Health system readiness and the implementation of rectal artesunate for severe malaria in sub-Saharan Africa: an analysis of real-world costs and constraints

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Summary

Background Rectal artesunate, an efficacious pre-referral treatment for severe malaria in children, was deployed at scale in Uganda, Nigeria, and DR Congo. In addition to distributing rectal artesunate, implementation required additional investments in crucial but neglected components in the care for severe malaria. We examined the real-world costs and constraints to rectal artesunate implementation.

Methods We collected primary data on baseline health system constraints and subsequent rectal artesunate implementation expenditures. We calculated the equivalent annual cost of rectal artesunate implementation per child younger than 5 years at risk of severe malaria, from a health system perspective, separating neglected routine health system components from incremental costs of rectal artesunate introduction.

Findings The largest baseline constraints were irregular health worker supervisions, inadequate referral facility worker training, and inadequate malaria commodity supplies. Health worker training and behaviour change campaigns were the largest startup costs, while supervision and supply chain management accounted for most annual routine costs. The equivalent annual costs of preparing the health system for managing severe malaria with rectal artesunate were US$2·63, $2·20, and $4·19 per child at risk and $322, $219, and $464 per child treated in Uganda, Nigeria, and DR Congo, respectively. Strengthening the neglected, routine health system components accounted for the majority of these costs at 71·5%, 65·4%, and 76·4% of per-child costs, respectively. Incremental rectal artesunate costs accounted for the minority remainder.

Interpretation Although rectal artesunate has been touted as a cost-effective pre-referral treatment for severe malaria in children, its real-world potential is limited by weak and under-financed health system components. Scaling up rectal artesunate or other interventions relying on community health-care providers only makes sense alongside additional, essential health system investments sustained over the long term.

Funding Unitaid.

Introduction

Of the estimated 400 000 annual malaria deaths, the majority are in children younger than 5 years living in sub-Saharan Africa.[1] Without prompt treatment with parenteral artesunate followed by oral artemisinin-based combination therapy, an episode of severe malaria in a child can rapidly lead to death.[2] Such comprehensive treatment presumes good access to higher level health-care facilities. Poor children living in remote, rural settings are challenged in accessing treatment and more likely to die from severe malaria.[3,4]

Community Access to Rectal Artesunate for Malaria (CARAMAL) was an observational study accompanying the roll-out of rectal artesunate, an efficacious pre-referral treatment for severe malaria, in highly endemic and difficult to reach rural settings in Uganda, Nigeria, and the Democratic Republic of the Congo targeted to children younger than 5 years, under real-world conditions. Rectal artesunate, a suppository, rapidly reduces parasite density and provides a child with severe malaria time to reach a referral health facility that can treat the illness appropriately. Before CARAMAL, one large randomised controlled trial found that rectal artesunate reduced severe malaria case fatality by 26% (relative risk 0·74; 95% CI 0·59–0·93).[5]

Rectal artesunate was delivered in rural communities via routine case management: community health workers (CHWs) trained on integrated community case management (iCCM),[6] and peripheral health-care facilities with no inpatient capacity. Implementation relied on appropriate training of health workers, supervision of health workers, and a regular supply of drugs.[7–9] Since the successful treatment of severe malaria relies on a cascade of health-care services from the

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For the French translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

Pre-referral rectal artesunate has been shown to effectively reduce severe malaria case fatality in children, in a large, multicentre, randomised controlled trial. However, the successful implementation of a systemic intervention such as rectal artesunate in rural communities relies on functional routine health system components to be effective. Neglected routine components are not typically assessed as part of randomised controlled trials, which are implemented under highly controlled conditions that often deviate from routine service delivery. As a result, the true costs of programme implementation, for which no previous data are available on a larger scale, could plausibly be overestimated or, more likely, underestimated. We used a broad search on PubMed from database inception to Oct 24, 2022, with the terms "rectal artesunate" AND (cost OR costs). We found very few studies overall (n=13). No studies collected primary expenditures on implementation costs, health system constraints, and health system strengthening or financing needs.

Added value of this study

We collected primary data on the cost of rectal artesunate implementation in three malaria-endemic settings in sub-Saharan Africa. Our aim was to quantify the real-world costs of preparing the health system for improved community-based case management of severe malaria. We quantified the costs of strengthening the routine, neglected health system components of the health system, as well as the incremental cost of introducing rectal artesunate, at scale. This study found that routine health system strengthening accounted for about 70% of the costs per child receiving rectal artesunate in Uganda, Nigeria, and DR Congo. The incremental cost of introducing rectal artesunate accounted for the minority, at 30% of the costs per child. The costs are high and reflect low operational capacity of the underlying health system, with considerable financing gaps, impeding the readiness of the health system to manage severe malaria. The study addresses a crucial gap in the evidence on how much funding is required to finance these essential functions of the health system, before other community-based interventions can be implemented successfully.

