Vaccine 41 (2023) 1496–1502

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost of introducing and delivering RTS,S/AS01 malaria vaccine within the malaria vaccine implementation program

Ranju Baral [a,*], Ann Levin [b], Chris Odero [c], Clint Pecenka [a], John Tanko Bawa [d], Kwadwo Odei Antwi-Agyei [d], Kwame Amponsa-Achaino [e], Mike Nenani Chisema [f], Rose Eddah Jalango [g], Rouden Mkisi [h], Scott Gordon [a], Winthrop Morgan [b], Farzana Muhib [i]

[a] Center for Vaccine Innovation and Access, PATH, Seattle, USA
[b] Levin and Morgan LLC, Maryland, USA
[c] Center for Vaccine Innovation and Access, PATH, Nairobi, Kenya
[d] Center for Vaccine Innovation and Access, PATH, Accra, Ghana
[e] Expanded Program on Immunization, Ministry of Health, Accra, Ghana
[f] Expanded Program on Immunization, Ministry of Health, Lilongwe, Malawi
[g] Expanded Program on Immunization, Ministry of Health, Nairobi, Kenya
[h] Center for Vaccine Innovation and Access, PATH, Lilongwe, Malawi
[i] Center for Vaccine Innovation and Access, PATH, WA DC, USA

ARTICLE INFO

Article history:
Received 8 November 2022
Received in revised form 11 January 2023
Accepted 17 January 2023
Available online 27 January 2023

Keywords:
Cost
Cost of delivery
Cost of introduction
Malaria vaccine
Financial cost
Economic cost

ABSTRACT

Background: The World Health Organization (WHO) recommended widespread use of the RTS,S/AS01 (RTS,S) malaria vaccine among children residing in regions of moderate to high malaria transmission. This recommendation is informed by RTS,S evidence, including findings from the pilot rollout of the vaccine in Ghana, Kenya, and Malawi. This study estimates the incremental costs of introducing and delivering the malaria vaccine within routine immunization programs in the context of malaria vaccine pilot introduction, to help inform decision-making.

Methods: An activity-based, retrospective costing was conducted from the governments' perspective. Vaccine introduction and delivery costs supported by the donors during the pilot introduction were attributed as costs to the governments under routine implementation. Detailed resource use data were extracted from the pilot program expenditure and activity reports for 2019–2021. Primary data from representative health facilities were collected to inform recurrent operational and service delivery costs. Costs were categorized as introduction or recurrent costs. Both financial and economic costs were estimated and reported in 2020 USD. The cost of donated vaccine doses was evaluated at $2, $5 and $10 per dose and included in the economic cost estimates. Financial costs include the procurement add on costs for the donated vaccines and immunization supplies, along with other direct expenses.

Findings: At a vaccine price of $5 per dose, the incremental cost per dose administered across countries ranges from $2.30 to $3.01 (financial), and $8.28 to $10.29 (economic). The non-vaccine cost of delivery ranges between $1.04 and $2.46 (financial) and $1.52 and $4.62 (economic), by country. Considering only recurrent costs, the non-vaccine cost of delivery per dose ranges between $0.29 and $0.89 (financial) and $0.59 and $2.29 (economic), by country. Introduction costs constitute between 33% and 71% of total financial costs. Commodity and procurement add-on costs are the main cost drivers of total cost across countries. Incremental resource needs for implementation are dependent on country's baseline immunization program capacity constraints.

Interpretation: The financial costs of introducing RTS,S are comparable with costs of introducing other new vaccines. Country resource requirements for malaria vaccine introduction are most influenced by vaccine price and potential donor funding for vaccine purchases and introduction support.

* Corresponding author.
E-mail address: rbaral@path.org (R. Baral).

https://doi.org/10.1016/j.vaccine.2023.01.043
0264-410X/

1. Introduction

In October 2021, two independent advisory groups to the World Health Organization (WHO), the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Group (MPAG), reviewed all available evidence on the RTS,S/AS01 malaria vaccine, including data from the three Malaria Vaccine Implementation Program (MVIP) countries: Ghana, Kenya, and Malawi [1]. Based on the evidence and the advice of these bodies, the WHO recommended widespread use of the vaccine in settings of moderate-to-high *Plasmodium falciparum* malaria transmission. The vaccine is provided to children in a schedule of 4 doses between the ages of 5 months and roughly 2 years [1].

