An ingredients-based approach to costing integrated malaria elimination strategies: an example from Myanmar

Shwe Sin Kyaw (kyaw.shwesin@gmail.com)  
Mahidol University Faculty of Tropical Medicine  
https://orcid.org/0000-0001-6285-5969

Gilles Delmas  
Shoklo Malaria Research Unit

Tom L Drake  
United Kingdom Department for International Development

Olivier Celhay  
Mahidol Oxford Tropical Medicine Research Unit

Wirichada Pan-ngum  
Mahidol University Faculty of Tropical Medicine

Sasithon Pukrittayakamee  
Mahidol University Faculty of Tropical Medicine

Yoel Lubell  
Mahidol Oxford Tropical Medicine Research Unit

Ricardo J Aguas  
Mahidol Oxford Tropical Medicine Research Unit

Richard Maude  
Mahidol Oxford Tropical Medicine Research Unit

Lisa J White  
University of Oxford

Francois Nosten  
Shoklo Malaria Research Unit

Research article

Keywords: MDA, P. falciparum, malaria elimination, costs, Myanmar

DOI: https://doi.org/10.21203/rs.3.rs-60017/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background Mass drug administration (MDA) has received growing interest to accelerate the elimination of multi-drug resistant malaria in the Greater Mekong Subregion. The potential effectiveness of delivering targeted MDA was demonstrated in a recent intervention in Kayin State, Myanmar. Policymakers and funders need to know what resources are required if MDA is to be included in elimination packages beyond existing malaria interventions.

Methods We used financial data from a malaria elimination initiative, conducted in Kayin State, to estimate the programmatic costs of the MDA component using a micro-costing approach. Three activities (community engagement, identification of villages for MDA, and conducting mass treatment in target villages) were evaluated. We then estimate the programmatic costs of implementing targeted MDA to support *P. falciparum* malaria elimination in Kayin State. A costing tool was developed to aid future analyses.

Results The cost of delivering MDA within an integrated malaria elimination initiative in Eastern Kayin State was approximately US$ 910 000. The cost per person reached for MDA was US$ 2·5.

Conclusion This cost analysis can assist policy makers in determining the resources required to clear malaria parasite reservoirs. The analysis demonstrated the value of using financial data from research activities to predict programmatic implementation costs of MDA in different numbers of target villages.

Background

Research in context

Evidence before this study
Research has shown that, when combined with existing malaria interventions including early diagnosis and treatment and distribution of insecticide treated bed-nets, mass drug administration (MDA) can accelerate malaria incidence reduction to zero and so should be considered for inclusion in malaria elimination strategies. So far, the resource requirements for such an elimination package and the added costs of MDA are not well-described.

Added-value of this study
Here, we estimated highly detailed programmatic costs of targeted mass drug administration implemented in Myanmar, using a micro-costing approach. We developed a costing tool to predict the budgets required for large-scale malaria interventions in other settings.

Implications of all the available evidence
This cost analysis will inform policy makers’ contemplating the selection of interventions to be included in their national malaria control programs, aimed at meeting their elimination timelines, on the expected cost of malaria interventions packages that include MDA.

Countries across the malaria endemic world are aiming to eliminate malaria and committed to identifying approaches aimed at interrupting its transmission [1]. Although substantial progress has been made through the scaling up of existing malaria interventions, the gains achieved are fragile and unevenly distributed among regions and countries. The development of artemisinin resistance in South-East Asia, followed by partner drug resistance [2], led to a call by all country governments in the Greater Mekong Subregion (GMS) to hasten *Plasmodium falciparum* malaria elimination [3].

In 2010, the World Health Organization (WHO) proposed mass drug administration (MDA) as a strategy to accelerate the elimination of multi-drug resistant *P. falciparum* malaria [4]. This strategy aims to treat every individual in a community with three rounds of a full dose of antimalarial drug, regardless of whether they have malaria symptoms. Many field trials and programmatic implementations of MDA have been carried out over the past century with varying degrees of success [5]. However, a trial MDA conducted in Zanzibar showed no impact on malaria incidence [6].