Implications of all the available evidence

The health system constraints and the large gaps in financing for health system strengthening should be a strong cause of concern for the implementation of rectal artesunate at scale, but also for other interventions being delivered via community-based health-care systems. The evidence highlights that strong political will is essential to align and sustain funding streams over the long run. Otherwise, it seems unlikely that health system constraints, access to treatment, and reductions in malaria mortality will resolve. The evidence also underlines the importance of incorporating health system constraints into costing and cost-effectiveness models, to avoid the risk of underestimating true financing needs.

community until post-referral treatment completion, the CARAMAL intervention funded both the introduction of rectal artesunate into community-level structures and some operational strengthening of existing routine systems along the continuum of care. This health system strengthening (HSS) included funding supervisions, some key supply chain inputs, and the training of referral facility workers on parenteral artesunate.

Although several studies have evaluated the costs of delivering services via CHWs[7,10–12] for a range of diseases, this is the first study, to our knowledge, that empirically assessed the real-world costs of introducing rectal artesunate at community level, on a large scale, including strengthening neglected routine health system components. Such real-world costs are not typically collected as part of randomised controlled trials, which are usually implemented under highly controlled conditions that often deviate from routine service delivery, and could plausibly underestimate true costs. In addition, we estimated the incremental cost of introducing rectal artesunate alone into an established system without additional HSS needs. In doing so, we documented important health system constraints, strategies implemented to overcome these, and their costs. The present analyses aim to inform operational guidance and financial planning in the replication or scale-up[13] of rectal artesunate as pre-referral treatment for severe malaria. The findings also provide economists and modellers with real-world parameter costs towards economic evaluations of comprehensive interventions for severe malaria.

See Online for appendix 2

Methods

Implementation settings

The three settings differed markedly in the incidence of severe febrile episodes and the distribution of children per community-based provider and referral health facility (table 1). The three settings were remote rural areas with high malaria endemicity and difficult access to higher level care, including parenteral malaria treatment (see appendix 2 p 26 for maps), representative of areas of high malaria morbidity and mortality in sub-Saharan Africa. CHWs were unpaid volunteers and trained on iCCM—ie, provision of treatment for malaria, pneumonia, and diarrhoea. Uganda had the highest coverage of community-based providers (CHWs and peripheral health-care facilities): national policy was that two CHWs be located in each village. In DR Congo and Nigeria, CHWs were strategically located in locations where other formal public health providers were

considered hard to reach. An overview of the whole CARAMAL project can be found elsewhere.[14] Briefly, the project aimed to test whether severe malaria fatality rates could be reduced by delivering rectal artesunate through established routine health systems, using a before-and-after plausibility design. The present manuscript deals with the costs of the programme.

The implementation of the CARAMAL project and the introduction of rectal artesunate took place between the fourth quarter of 2018 (Q4 2018) and Q4 2020 in Uganda, Nigeria, and DR Congo. The intervention was implemented by local ministries of health supported by UNICEF (which we refer to as "implementers" throughout).

The CARAMAL study protocol was approved by the Research Ethics Review Committee of WHO (ERC.0003008), the Ethics Committee of the University of Kinshasa School of Public Health (012/2018), the Health Research Ethics Committee of the Adamawa State Ministry of Health (S/MoH/1131/I), the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007-05/05/2018), the Higher Degrees, Research and Ethics Committee of the Makerere University School of Public Health (548), the Uganda National Council for Science and Technology (SS 4534), and the Scientific and Ethical Review Committee of the Clinton Health Access Initiative (112; date Nov 21, 2017). Parents or guardians of children involved in the study provided consent for their participation. The study was registered on ClinicalTrials.gov (NCT03568344).

Scope of the evaluation

Implementation activities were costed under a health system perspective and covered costs of services incurred by the Ministry of Health (MoH) to prepare the system to manage severe malaria with rectal artesunate. A community-based system prepared to manage sick children with suspected severe malaria included training health workers, an operational supervision system, adequate quantities of drug stock ordered and distributed, and sufficient funding for behaviour change campaigns among other monitoring and evaluation activities. The perspective therefore excludes any incremental patient-level treatment costs of severe malaria and household costs (eg, additional or reduced drug consumption due to behavioural changes in treatment-seeking patterns; transport) but includes the country's gross procurement of rectal artesunate and injectable artesunate, based on MoH stock orders (and not on actual drug units consumed), since possessing stock is a necessary condition for reaching readiness.

