcomes; patients who did not follow referral advice might have had a favourable course of recovery and received oral antimalarial drugs outside the formal health system. The Disease Control Priorities Project reported a cost of US$169–891 per DALY averted for community-based treatment of non-severe acute respiratory infections and $606–2020 per DALY averted for interventions targeting diarrhoeal diseases through vaccination and oral rehydration therapy.[15] These interventions receive support from WHO, UNICEF, and other partners for rapid scale-up in more than 40 countries as part of the community component of the Integrated Management of Childhood Illnesses to reach the Millennium Development Goal target for child mortality.

The challenge to provide prompt, effective, and affordable antimalarial treatment remains formidable in endemic countries. Once the disease becomes severe, therapeutic options for patients are limited in rural areas, owing to poor availability and accessibility of services. A large proportion of childhood deaths could be prevented with early administration of antibiotics, antimalarial drugs, and oral dehydration treatment in the home and community through community health workers.[27] In this analysis, we assumed that prereferral treatment would be provided as part of an intervention package and that community health workers could be trained in a short time without the need for large infrastructure developments. Therefore, our cost-effectiveness results are applicable only to settings where programmes for community health workers are already in place. Furthermore, we did not include costs associated with policy change (consultation, consensus building, and policy formulation; revision and preparation of treatment guidelines; training of health workers; and publicity) for which no cost data exist. The provision of health services in the community is estimated to be less developed than referral systems in most countries, and the optimum sum of investments at these two levels are expected to differ between countries.[28] For example, the success with home-based management of malaria has been mixed with little or no effect on clinical outcomes.[29] Ethiopia is training 30 000 health extension workers every year, and Kenya, Uganda, Ghana, and South Africa are considering nationwide programmes for community health workers.[27] Substantial cost savings linked to economies of scale and scope can be achieved by spreading fixed costs in a larger population, lowering the yearly average cost per beneficiary, and providing a range of community-based care and support.

The success of prereferral treatment also depends on the caregiver; once a child is given rectal artesunate, the caregiver needs to both accept and adhere to referral advice for a successful outcome. Moreover, promptness in seeking care at both stages affects the life-saving potential of prereferral treatment. Rectal artesunate is a fast-acting drug and can interrupt disease progression to the extent that the child might seem to be recovering or get to a stage at which oral antimalarial treatment is possible.[6] This interruption of disease progression poses an important challenge to deployment; previous studies reported that provision of treatment in communities caused referral delays of 2 days or more,[30] which is especially important if severe illness is not malarial. Engagement and empowerment of communities through community health workers might positively affect health-seeking behaviour.[27] Potential favourable recovery after prereferral treatment emphasises the accessibility and and affordability of oral antimalarial drugs. Monotherapy with prereferral artesunate might contribute to the development of resistance if not followed by consolidation treatment with antimalarial drugs;[8] however, the number of patients in need would be low, and the drug has a short half-life and is delivered with referral advice.

Improvement in management of sick children at the household and community level is urgent. This life-saving, cost-effective intervention has the potential to significantly improve management of severe childhood malaria. Prereferral rectal artesunate merits serious consideration by health policy makers as part of an intervention package

to facilitate progress towards internationally set malaria and child survival targets.[31] Nevertheless, the success of interventions in the community ultimately depends on whether formal health systems can provide front-line health workers with drugs and other necessary health commodities, regular monitoring and supervision, and linkages to referral systems.

Contributors

YT and JGB initiated the study, and YT coordinated the research and did the analysis with EK. All authors contributed to the study design and interpretation of the analysis results. SD and RP reviewed the literature. YT wrote the Article, and EK, RL, and JGB reviewed and commented on the Article. All authors read and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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