A series of targeted MDA projects have recently been piloted in countries in the GMS [7–10] and Africa [11, 12]. These trials have demonstrated that MDA is feasible and well-accepted by communities, with high levels of community participation. MDA using a therapeutic dose of an effective antimalarial medication can clear the malaria parasite reservoir, including asymptomatic infections that would otherwise not be treated [13]. This approach can rapidly reduce malaria parasite prevalence if highly efficacious antimalarial drugs are used [14].

In addition to the effectiveness of interventions, policymakers must be able to evaluate the costs of malaria elimination, to determine which intervention or package of interventions should be invested in, given the constraints of budget limitations. Even when the epidemiological impact of intervention packages is well characterised, efficient resource-allocation decisions can only be made when all resources consumed are explicitly valued and visible. Cost analyses have been conducted for most malaria control activities [15], but to date, few costing exercises of MDA have been performed [16–18].

The Malaria Elimination Task Force (METF), established by the Shoklo Malaria Research Unit, which is based on the Thai–Myanmar border, delivered an integrated malaria elimination strategy that layered targeted MDA over a series of malaria control and research activities in the region. Here, we used financial data from METF targeted MDAs in 61 selected villages in Kayin State, Eastern Myanmar as a basis for a costing exercise to analyse the costs of delivering MDA in targeted Myanmar villages and calculate the scalable cost of delivering targeted MDA to support *P. falciparum* malaria elimination.

**Methods**
Study area

Kayin State lies on Myanmar’s international border, with Thailand to the East. It is a mountainous region, with the rocky Dawna mountain range running the length of eastern Kayin State. The climate is hot and humid, with average maximum temperatures of between 29 and 37°C and average annual rainfall of approximately 5000 mm [19]. The METF covers a population of 365,000 people. The residents of Kayin State traditionally rely on agriculture for their livelihoods; major crops include rice, rubber, sugarcane, coffee, and seasonal fruit and vegetables.

Kayin State has experienced decades of armed conflict between various Kayin militant groups and the national government [20]. Therefore, it is a politically sensitive area, and government accessibility to the region is limited. Consequently, basic infrastructure, such as roads, electricity, schools, and health care facilities, are under-developed.

Data collection

A series of consultations were held with METF, and the importance of the costing exercise was explained. Permission to access financial reports relating to the MDA conducted by METF (2015) was obtained and all information required for the costing analysis was collected.

Costing

A micro-costing approach was used to estimate the costs of activities necessary to conduct a targeted MDA in four townships in Kayin State (Myawaddy, Hpapun, Hlaingbwe, and Kawkareik). This approach is particularly useful for estimating the unit delivery costs of community-based interventions or treatments and new technologies. It enables the accurate assessment of health interventions by collecting details on resources used and respective unit costs.

Cost model

A cost model was developed to estimate the implementation cost of all activities related to targeted MDA in four townships in Kayin State. The costs of implementing MDA include (i) community engagement, (ii) identification of villages for MDA via ultrasensitive polymerase chain reaction (uPCR) surveys, and (iii) conducting mass treatment in target villages. METF rolled-out their MDA campaigns in phases. The malaria elimination initiative was delivered to 1226 villages, of which 30 received targeted MDA in 2015. First, we estimated the cost of implementing MDA during 2015 based on 2015 financial data; these costs were then extrapolated to a total of 61 villages that received targeted MDA.

All resource ingredients required to perform the three MDA implementation activities were identified, measured, and valued by reviewing financial reports and conducting interviews with key staff. Then, each cost was assigned to a primary resource cost centre. Costs in resource centres were re-classified into relevant activity cost centres.

Cost model ingredients
1. Staff costs. These comprised basic salaries for both national and international staff, plus their allowances, which included benefits and overtime. These staff costs were shared resources, so the allocation of these shared resources was based on the proportion of the time these staff contributed to various services.

2. Travel costs. These included all transportation costs, including bus, taxi, and boat fares; toll fees; petroleum consumed during the project; motorbikes and their maintenance; and other travel-related expenses, such as accommodation and per diems. The cost of transportation of medical and non-medical products and travel expenses for monitoring and training were also included in the travel cost centre.