Full implementation costs are composed of two parts and labelled as either startup costs or annual recurring costs. Startup activities were one-time activities designed to launch the project. Recurring activities were routine activities underlying the functioning of the existing health system (eg, iCCM) that recurred annually. A year's worth of recurring activities was calculated from total expenditure per activity in the second year, per unit of time (quarters or number of months covered) before being converted to an annual cost.

	Uganda	Nigeria	DR Congo
Implementation areas	Apac, Kole, Kwania, and Oyam districts	Adamawa State—all local government areas in settings with active iCCM sites	Kenge, Ipamu, and Kingandu health zones
Number of children (2019)	259 681	188 897	149 671
Number of children per community-based provider	46	284	690
Number of children per referral health facility	11 816	55 022	7045
Rate of severe febrile illness per 1000 children	14·9	5·3	16·9
Community parasite rates in children	53–78%	38–61%	40–57%

Refers to children younger than 5 years in all cases. Numbers are drawn from CARAMAL patient surveillance system. Community-based providers include both community health workers and peripheral health-care facility workers. For details see Lengeler et al (2022).[14] Note that implementation was carried out in a larger number of areas than those highlighted in Lengeler et al (2022),[14] so the number of implementation areas and the number of children is larger in the present table. iCCM=integrated community case management.

Table 1: **Number of children younger than 5 years per health-care provider and rate of severe febrile illness, by CARAMAL country**

We present these as economic costs expressed in real 2019 US dollars (for conversion methods see appendix 2 p 28). Economic costs included level of effort costed via per diems, time spent travelling, and vehicle use, as well as donated commodities such as rectal artesunate and injectable artesunate adjusted to include cost, insurance, and freight,[15] using Global Fund prices.[16] Research activities were excluded. Costs due to COVID-19 (eg, personal protective equipment) were also excluded since they were purely incremental and did not change malaria-related costs.

In addition, we separated full implementation costs into HSS costs and incremental rectal artesunate-specific costs. HSS costs refer to costs of routine activities of the health system related to severe malaria case management, which required improvement and funding support to meet the MoH guidelines (eg, supervisions not occurring at recommended frequency, health workers at each level not receiving systematic refresher training, referral health facilities experiencing injectable artesunate stockouts, etc). We refer to these costs as system strengthening, rather than merely routine, to highlight that they either fully took over the funding of routine activities or complemented funding of essential, but often neglected, activities that national or donor financing was hitherto insufficient to cover. In contrast, rectal artesunate-specific costs were the incremental costs of introducing rectal artesunate into a health system with sufficient financing at baseline to operate in line with MoH guidelines. These rectal artesunate-specific costs included only activities that were additional to the aforementioned routine components of the health system. Rectal artesunate-specific costs included the proportion of

training time judged specific to rectal artesunate; the procurement and distribution of rectal artesunate; the cost proportion of the initial behavioural change campaign, supervision, or monitoring and evaluation relevant to rectal artesunate and severe malaria; and any novel elements that supported the introduction and maintenance of rectal artesunate that would not have been introduced otherwise. Expert opinion (UNICEF staff, including authors MM, FK, SL, MS, OO, EE, and VBu) decided these rectal artesunate-specific proportions. We calculated the rectal artesunate-specific costs for startup activities and annually recurring activities separately, and present them as shares of full implementation startup and recurring costs.

Finally, we calculated two separate per-child costs: (1) the equivalent annual cost per child younger than 5 years at risk of severe malaria by dividing total equivalent annual cost by the total number of children younger than 5 years in the implementation areas (using WorldPop data); and (2) the equivalent annual cost per child younger than 5 years treated with rectal artesunate. We obtained the equivalent annual cost by annualising startup costs over 10 years, a time horizon reflecting longevity of a community-based programme[10] with recurring components (eg, biannual refresher training) aimed at maintaining the programme over time (for formula see appendix 2 p 29), before adding the annually recurring cost. We used a discount rate of 3%.[17]

For **WorldPop** see https://www.worldpop.org

As a secondary outcome, we estimated a proxy for the affordability of integrating rectal artesunate and HSS by comparing the public health expenditure per capita (World Bank[18]) with the recorded (non-discounted, non-annualised) implementation expenditures per capita. To obtain the latter we divided implementation startup costs and annual HSS costs by the total population in the study area. We then computed the ratio of implementation expenditures per capita to public health expenditures per capita.