As countries begin to introduce the malaria vaccine into their national programs, the economic implications of introducing and sustaining implementation become critical. Four doses of the malaria vaccine are recommended, which requires parents and children to make one or more new vaccination visits during the first year of a child's life. The fourth dose is recommended to be provided around the child's second birthday. Governments and other vaccine financing institutions, such as Gavi, the Vaccine Alliance, will need to determine how to financially support the introduction and scale-up of the malaria vaccine to achieve the intended health impact and to ensure financial sustainability of this intervention. Due to the need for additional off-schedule visits, there was considerable concern that the delivery cost for new touchpoints would be higher than for other vaccines using a traditional schedule.

The MVIP is under coordination by WHO and funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria; Gavi; and Unitaid [2]. GSK, the vaccine developer and manufacturer, donated vaccine doses for use during pilot implementation. The MVIP provided funds to the implementing countries for vaccine introduction support, either as direct payments or through government disbursement. Ministries of Health (MOHs) in the pilot countries led the vaccine implementation, with technical assistance from partner agencies, particularly WHO and PATH. The three countries implemented the vaccine using existing routine immunization systems in selected sub-national pilot implementation areas.

This study examines the cost of introducing and delivering the malaria vaccine within sub-national areas of Ghana, Kenya, and Malawi. Findings from this study were generated by examining the costs incurred during the pilot implementation. The cost of delivery estimates from this study are also useful to other countries in the region that are considering sub-national use of the malaria vaccine.

2. Methods

2.1. Scope

This study evaluates the costs incremental to the existing routine immunization program from each government's perspective in Ghana, Kenya, and Malawi. Retrospective data on activities, expenditures, and outcomes from the pilot implementation between 2019 and September 2021 were considered. Direct expenses supported by donor agencies were included as financial costs to the government, as a proxy for actual costs of implementation to the government. Expenses related to donors' technical assistance to the immunization programs for the MVIP were excluded. Any existing resource use within the health system used for the malaria vaccine implementation were valued and considered in generating the cost estimates.

2.2. Data

All activities executed during the study period in support of the MVIP were identified from country introduction plans [3–5] and project activity reports. Expenditure data on each activity implemented were collected separately from each partner agency responsible for conducting the activity. In the few events where actual expenditure data were unavailable, the program budget informed resource use. Substitution of expenditure by budget had minimal impact, if any impact at all, on the overall cost estimates and by category.

Primary data were collected from representative samples of 24–30 health facilities, vaccine stores, and administrative units within the MVIP implementation areas in each country (see Appendix 1). This included data on vaccine distribution costs (resource use and frequency of distribution at various levels), delivery (e.g., number of children vaccinated per clinic, time taken by health workers per vaccination, and proportion of children vaccinated during routine clinics versus outreach settings). These data were used to estimate recurrent delivery costs. Target populations for vaccination and coverage were based on national administrative, official figures for the project.

Expenditure data were collected in the local currency and inflation adjusted using the World Bank's inflation rate and official exchange rates [6,7]. Cost estimates are presented in 2020 USD.

2.3. Costing approach

The study employed an activity-based costing approach, where all activities associated with the introduction and delivery of the malaria vaccine were identified and costed individually. All activities were grouped into key categories of the vaccination program, including vaccine procurement, planning and coordination, training, communication, sensitization, social mobilization, service delivery, supervision, and monitoring of vaccine delivery [8–10]. Within each category, the levels and types of sub-activities vary by country, based on the need and the immunization program. See cost categories in supplementary appendix 2 and detailed activities used for costing in supplementary appendix 3.

The Malaria Vaccine Introduction Costing tool (MVICT), an Excel-based tool developed specifically for costing malaria vaccine introduction, was used for this study. An earlier version of the MVICT was reviewed by WHO's Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC) and was also used previously for malaria vaccine cost projections [11].

This study estimates incremental financial and economic costs. Financial costs represent the financial outlays or actual expenditure on goods and services. Any direct expenses supported by partner agencies for program implementation are considered financial cost to the governments in this analysis. Economic costs represent the value or opportunity costs of all resources and includes financial costs plus in-kind value of resources used for the program, for example, salaries of current health personnel. The costs associated with vaccine doses are considered only as economic costs. The cost of other immunization supplies, such as injection supplies and safety boxes, and procurement add-on costs that include shipping, freight, and handling, are included both as financial and economic costs. The procurement add-on costs were calculated as a percentage of the base price of vaccine/injection supplies.