3. Consumables costs. These included the cost of media, pamphlets, and other health education materials for community engagement activities; uPCR sample preparation and analysis; antimalarial drugs; and medication to treat any adverse effects. The costs of consumables used for uPCR sample collection and analysis were estimated based on the mean number of uPCR samples and the unit cost of sample collection.

4. Overheads. These consisted of central and field office rental fees, utility bills, office computers and software, and office furniture. These costs were annualised over the years they were expected to be used to estimate annual equivalent values. The useful life of traded capital goods was taken from WHO-CHOICE (https://www.who.int/choice/cost-effectiveness/inputs/capital_goods/en/).

5. Incentives. These comprised community incentives, e.g. the cost of large water containers for a community or the cost of constructing sanitary pit latrines in the common areas of villages targeted for MDA. Participants were also provided with snacks and drinks during the MDA campaign and after completing MDA.

All costs of resources consumed during the MDA campaign were initially analysed in the local currency and then converted to United States dollars (US$), based on historical exchange rates from the Forex website. The median exchange rate in 2015 (1 US$ = 33·14 Thai Baht) was used for the currency conversion.

**Online tool**

The cost model is available online: https://moru.shinyapps.io/Mass-Malaria-Interventions-Costing-Tool/. Details of the model’s construction and parameters used are given in the supplementary information.

**Malaria in Kayin State**

Malaria transmission is low, seasonal, and spatially heterogeneous in Kayin State [21]. Five decades ago, malaria was a significant problem, but following rigorous treatment and implementation of malaria posts by the METF, annual incidence of malaria has gradually decreased in the region. Malaria posts are operated by trained members of the community. Malaria infections, confirmed at malaria posts by a rapid diagnostic test (RDT), comprise approximately 12% of all febrile illness [13]. In Myanmar, malaria infection is frequently asymptomatic [22]. A recent survey using uPCR showed a malaria prevalence of 21%, with *P. falciparum* and *P. vivax* comprising 3% and 15% of infections, respectively [13]. MDA was
conducted in 61 selected villages in five phases over two years, with more than 80% participation of village members. As a result, the incidence of *P. falciparum* malaria was reduced by 92%. Following targeted MDA in the region, 71% of METF villages reported no *P. falciparum* malaria [23].

**Results**

The METF implemented an integrated malaria elimination initiative in 1226 villages in Kayin State from May 2014 to December 2019. This included targeted MDA in 61 villages in areas with high levels of sub-microscopic *P. falciparum* malaria, to contain further spread of multi-drug resistant malaria. The total cost of the targeted MDA was estimated using a micro-costing approach. Figure 2 shows the detailed breakdown of total cost of targeted MDA in Kayin State, which involved three activities: i) community engagement (CE), ii) identification of target villages by uPCR, and iii) targeted mass treatment in selected villages. Villages were selected for MDA if the measured uPCR prevalence for *P. falciparum* was more than 20%. CE is a crucial activity required both before and during MDA. The total cost of CE activity for 61 villages (5% of 1226 villages) was US$ 76 330. The average cost per person for providing CE was US$ 0·20.

Villages for MDA were identified based on their malaria prevalence relative to other villages in Kayin State. A malaria prevalence survey was conducted, using a uPCR assay, to measure the true prevalence of malaria in 272 randomly selected villages. Consumables comprised the largest proportion of the total cost of identifying MDA villages, accounting for 80% of all costs. This was because of the cost of uPCR analysis, which was approximately US$ 25 per test. The high cost of the tests was due to the need for expensive equipment, reagents and consumables for high-volume PCR to obtain the desired sensitivity [24]. The total cost of the prevalence survey for 272 villages was US$ 541 042, with the average cost per village of US$ 1 989.

The cost of providing three rounds of three-day antimalarial mass treatment in 61 villages was US$ 291 759. The staff costs were the largest contributor to the total cost of mass treatment (46%), followed by consumables (21%). This was because the METF provided supervised treatment for every dose of antimalarial treatment. Therefore, staff needed to stay for at least four days in a village in each treatment round to cover any latecomers and to watch for any side effects of the treatment.. The average cost per village for providing a full course (three-day treatment) of antimalarial drugs for three consecutive months was US$ 4 455. The cost per person reach for providing three rounds of antimalarial mass treatment was US$ 0·8.