Implementation components

We summarise the baseline country-specific health system constraints before the intervention and the main implementation components that were funded by CARAMAL in appendix 2 (pp 3–5). We also present the aims of each component and whether they solve a supply-side or demand-side constraint.[19,20] A detailed account of baseline and intervention components, both recurring and startup, can be found in appendix 2 (pp 6–13). In addition, we provide a narrative account of the intervention components in appendix 2 (pp 30–31). Information on the baseline state of the health system was obtained from a survey of a stratified random sample of health-care providers conducted in Q4 2018 and rapid readiness assessment of all referral health facilities in the CARAMAL study areas in Q4 2017.[14] Information on baseline supervisory and behaviour change campaign activity, as well as funding gaps, was obtained from an interview with each local UNICEF implementation team throughout the implementation period.

The main implementation components included training of CHWs, peripheral health-care facility workers, and referral health facility workers, strengthening supervisions, procurement and supply chains, behaviour change campaigns, monitoring and evaluation, and other supportive interventions. The distribution of rectal artesunate to communities was streamlined in a sustainable manner without creating a parallel supply chain for the project: CHWs were meant to restock rectal artesunate during supervisory visits. Under such circumstances, the absence of supervision implied rectal artesunate stockouts. CARAMAL therefore covered the full costs of routine supervision (per diems and travel expenses for supervisors or CHWs). To minimise commodity stockouts in the community, implementers in Uganda increased supervisory frequency from biannually to quarterly. In addition, parish coordinators were funded to restock rectal artesunate on a monthly basis since quarterly supervisions were not frequent enough to meet rectal artesunate demand (these were costed as an additional supply chain activity in Uganda). While systematic supervisions were a challenge in all countries, increasing their frequency was not necessary in DR Congo and Nigeria, where they were supposed to occur on a monthly basis.

Data

Expenditure data provided by UNICEF were annual, between Q4 2018 and Q4 2020, and separate for Uganda, Nigeria, and DR Congo. UNICEF determined the format in which expenditure data would be transferred to the research team in accordance with their institutional obligations. Total expenditures were divided into implementation activities, and further disaggregated into sub-activities for which a total expenditure was given by year. Additional items were added by the research team and completed via interviews with UNICEF staff aimed at obtaining in-depth understanding of activities and their purpose (sample expenditure table in appendix 2 p 14). Where co-funding from external donors was reported in annual reports or interviews, these were used to obtain costs. Specifically, these included donations of injectable artesunate, rectal artesunate, or co-funding of iCCM monitoring and evaluation systems. Relevant quantities such as number of rectal artesunate capsules procured or health workers trained were obtained from implementer interviews or CARAMAL annual reports. Analyses were done in R (version 4.2.2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Full startup costs in real 2019 US dollars were $613 304, $997 338, and $760 581 in Uganda, Nigeria, and DR Congo, respectively. Annually recurring costs were $612 033, $301 554, and $540 601 in Uganda, Nigeria, and DR Congo. We present programme component shares of full implementation costs in figure 1A, separately for startup and annual HSS costs (see appendix 2 pp 6–13 for activity lists). Startup investments in health worker training accounted for large shares of full startup costs in the three countries. Training costs accounted for a greater share of startup costs in Nigeria relative to Uganda and DR Congo (61·2% *vs* 32·6% and 17·8% of startup costs, respectively). The difference was due to transport and per diems paid to federal MoH officials (24% of total training costs) and the separate training programmes for CHWs and peripheral health-care facility workers in Nigeria, resulting in two sets of fixed costs (appendix 2 pp 8–10). We present training costs per CHW and peripheral health-care facility worker in appendix 2 (p 15). In addition to training, large investments were made in behaviour change campaigns. Behaviour change campaign activities accounted for 39·6% of startup costs in Uganda, 22·1% in Nigeria, and 27·1% in DR Congo. Investments in other supportive startup activities were made in DR Congo (19·3% of startup costs), mainly towards strengthening the quality of care for severe febrile illness at referral health facilities.