Activities and costs are categorized as initial setup (introduction) or recurrent. Resources that last longer than one year are considered introduction costs. These include costs associated with purchasing capital resources (such as cold chain equipment and

vehicles), as well as nonrecurrent activities for introduction, such as training, social mobilization, and materials development. The nonrecurrent activities for introduction are assumed to have a useful life year of three years, reflecting the duration of the MVIP. The costs of capital items (such as cold chain equipment, vehicles, and computers) are annualized over their respective estimated useful life years. Introduction costs are considered capital costs and are discounted (only for economic cost). Recurrent costs consist of the value of resources used within one year and include operational costs of the program, such as the value of vaccines and immunization supplies, vaccine distribution, service delivery, monitoring and evaluation, and supervision [10].

2.4. Capacity consideration and shared input

Some initial capital investments were made during the MVIP to ease capacity and infrastructure constraints. These include cold chain expansion, waste management system installation, and other systems investments like vehicles or computers. These investments were captured as full costs to the program and included both as financial and economic costs. To account for the incremental resource requirements for distribution, inputs shared with the existing system were attributed to malaria vaccine based on the direct allocation informed by the respective immunization programs. Costs associated with vaccinators time was estimated based on time required to administer the vaccine. For all other resources, we assumed sufficient existing spare capacity in the immunization system to accommodate malaria vaccine delivery. Children received malaria vaccine within the routine immunization settings. No additional outreach or campaign activities outside of the routine Expanded Program on Immunization (*EPI*) delivery are considered. Resources used for service delivery are estimated as average additional time spent per vaccination in routine static and routine outreach settings, as reported by the health workers during facility surveys.

2.5. Cost estimates

The cost estimates generated are the incremental cost per dose delivered, cost of delivery per dose, and cost per fully immunized child (FIC). Cost per dose delivered is estimated by dividing the total cost over the period of analysis by the total number of vaccinations delivered during the same period. Cost of delivery per dose is estimated similarly but excluding costs related to vaccine and immunization supplies. A fully immunized child is defined as a child receiving all four doses of RTS,S. For dose-dependent activities—for example, vaccine and immunization supplies procurement and vaccine administration total cost was allocated proportional to the number of doses delivered by per-dose type. For activities that are independent of dose administration (e.g., planning and coordination activities, initial training, and stakeholder sensitization), activity costs were allocated equally to all four doses. Cost of delivering the fourth dose is considered separately in anticipation that the fourth dose may require additional efforts during the second year of life. Activities identified as specifically targeting fourth-dose administration were allocated only to the fourth-dose unit cost calculation.

2.6. Sensitivity analysis

Table 1 indicate key data inputs and assumptions used to generate primary cost estimates. To understand the implications of input values on the cost estimates, one-way sensitivity tests were performed for a subset of critical input data, over a range of alternative values, including vaccine price, wastage rates, coverage, discount rate, and time spent per vaccination.

2.7. Role of funding source

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

3. Results

During the study period (2019–2021), 350,000 children in Malawi, 415,000 in Ghana, and 300,000 children in Kenya were targeted to receive vaccination (Table 1). During the same period, 800,000 doses of the malaria vaccine were administered in Malawi, 895,000 doses in Ghana, and 615,000 doses in Kenya. Of the target population, only 18 % (in Malawi and Ghana), and less than 9 % (in Kenya) received the fourth dose. This was a result of most children not yet being age-eligible at the end of the study period, despite receiving the first 3 doses.

3.1. Cost of RTS,S/AS01 immunization

Unless otherwise noted, all cost estimates are presented for an assumed vaccine price of US$5.00 per dose. In the sensitivity analysis, costs were estimated assuming $2-$10 range of vaccine price per dose [12]. The total costs (financial) of malaria vaccine introduction and delivery for the duration of the analysis were estimated at $1.8 million in Malawi, $2.6 million in Ghana, and $1.8 million in Kenya (Table 2). The total program cost included annualized introduction costs and annual recurrent costs for the duration of the analysis. Introduction costs constituted approximately 33 %, 49 %, and 71 %, of the total financial costs in Malawi, Ghana, and Kenya, respectively. Similarly, of the total economic costs, introduction costs constituted approximately 11 %, 18 %, and 30 % in Malawi, Ghana, and Kenya, respectively.

Based on a health facility survey of health workers, the average amount of time spent on vaccination per child was six minutes in Malawi, nine minutes in Ghana, and between 12 and 14 min in Kenya. These averages were used to estimate the service delivery cost at point of care in each country.