The total cost of an integrated MDA initiative, including detection of hotspots and mass treatment in 61 villages (5% of villages), would be approximately US$ 910 000 over 2 years. The cost per capita for three rounds of targeted MDA was estimated to be US$ 2·5. The intervention was an integrated strategy for the prevention, early detection, and treatment of clinical malaria in all villages, combined with MDA in targeted villages; therefore, the cost per capita quoted is derived from the total cost of the integrated MDA package of interventions but excluding early detection and case management divided by the total
Estimating the programmatic cost of targeted MDA to support *P. falciparum* malaria elimination in Kayin State

The METF screened 272 villages (22% of all villages) to determine malaria prevalence and then performed MDA in 61 selected villages (5% of all villages) based on the survey results. The cost of targeted MDA is highly dependent on the number of target villages. The more villages targeted for MDA, the faster the decline in prevalence in the whole area (assuming all MDA can be implemented in a reasonable amount of time, as MDA is a time-limited process), but the greater the resources need to be invested. The cost of conducting the prevalence survey for 272 villages was kept constant, and we then estimated the programmatic cost of targeted MDA for different proportions of target villages. The detailed breakdown of the cost of targeted MDA, depending on the percentage of villages targeted for MDA, is shown in Table 1. For example, if 10% of villages are assumed to be provided with MDA, the total programmatic cost of targeted MDA would be approximately US$ 1·15 million. The average cost per village and the average cost per person reached would be US$ 944 and US$ 3·2, respectively in this example.
Table 1
Two-year programmatic costs of targeted MDA with different numbers of villages selected for MDA

| Cost of screening 272 villages using uPCR | Percentage of villages targeted MDA | Number of villages | Cost of community engagement | Cost of mass treatment | Total cost | Cost per village * | Cost per person reached** |
|------------------------------------------|-----------------------------------|-------------------|----------------------------|-----------------------|-----------|-------------------|---------------------------|
| 541 042                                  | 1%                                | 13                | 56 735                     | 111 551               | 709 328   | 579               | 1.9                       |
| 541 042                                  | 2%                                | 25                | 61 534                     | 155 684               | 758 260   | 618               | 2.1                       |
| 541 042                                  | 3%                                | 37                | 66 332                     | 199 816               | 807 190   | 658               | 2.2                       |
| 541 042                                  | 4%                                | 50                | 71 531                     | 247 626               | 860 199   | 702               | 2.4                       |
| 541 042                                  | 5%                                | 62                | 76 330                     | 291 759               | 909 131   | 742               | 2.5                       |
| 541 042                                  | 6%                                | 74                | 81 128                     | 335 891               | 958 061   | 781               | 2.6                       |
| 541 042                                  | 7%                                | 86                | 85 927                     | 380 024               | 1 006 993 | 821               | 2.8                       |
| 541 042                                  | 8%                                | 99                | 91 126                     | 427 834               | 1 060 002 | 865               | 2.9                       |
| 541 042                                  | 9%                                | 111               | 95 924                     | 471 966               | 1 108 932 | 905               | 3.0                       |
| 541 042                                  | 10%                               | 123               | 100 732                    | 516 099               | 1 157 864 | 944               | 3.2                       |

* Cost per village is estimated by dividing the total cost of targeted MDA by the total number of villages in the four townships (1226 villages). These targeted MDA costs will be shared among all villages in the region because targeted MDA is provided in addition to other malaria interventions, so the total cost is distributed among all villages in the region.