Supervisions were the largest component of annual HSS costs. Recurring supervision costs amounted to 36·0% of annual recurring costs in Uganda, 37·9% in Nigeria, and 25·1% in DR Congo (figure 1A). We provide annual supervision unit costs per CHW for Uganda and Nigeria in appendix 2 (p 15). Annual supply chain costs were 30·0%, 17·7%, and 15·8% of annual recurring costs in Uganda, Nigeria, and DR Congo, respectively. Apart from the procurement of rectal artesunate in each country, sub-components varied. Injectable artesunate was donated or procured and therefore costed annually. In Uganda, annual costs also included the monthly restocking of CHWs with rectal artesunate by parish coordinators (appendix 2 pp 6–13). We present monthly unit costs per CHW for these supportive interventions in appendix 2 (p 16). The large majority of costs went towards community-level and peripheral-level rather than referral-level activities (appendix 2 p 27). Figure 1B presents the share of full startup and annual recurring costs (ie, the share of costs presented in figure 1A) that are rectal artesunate-specific. Rectal artesunate-specific startup components in a functional and well funded health system would cost 61·7%, 93·6%, and 72·2% of actual startup costs in Uganda, Nigeria, and DR Congo, respectively (figure 1B). Large initial health worker training costs (see appendix 2 pp 18–19 for sample schedule) and investments in behaviour change campaigns accounted for the majority of the cost of setting up rectal artesunate within the community-based health systems. In DR Congo, supplementary and time-limited MoH supervisions were conducted for 3 months after the completion of training.

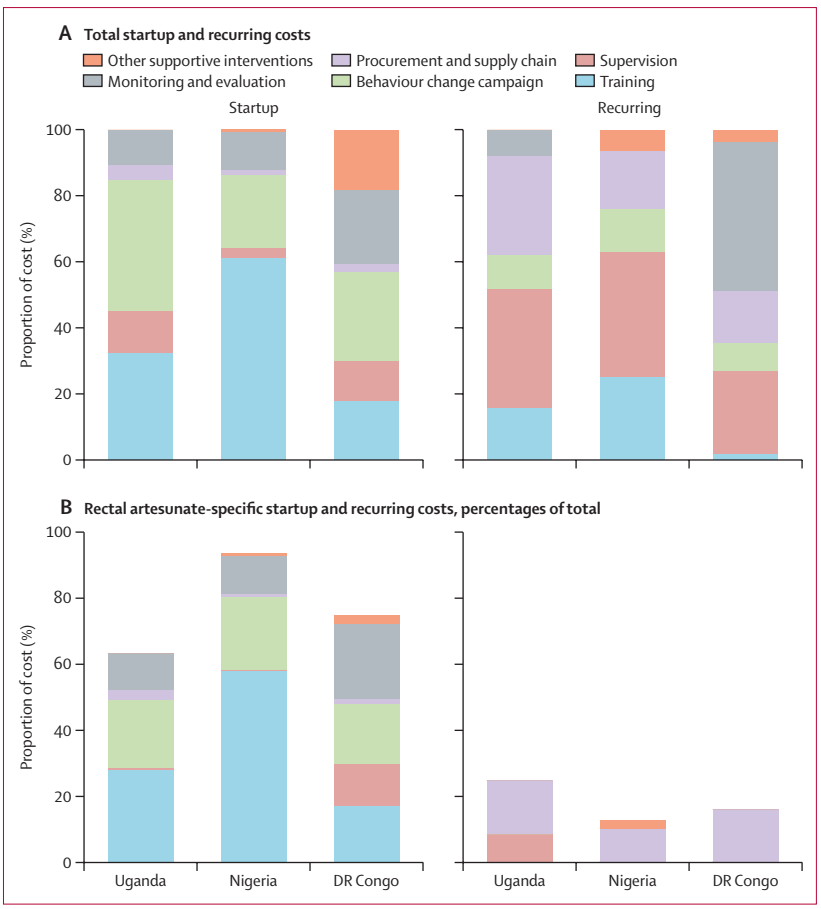

Figure 1: **Total and incremental rectal artesunate-specific startup and recurring costs, by programme component**

(A) Proportion of total intervention startup and recurring costs that each programme component accounted for. (B) Rectal artesunate-specific proportion of the total presented in panel A. The proportions are calculated from total costs in real 2019 US dollars. Total startup costs were $613 304, $997 338, and $760 581 in Uganda, Nigeria, and DR Congo, respectively. Annually recurring costs were $612 033, $301 554, and $540 601 in Uganda, Nigeria, and DR Congo.

The required investment to maintain rectal artesunate after startup in a system that already funds its community-based programmes sustainably can be seen in figure 1B, right. Rectal artesunate-specific annual costs are a fraction of total annual recurring costs at 24·7%, 13·0%, and 16·0% in Uganda, Nigeria, and DR Congo. As expected, the bulk of these activity costs are the procurement and the distribution of rectal artesunate to CHWs and peripheral health-care facility workers. While these are similar shares in Nigeria and DR Congo, the share is higher in Uganda. As explained previously (Methods and appendix 2 pp 6–7), implementers rolled out specific interventions to ensure rectal artesunate was systematically distributed to the large number of CHWs in Uganda (nearly twice the number of CHWs in Nigeria and more than 100 times that in DR Congo). The