The unit cost estimates are reported in Table 3. The overall financial cost per dose administered ranges between $2.30 and $3.01. The non-vaccine cost of delivery, excluding procurement add-on costs, ranges between $1.04 and $2.46 (financial). Similarly, the overall economic cost per dose administered ranges between $8.28 and $10.29. Excluding the initial setup costs, the recurrent cost of delivery per dose ranges from $0.29 to $0.86 (financial), and from $0.59 to $2.29 (economic).

The cost of the fourth dose administered and cost per FIC calculations used actual coverage data during the study period (Table 3). Only a small proportion of the target population, 18 % in Ghana and Malawi, and ~9 % in Kenya, received fourth-dose vaccination during the study period. The cost of fourth dose administered and cost per FIC are upward biased as the "coverage" denominator excluded children who were not yet age eligible to receive the fourth dose during the study period. Less than 40 % of children who received 3 doses were age-eligible to receive the fourth dose during the study period. To better estimate the potential costs of dose 4 and FIC, alternative unit cost estimates were generated using coverage for all doses at 2021 levels and the results are presented in Table 4. The adjusted cost of delivery for the fourth dose ranges from $1.75 to $2.55 (financial), and the cost per FIC range between $32.70 and $38.86 (economic).

3.2. Cost drivers of RTS,S/AS01 immunization

The distribution of resource requirements for each cost category, as a proportion of total costs, is shown in supplementary

Table 1
Key inputs and assumptions.

Categories	Malawi	Ghana	Kenya	Data source
Target population and coverage				
Target population	348,698	415,183	298,723	WHO/MVIP
Doses administered (total)	800,977	895,547	615,169	WHO/MVIP
Dose 1	279,643	293,916	230,462	WHO/MVIP
Dose 2	241,835	272,557	197,222	WHO/MVIP
Dose 3	218,389	255,986	159,307	WHO/MVIP
Dose 4	61,130	73,088	28,178	WHO/MVIP
Vaccine product characteristics				
Vaccine presentation	Two dose vial	GSK		
Vaccine packaged volume	9.2 cu.cm/dose	GSK		
Vaccine wastage	10 % (5–20 %)	Assumed		
Injection & safety boxes wastage	10 % (5–20 %)	Assumed		
Buffer stock	25 %	Assumed		
Vaccine product cost assumptions				
Vaccine price per dose	$5 ($2 - $10)	Assumed		
(Penny, 2016)				
Cost per injection syringe	$0.03	$0.05	$0.05	WHO/MVIP
Cost per reconstitution syringe	$0.04	$0.04	$0.04	WHO/MVIP
Cost per safety box (100 syringe capacity)	$0.45	$0.80	$0.80	WHO/MVIP
Procurement add-on charges				
Freight, insurance, inspection	18.5 %	7.6 %	4.6 %	WHO/MVIP; derived based on first shipment order
Handling	3.0 %	3.0 %	3.0 %	
Service delivery				
Proportion of children vaccinated during routine outreach session	51.83 %			
(46–63 %)	48.76 %			
(20–95 %)	26.00 %			
(5–60 %)	Primary data, MVIP facilities			
Average time spent per vaccination during routine outreach session (in min)	6 (4–7)			
	9 (2–20)	12 (5–20)		
Average time spent per vaccination during routine fixed session (in min)	6 (4–9)	9 (4–25)	14 (5–30)	
Cold chain requirements				
Cold chain capacity expansion requirements	No additional requirements	Refrigerator of various types (N = 29) and Cold boxes (N = 180)	Refrigerators of various types (N = 83)	MVIP
Salaries				
Staff salary per month, range by staff cadre (in local currency units)	112,800 MWK to 1,296,204 MWK	937 GHC to 5,717 GHC	63,562 KSH to 227,513 KSH	MOH/*EPI*
Vaccinators average salary per month	212,310 MWK			
(US$ 290)				
	1,387GHC			
(US$ 303)	82,873 KSH			
(US$ 627)				
Others				
Exchange rate, 2018–2020	732.33–745.54	4.58–5.21	101.30–101.99	World Bank database,
Inflation rate, 2018–2020	9.37 %-12.42 %	7.18 % −7.81 %	4.69 %	
Useful life years for non-capital introduction activities	3 years	3 years	3 years	Assumed
Discount rate	3 % (1–5 %)	3 % (1–5 %)	3 % (1–5 %)	Assumed

Table 2
Total cost of program implementation (in USD) during 2019–2021, in USD.