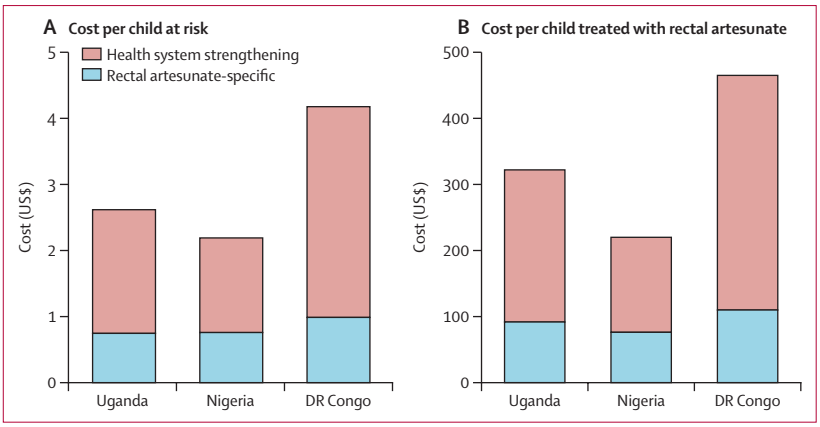

Figure 2: **Health system strengthening versus rectal artesunate-specific equivalent annual cost of implementation, per child at risk of severe malaria and per child treated with rectal artesunate**
Refers to children younger than 5 years in all cases. Costs are calculated as equivalent annual costs and in 2019 real US dollars. Startup costs were annualised over 10 years. The denominator in panel A is the total number of children in implementation areas, or otherwise all children at risk of severe malaria. The number of children covered by the implementation in Nigeria was calculated as the total number of children in Adamawa State multiplied by the proportion of settlements in Adamawa covered by the integrated community case management programme (ie, areas where the project was rolled out; 24·7%). The denominator in panel B was based on the total number of children recruited at the study sites either from a community health worker or a peripheral health-care facility (where, according to guidelines, a child with suspected severe malaria should be given rectal artesunate and referred; this assumes that once health system strengthening is sufficiently funded over the 10 year annualisation period, rectal artesunate is stocked regularly and available). Since rectal artesunate was implemented in additional districts or local government areas in Uganda and Nigeria, compared with the areas where patients were enrolled, the number treated of children was scaled up proportionally. For the number of children treated with rectal artesunate see appendix 2 p 25 and Lengeler et al (2022).[14]

complementary proportions (75·3% in Uganda, 87·0% in Nigeria, and 84·0% in DR Congo) represent the very large annually recurring HSS costs, necessary to maintain a functional community-based health system, regardless of rectal artesunate introduction.

We now turn to the economic costs per child younger than 5 years. The equivalent annual costs per child at risk of severe malaria were $2·63 in Uganda, $2·20 in Nigeria, and $4·19 in DR Congo (figure 2A). The costs for annual HSS made up the bulk of annual costs in all three project countries at $1·88, $1·44, and $3·20 in Uganda, Nigeria, and DR Congo, respectively, with rectal artesunate-specific costs accounting for a minority at $0·75 in Uganda, $0·76 in Nigeria, and $0·99 in DR Congo.

The equivalent annual costs per child younger than 5 years treated with rectal artesunate were $322 in Uganda, $219 in Nigeria, and $464 in DR Congo (figure 2B). HSS costs per child were $230, $143, and $354 in Uganda, Nigeria, and DR Congo, while rectal artesunate-specific costs were $92, $76, and $110, respectively. We present absolute variation in startup, annually recurring, and total costs per child at risk and per child treated in table 2 (gross total costs and per-child costs by programme component are shown in appendix 2 pp 20–21; sensitivity analysis is presented in appendix 2 pp 22–23). Costs per child younger than 5 years are substantially higher in DR Congo than in Uganda or Nigeria due to the large financing requirements for monitoring and evaluation.

In proportions, HSS costs per child (regardless of which per-child cost we consider) accounted for 71·5% (Uganda), 65·4% (Nigeria), and 76·4% (DR Congo) of total annual implementation costs, and rectal artesunate-specific costs per child younger than 5 years accounted for the minority at 28·5% (Uganda), 34·6% (Nigeria), and 23·6% (DR Congo) of the full cost per child.

Expenditures (financial non-annualised, non-discounted costs) during the startup year (startup plus 1 year of HSS) amounted to 2·2%, 0·4%, and 8·2% of the public health expenditure per capita in Uganda, Nigeria, and DR Congo. For each year after that, HSS expenditures amounted to 1·1%, 0·1%, and 4·1% of public health expenditures per capita. The substantially lower affordability in DR Congo is driven by a considerably lower per-capita health expenditure ($18·52 per capita) compared with Uganda ($43·14) and Nigeria ($83·75).

Discussion

CARAMAL introduced and monitored rectal artesunate in three distinct sub-Saharan African countries with high malaria burden, via community-level health-care providers. Implementation leveraged pre-existing community-level health infrastructure to deliver rectal artesunate in remote settings where access to health care was poor. It further strengthened core system components in the management of severe malaria. Training, supervision, the supply chain, behaviour change campaigns, monitoring and evaluation, and context-specific additional interventions were strengthened operationally and financially.

Using primary expenditure data and applying a health system perspective, we quantified the startup and annually recurring costs required to prepare community health systems for the effective management of suspected severe malaria cases in children younger than 5 years. The equivalent annual costs per child younger than 5 years at risk of severe malaria were $2·63 in Uganda, $2·20 in Nigeria, and $4·19 in DR Congo, while the costs per child treated with rectal artesunate were $322, $219, and $464, respectively. We also decomposed these full costs into the incremental cost of introducing rectal artesunate into the system, net of routine components, versus the HSS cost. The HSS components accounted for the largest share at 71·5% (Uganda), 65·4% (Nigeria), and 76·4% (DR Congo), with rectal artesunate-specific costs accounting for the minority remainder. Obviously, it would be considerably less costly to introduce rectal artesunate into settings where iCCM were already adequately financed and supply chains functional.

These costs are high and reflect low operational capacity and routine financing gaps, impeding the readiness of the health system to manage severe malaria from community to tertiary care level. Moreover, the health system constraints and the vast gaps in annual HSS financing should also be strong causes of concern

for other, new interventions that aim to be delivered via community-based health-care systems (eg, vaccines). Without ensuring adequate funding and strengthened operational capacity, the risk of failure remains high. Several other studies have encouraged the integration of health system constraints into costing as a crucial step towards realistic budgeting and cost-effectiveness analyses, across a range of diseases.[19–23]

Due to CARAMAL's focus on severe disease and the health system constraints at different levels of the system, comparing our estimates with costs of other malaria interventions might be misleading. A review of the costs of CHW programmes in low-income and middle-income countries found only seven studies reporting these on malaria, with large heterogeneity in methods and scope.[7] Among these, no studies focused on severe malaria exclusively. No studies to our knowledge included the cost of training and supervising community-based providers, which included peripheral health-care facilities, beyond merely CHWs, or the cost of preparing referral-level facilities with training and commodity provision for treating severe malaria. Additionally, while we adopted a health system perspective here, other studies included patient-level costs, with large estimated indirect costs. Although these societal perspectives are useful, they are beyond the present study's scope. In spite of these differences, our estimate of the CHW unit cost of training, a more commonly reported cost in other studies, lay within the broader range of other estimates in sub-Saharan Africa.[10] Finally, it is important to stress that the investment made to prepare the health system for the management of severe malaria would also benefit the treatment of other common diseases covered by iCCM.[24] For instance, regular training on managing drug stocks and submitting monthly drug reports as well as systematic supervisions of health workers are factors associated with the availability of drugs, such as amoxicillin to treat pneumonia and zinc and oral rehydration salts against diarrhoea.[25] Subsequent cost-effectiveness analyses should include such benefits when trading them off against the large HSS costs.

While the above investments are necessary to prepare communities to fight against severe malaria, they are probably insufficient to truly overcome access barriers and save the lives of those in the poorest and most remote locations. CARAMAL did not identify a beneficial effect of rectal artesunate on child survival.[26] Sick children must complete referral, which was often not the case,[27] and post-referral treatment with artemisinin-based combination therapy must be guaranteed, which was also often not the case.[28] Only then could rectal artesunate realise its full potential and more deaths be averted. Until then, rectal artesunate is unlikely to be cost-effective, as has previously been claimed under controlled conditions.[29]

Finally, affordability of the intervention was substantially more favourable in Uganda and Nigeria than in DR Congo, where public health expenditures were the smallest. The startup year amounted to 2·0%, 0·4%, and 8·2% of the public health expenditure per capita in Uganda, Nigeria, and DR Congo, and 0·9%, 0·1%, and 4·1% for every subsequent year after that. The DR Congo numbers are concerning considering that donor-driven contributions in DR Congo have dropped from 43% to 35% of total public health expenditures per capita between 2016 and 2018 at a time when total health expenditures per capita in DR Congo have decreased by $2.[18] More broadly, it remains a stark reality that many iCCM systems in sub-Saharan Africa are largely dependent on donor funding.[30] Our study confirms that partial financing, often resulting from non-harmonised funding schemes,[31] cannot sustain complex community health systems. Unless donor funding streams are aligned, harmonised, and sustained over the long run, it seems unlikely that health system constraints, access to treatment, and reductions in malaria mortality will resolve.