Metric	Malawi		Ghana		Kenya	
	Financial	Economic	Financial	Economic	Financial	Economic
Total cost (2019–2021), with annualized introduction costs	1,843,703	6,633,243	2,664,278	9,216,838	1,851,237	5,975,202
Total introduction cost, annualized	603,793	747,076	1,298,666	1,632,181	1,320,478	1,810,386
Total recurrent cost	1,239,910	5,886,167	1,365,612	7,584,656	530,759	4,164,816
Average annual cost, annualized	614,568	2,211,081	888,093	3,072,279	617,079	1,991,734

appendix 4. Introduction costs constituted 33–71 % of financial costs and 11–30 % of economic costs. Procurement of vaccine and immunization commodities accounted for up to 55 % of the financial and 82 % of economic introduction costs. Looking specifically at the initial setup costs, training, planning, and coordination were the key cost drivers, accounting for between 63 and 86 % of the financial cost and between 44 and 64 % of economic costs. Training is the major cost driver of initial setup costs across all countries. Commodity procurement remains the main recurrent cost driver, accounting for up to 92 % economic costs and 82 % of financial cost. A small proportion of costs were attributed to training in Malawi and included in recurrent costs. This expenditure reflected the need to re-train staff specifically on eligibility criteria in the initial phases of vaccine introduction.

Table 3
Unit cost estimates (in USD) of malaria vaccination.

Metric	Malawi		Ghana		Kenya	
	Financial	Economic	Financial	Economic	Financial	Economic
Cost per dose	2.30	8.28	2.98	10.29	3.01	9.71
Cost per dose, doses 1–3	2.11	8.06	2.58	9.77	2.45	8.72
Cost per dose, dose 4	4.52	10.99	7.34	15.95	13.96	25.32
Cost of delivery per dose	1.04	1.52	2.30	4.09	2.46	4.62
Cost of delivery per dose, doses 1–3	0.85	1.30	1.91	3.59	1.94	3.86
Cost of delivery per dose, dose 4	3.25	4.23	6.67	9.77	13.45	20.46
Cost of delivery per dose, recurring only	0.29	0.59	0.86	2.29	0.35	1.19
Cost per 3-dose administrations	8.44	30.37	10.41	36.01	11.62	37.51
Cost of delivery per 3-dose administrations	3.81	5.57	8.07	14.39	9.65	18.72
Cost per FIC	10.86	35.16	15.07	45.24	21.30	51.49
Cost of delivery per FIC	5.81	8.11	12.39	20.52	19.26	32.03

Abbreviations: FIC, fully immunized child; USD, US dollar.

Table 4
Unit cost estimates (in USD) of malaria vaccination using alternative coverage assumption (from 2021 MVIP).*

Metric	Malawi		Ghana		Kenya	
	Financial	Economic	Financial	Economic	Financial	Economic
Cost per dose	2.09	8.00	2.52	9.67	2.67	9.35
Cost per dose, doses 1–3	1.97	7.86	2.35	9.45	2.54	9.01
Cost per dose, dose 4	3.02	9.12	3.22	10.52	3.03	9.71
Cost of delivery per dose	0.82	1.24	1.83	3.45	2.13	4.14
Cost of delivery per dose, doses 1–3	0.70	1.10	1.68	3.27	2.03	3.99
Cost of delivery per dose, dose 4	1.75	2.36	2.55	4.34	2.52	4.70
Cost of delivery per dose, recurring only	0.23	0.50	0.68	2.03	0.31	1.79
Cost per 3-dose administrations	7.55	28.96	9.04	34.75	11.50	40.21
Cost of delivery per 3-dose administrations	2.99	4.49	6.63	12.53	9.30	18.66
Cost per FIC	8.91	32.70	10.27	38.86	10.65	36.72
Cost of delivery per FIC	3.86	5.65	7.59	14.14	8.61	16.67

Abbreviations: FIC, fully immunized child; USD, US dollar.
* *Coverage:* Malawi: 93%/84%/80%/47% for dose 1/2/3/4; Ghana: 75%/73%/75%/46% for dose 1/2/3/4; Kenya: 72%/66%/58%/54% dose 1/2/3/4.