We acknowledge several limitations to the paper. Firstly, reported costs are not purely incremental. In theory, some included activity costs, such as supervisions, should already have been covered by the health system but, in practice, were often not carried out before the intervention. It was, however, not possible to ascertain the exact

	Equivalent annual cost per child at risk, US$			Equivalent annual cost per child treated, US$		
	Startup	Recurring	Total	Startup	Recurring	Total
Uganda						
Training	0·09	0·37	0·46	11	46	56
Supervision	0·03	0·85	0·88	4	104	108
Behavioural change campaign	0·11	0·24	0·35	13	30	43
Procurement and supply chain	0·01	0·71	0·72	2	86	88
Monitoring and evaluation	0·03	0·18	0·21	3	23	26
Other supportive interventions	0·00	0·00	0·00	0	0	0
Total	0·27	2·36	2·63	33	288	321
Nigeria						
Training	0·37	0·40	0·77	37	40	77
Supervision	0·02	0·61	0·62	2	60	62
Behavioural change campaign	0·13	0·21	0·34	13	21	34
Procurement and supply chain	0·01	0·28	0·29	1	28	29
Monitoring and evaluation	0·07	0·00	0·07	7	0	7
Other supportive interventions	0·00	0·10	0·10	0	10	10
Total	0·60	1·60	2·20	60	159	219
DR Congo						
Training	0·10	0·06	0·17	11	7	18
Supervision	0·07	0·91	0·98	8	100	108
Behavioural change campaign	0·16	0·31	0·47	17	35	52
Procurement and supply chain	0·01	0·57	0·59	1	63	65
Monitoring and evaluation	0·13	1·62	1·76	15	180	195
Other supportive interventions	0·10	0·13	0·24	12	15	26
Total	0·58	3·61	4·19	64	400	464

In some cases the individual costs of each programme component do not sum exactly to the total due to rounding.

Table 2: **Equivalent annual costs per child younger than 5 years at risk and treated**

proportion of failed supervisions. In such cases, CARAMAL financed the full activity instead of just the incremental proportion. This was particularly important for two reasons: (1) the lack of funding for supervision appears to be a persistent issue in iCCM and has been reported in other settings in sub-Saharan Africa;[32–34] and (2) overcoming constraints in supervisory activity operationally and financially also meant ensuring that rectal artesunate reached communities, since supervisors often restocked CHWs directly. Second, while treatment level costs are beyond the scope of the analysis, rectal artesunate roll-out might have knock-on effects and unintended consequences along the patient's continuum of care. Any changes in patient behaviour (eg, reduced or increased referral completion) or health facility or drug utilisation (eg, fewer days of hospitalisation) could additionally increase or reduce costs. A substantial proportion of these incremental costs (or cost savings) would likely be out-of-pocket patient costs and therefore require a broader, societal perspective to be accurately assessed. Third, although we have conducted sensitivity analysis, the level of aggregation of our data did not allow for measuring within-setting variation in costs. Finally, while rectal artesunate-specific costs seem to be quite similar across settings, the bulk of the total costs are driven by setting-specific health system constraints. A number of these are shared across settings (eg, lack of funding for supervisions, stockouts, etc); others, however, are not. Therefore, caution should be used when generalising these costs to other settings that might differ in the constraints they face, to avoid overestimating or, more likely, underestimating true costs.

Contributors

MJL, CB, and CL conceived the study. MJL designed the methodology and led the formal analysis and the data collection process. GNV, RS, and VBa contributed to data collection, data curation, and analysis. MM, FK, OO, EE, SL, MS, and VBu provided raw expenditure data. MWH, AS, GD, TTL, NCB, AT, EO, JO, PA, CL, CB, and MJL provided other data. VBu, MM, FK, OO, EE, SL, MS, MJL, RS, GNV, and VBa accessed and verified the expenditure data. NC, VBu, HGN, TV, AT, EO, and PA provided project and coordination support. MJL wrote the first version of the manuscript. KG, CL, and CB contributed to reviewing and editing the first draft. All authors contributed to reviewing and editing the manuscript. All authors approved the final draft of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

All authors had financial support from Unitaid for the submitted work.

Data sharing

The expenditure data cannot be made publicly available; UNICEF shared these data confidentially with the consortium's research partners, for the purposes of the study and according to contracts.

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