3.3. Sensitivity analysis

The analysis shows that unit cost per dose administered and cost per FIC are most sensitive to vaccine price and coverage assumptions. Over a $2-to-$10 cost-*per*-dose assumption, the financial cost per dose ranges between $1.59 and $3.48 (Malawi), $2.62 and $3.56 (Ghana), and $2.76 and $3.43 (Kenya). Similarly, the economic cost per dose ranges between $4.27 and $14.96 (Malawi), between $6.64 and $16.38 (Ghana), and between $6.84 and $14.49 (Kenya). The vaccine cost per dose assumption impacts the financial unit cost estimate due to its impact on procurement add-on costs, which are calculated as a percentage of vaccine price. Using a high-coverage assumption (90 %) for all doses, the cost of delivery per dose is estimated at $0.72, $1.36, and $1.48 (financial) in Malawi, Ghana, and Kenya, respectively. Under a low-coverage assumption (30 %) for all doses, the cost of delivery per dose is estimated at $2.16, $4.09, and $4.45 (financial) in Malawi, Ghana, and Kenya, respectively. For the cost of delivery per dose, time spent per vaccination, although important for programmatic reasons, is not a major cost driver of the unit costs. Results from the sensitivity analysis are summarized in tornado graphs, by country, in supplementary appendix 5.

4. Discussion

This study quantifies the cost of introducing and delivering the malaria vaccine through national immunization programs using retrospective data on resource use observed during the MVIP. One of the strengths of this approach is that it captures the actual resource used in the pilot implementation countries. In a few instances where the allocation of expenditures by specific sub-activities was unavailable, it was approximated using budgets. International donor agencies supported the MVIP, potentially inflating estimates of program implementation costs [13]. To address the possibility of overestimation, costs incurred by international donors through provision of technical assistance were excluded to reflect the true cost of vaccine implementation to each government. These costs could increase as the programs are not yet fully "normalized" and costs could drift down somewhat as additional efficiencies are found. Nonetheless, these estimates provide useful insight into the cost of malaria vaccine introduction and delivery in other settings and for scaling up the vaccine introduction in MVIP countries.

The economic cost per dose administered is approximately-three- to fourfold higher than the financial costs or the direct outlays of expenditure ($8.28–$10.29 versus $2.30–$3.01). At a vaccine price of $5.00 per dose, between 50 and 82 % of the total economic cost is attributed to vaccine and immunization supplies procurement. For the non-vaccine cost of delivery, which is reflective of costs to countries receiving donation doses, the financial costs are roughly half the economic cost ($1.04–$2.46 versus $1.52–$4.62). Considering only the recurrent costs that reflect the longer-term costs to the immunization programs, the cost of delivery per dose ranges from $0.29 to $0.86 (financial) and $0.59 to $2.29 (economic). The difference between the financial and economic costs in the cost of delivery is primarily attributable to the valuation of opportunity cost of labor in the latter, as sufficient spare capacity in the system is assumed.

Previous cost projections of the malaria vaccine provision in the same settings [11] using the MVIP plans, and adapted activities were used to project cost. That analysis projects the cost per dose

administered at $1.70–2.24 per dose (financial) and $8.22–$8.73 per dose (economic) across the three pilot countries. These ranges are slightly lower than the estimates from the current study, which uses actual MVIP expenditures and outcomes. Consistent with the previous results, the cost of delivery remains a small fraction of the total program cost, although the range of the cost-of-delivery estimates in the previous analysis was narrow ($0.23–$0.90) per dose. The current estimates are not directly comparable to the previous prospective cost estimates [11], due to the underlying assumptions on vaccine coverage and procurement add-on costs, among others. Assumed vaccine coverage in the previous analysis is higher than the actual coverage observed during the MVIP for the study period, especially for the fourth dose, as most children were not eligible to receive all 4 doses within the study time frame. The procurement add-on costs in the previous analysis were higher at 35 %, 21 %, and 15 %, of the per unit product cost in Malawi, Ghana, and Kenya, respectively. In the current analysis, by comparison, these costs were 21.5 %, 10.6 %, and 7.6 %, respectively. The average time spent on vaccination, informed by a survey of health workers, was much higher in the current analysis: Malawi (six minutes), Ghana (nine minutes), and Kenya (12–14 min), compared with the four to five minutes seen in the previous analysis (informed by *EPI* representatives). This higher average time spent on vaccination contributed to the higher economic cost associated with service delivery. Also, the previous study assumed sufficient spare capacity on cold chain for vaccine storage and did not include any fixed costs associated with capacity strengthening. Within the current analysis, cold chain strengthening, and other capital investments accounted for roughly 10 % of the total financial cost and 3 % of total economic costs in Ghana and Kenya. In Malawi, the costs of capacity strengthening were minimal (1 % or less).

A few other previous studies projected the costs of RTS,S vaccine implementation. Using a generic set of activities, assumptions, and input data across countries, this study [14] estimated the cost of delivery per dose to be $1.13 and $2.17 in Ghana and Kenya, respectively (in 2013 USD). Another study reported a lower cost of delivery of $0.20 in Ghana and $0.37 in Kenya, assuming full coverage of all children [15]. Although not directly comparable, our cost-of-delivery estimates are broadly similar with the results reported from these studies. Cost-of-delivery estimates for other routine immunizations in the pilot countries or in similar settings are limited, and comparability remains challenging, given differences in vaccine delivery strategy, targeted age group, and study methodology. One study evaluated the cost of other new vaccine introduction in Ghana and estimated the incremental cost of delivery (excluding vaccine cost) to be $0.90 [16]. Non-vaccine cost of delivery per dose for routine *EPI* vaccines are reported to be $1.50 in Kenya [17] and $0.52 in Malawi [18]. A recent systematic review estimated the mean economic incremental cost per dose for single, newly introduced vaccines at health facilities, including vaccines such as pneumococcal conjugate vaccine and rotavirus vaccine, to be $0.84 (range: $0.48–$1.38) [13]. These regional estimates are derived from three countries (Benin, Rwanda, and Uganda) and may not be fully representative of the region. Similarly, the cost of introducing a human papillomavirus (HPV) vaccine on a pilot basis at health facilities and schools and using multiple delivery strategies were estimated to range between $1.74 and $2.24 (financial) and $2.22 and $4.29 (economic) [13,19]. The cost of delivery per dose from the current study, which ranges from $1.04 to $2.30 (financial) and $1.52 to $4.62 (economic) across pilot countries, is not substantially different from the existing evidence in the literature and closely aligns with HPV estimates from its pilot introductions [19]. However, comparisons of these results to findings from the literature should be made cautiously, since the methods and the delivery strategies are different, and since these estimates are drawn from ongoing pilot studies rather than a full national introduction.

A few limitations of this analysis are worth noting. The analysis uses data on MVIP costs and outcomes that were collected through the end of September 2021. During the analysis period, less than 40 % of children who completed the first three doses were eligible to receive the fourth dose of the vaccine. The estimates of cost per dose for the fourth dose included the full cost of introduction, but the number of children vaccinated with the fourth dose at the time does not account for those children who were not yet eligible to receive the fourth dose. This led to a biased estimate of cost per dose, specifically for the fourth dose (upward bias). Consequently, the estimates of cost per FIC are also biased upwards. Therefore, estimates were also presented under assumed coverage levels for the fourth dose, as indicative of the potential costs of delivery by dose and cost per FIC. The cost estimates should be interpreted within the context of input and data used in this analysis.

Further, the procurement add-on costs for both vaccine and immunization supplies were calculated as a percentage of product cost and derived from the actual payments made for other immunization products during the MVIP, by country. Due to the targeted introduction in limited geographies, the volume of the products is small, and the procurement add-on costs may not reflect the actual costs that would be incurred for procuring high volume. During national introduction, immunization products for RTS,S can be expected to be added to the routine order made through established UNICEF mechanism.

One of the strengths of this analysis is that the cost estimates are based on the actual costs observed during the pilot implementation of the malaria vaccination program. Activities and resource input are country specific and reflect the variation in program implementation and resource needs across countries. Country-specific activities and resources used are realistic to the local context and scale of implementation, although they may result in limited generalizability of unit cost estimates for cross-country comparisons, as country contexts are different.

The literature for cost of delivery estimates in public health interventions are expanding, but remain limited, especially in the low- and middle-income countries (LMIC) settings [13,20]. When available, the cost estimates have a wide range, and variations in methods limit the ability to compare the costs across country income groups. Multi-country studies like the current one contribute to generating cross-country estimates using standard sets of methodologies and harmonized sets of inputs and help generate comparable data and ranges that may be explored for application to broader settings.

As country decision-makers face an important question of broader rollout of the RTS,S vaccine in their immunization programs, the cost estimates generated in this study can serve as a starting point for planning and projecting the cost of implementation and for understanding its impact on national immunization budgets. The cost of delivering the malaria vaccine within the routine immunization system can inform the subsequent implementation and vaccine rollout, as well as discussions about vaccine cost-effectiveness.s.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank all our colleagues within the MVIP partnership for their collaboration and support for providing all the data and feedback throughout the years for conducting the MVIP economic analysis. This work would not have been possible without the support from Ministries of Health in Ghana, Kenya, and Malawi, WHO, and PATH MVIP staff. We also acknowledge the staff in the health facilities and vaccine stores who provided us with useful information during the conduct of this study. This work was funded by a grant from the World Health Organization (Grant # 2020/1034519).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.01.043.

References

[1] World Health Organization (WHO). Malaria vaccine: WHO position paper–March 2022. Geneva: WHO; 2022. Weekly epidemiological record, No. 9. Available from: https://apps.who.int/iris/bitstream/handle/10665/352332/WER9709-eng-fre.pdf.
[2] WHO welcomes global health funding for malaria vaccine [press release]. Geneva, Switzerland; WHO; November 17, 2016. Available from: https://www.who.int/news-room/detail/17-11-2016-who-welcomes-global-health-funding-for-malaria-vaccine.
[3] Republic of Kenya, Ministry of Health (MOH). Malaria vaccine implementation program, malaria vaccine rollout plan. Nairobi, Kenya: MOH; 2018.
[4] Republic of Ghana, Ministry of Health (MOH). Malaria vaccine implementation program, malaria vaccine rollout plan. Accra, Ghana: MOH; 2018.
[5] Republic of Malawi, Ministry of Health (MOH). Malaria vaccine implementation program, malaria vaccine rollout plan. Lilongwe, Malawi: MOH; 2018.
[6] The World Bank website. Official exchange rate (LCU per US$, period average) data page. Accessed April 2022. Available from: https://data.worldbank.org/indicator/PA.NUS.FCRF.
[7] The World Bank website. Inflation, consumer prices (annual %) data page. Accessed April 2022. Available from: https://data.worldbank.org/indicator/FP.CPI.TOTL.ZG.
[8] Brenzel L. Common approach for the costing and financing analyses of routine immunization and new vaccine introduction costs (NUVI). Seattle: Bill & Melinda Gates Foundation (BMGF); 2013.
[9] World Health Organization Website. Department of Vaccines and Biologicals. Guidelines for estimating costs of introducing new vaccines into the national immunization system. Geneva: World Health Organization; 2002.
[10] Levin A, Boonstoppel L, Brenzel L, et al. WHO-led consensus statement on vaccine delivery costing: process, methods, and findings. BMC Med 2022;20(8). https://doi.org/10.1186/s12916-022-02278-4.
[11] Baral R, Levin A, Odero C, et al. Costs of continuing RTS, S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. PLoS One 2021;16(4). https://doi.org/10.1371/journal.pone.0244995.
[12] Penny MA, Verity R, Bever CA, Sauboin C, Galactionova K, Flasche S, et al. Public health impact and cost-effectiveness of the RTS, S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016;387(10016):367–75. https://doi.org/10.1016/S0140-6736(15)00725-4.
[13] Vaughan K, Ozaltin A, Mallow M, et al. The costs of delivering vaccines in low- and middle-income countries: findings from a systematic review. Vaccine: X. 2019. Available from: https://thinkwell.global/wp-content/uploads/2020/02/Vaccine-X-Publication-of-Systematic-Review.pdf.
[14] Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS, S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: a generalizable approach drawing on publicly available data. Vaccine 2015;33(48):6710–8. https://doi.org/10.1016/j.vaccine.2015.10.079.
[15] Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The costs of implementing vaccination with the RTS,S malaria vaccine in five sub-Saharan African countries. MDM Policy Practice. 2019;4(2):2381468319896280. doi: 10.1177/2381468319896280.
[16] Le Gargasson JB, Nyonator FK, Adibo M, Gessner BD, Colombini A. Costs of routine immunization and the introduction of new and underutilized vaccines in Ghana. Vaccine 2015;33(Suppl 1):A40–6. https://doi.org/10.1016/j.vaccine.2014.12.081.
[17] Mvundura M, Lorenson K, Chweya A, et al. Estimating the costs of the vaccine supply chain and service delivery for selected districts in Kenya and Tanzania. Vaccine 2015;33(23):2697–703. https://doi.org/10.1016/j.vaccine.2015.03.084.
[18] Pecenka C, Munthali S, Chunga P, et al. Maternal influenza immunization in Malawi: piloting a maternal influenza immunization program costing tool by examining a prospective program. PLoS One 2017;12(12):e0190006.
[19] Immunization Economics website. Immunization Delivery Cost Catalogue findings page. Accessed April 2022. Available from: http://immunizationeconomics.org/ican-idcc-findings#anchor-top.
[20] Portnoy A, Vaughan K, Clarke-Deelder E, et al. Producing standardized country-level immunization delivery unit cost estimates. Springer 2020;38:995–1005. https://doi.org/10.1007/s40273-020-00930-6.