** Cost per person reached is calculated by the total cost divided by the total population in that area (365 000).

MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction

Comparing the programmatic cost of targeted MDA using different infection diagnostic approaches
We estimated the programmatic cost of targeted MDA using different molecular diagnosis methods, such as uPCR, RNA testing and ELISA testing. The unit cost of molecular tests varies, so the programmatic cost of targeted MDA in Kayin State will differ if we use techniques other than the more expensive uPCR method. The percentage of the prevalence survey was kept the same as the MEFT project (22% of all villages); only the percentage of villages where CE and mass treatment were provided was varied. Table 2 shows the comparison of the programmatic cost of targeted MDA using three different molecular diagnosis methods. The unit costs set for the RNA and ELISA tests per sample were US$ 20 and US$ 5, respectively (F. Nosten, personal communication). The total programmatic cost would be decreased by approximately 37% if METF used the ELISA method to identify villages to target for MDA. Similarly, the cost of targeted MDA would be reduced by 9% if uPCR was switched to RNA testing.
Table 2
Detailed costs of targeted MDA using three different molecular assays to identify hotspot villages. Cells are highlighted with different colours to illustrate the areas of equivalent costs in the three strategies.

| Percentage of villages targeted for MDA | Number of villages targeted for MDA | Prevalence survey using uPCR | Prevalence survey using RNA test | Prevalence survey using ELISA test |
|---------------------------------------|----------------------------------|-----------------------------|---------------------------------|----------------------------------|
|                                       |                                  | Total cost                  | Cost per person reached         | Total cost                      | Cost per person reached         |
| 1%                                    | 13                               | 709                         | 1·9                             | 624                             | 1·71                           |
|                                       |                                  | 328                         |                                 | 278                             |                                |
| 2%                                    | 25                               | 758                         | 2·1                             | 673                             | 1·84                           |
|                                       |                                  | 260                         |                                 | 210                             |                                |
| 3%                                    | 37                               | 807                         | 2·2                             | 722                             | 1·98                           |
|                                       |                                  | 190                         |                                 | 140                             |                                |
| 4%                                    | 50                               | 860                         | 2·4                             | 775                             | 2·12                           |
|                                       |                                  | 199                         |                                 | 149                             |                                |
| 5%                                    | 62                               | 909                         | 2·5                             | 824                             | 2·26                           |
|                                       |                                  | 131                         |                                 | 081                             |                                |
| 6%                                    | 74                               | 958                         | 2·6                             | 873                             | 2·39                           |
|                                       |                                  | 061                         |                                 | 011                             |                                |
| 7%                                    | 86                               | 1 006                       | 2·8                             | 921                             | 2·53                           |
|                                       |                                  | 993                         |                                 | 943                             |                                |
| 8%                                    | 99                               | 1 060                       | 2·9                             | 974                             | 2·67                           |
|                                       |                                  | 002                         |                                 | 952                             |                                |
| 9%                                    | 111                              | 1 108                       | 3·0                             | 1 023                           | 2·81                           |
|                                       |                                  | 932                         |                                 | 882                             |                                |
| 10%                                   | 123                              | 1 157                       | 3·2                             | 1 072                           | 2·94                           |
|                                       |                                  | 864                         |                                 | 814                             |                                |

MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction; HS-RDT, highly sensitive rapid diagnostic test; MPW, malaria post worker.
Table 3
The parameters used in the costing model and the value of the parameters used to estimate the costs of *P. falciparum* malaria elimination in Kayin State, Myanmar

| Parameter                                              | Value | Unit       |
|--------------------------------------------------------|-------|------------|
| Programme assumptions                                  |       |            |
| Total number of villages                               | 1 226 | Village    |
| Average village population                             | 250   | People     |
| Project duration                                       | 12    | Month      |
| Village Accessibility                                  |       |            |
| Motorbike                                              | 50    | Percentage |
| Rented car                                             | 50    | Percentage |
| Salaries for central staff                             |       |            |
| General director                                       | 8 000 | US$        |
| Salaries for field staff                               |       |            |
| Team leader                                            | 1 000 | US$        |
| Programme manager’s assistant                          | 500   | US$        |
| Lab staff                                              | 500   | US$        |
| Community health worker                                | 50    | US$        |
| Logistics                                              | 200   | US$        |
| Travel Costs                                           |       |            |
| Travel cost per village via motorbike                  | 25    | US$        |
| Travel cost per village via rented car                 | 100   | US$        |
| Parameters for community engagement (CE)               |       |            |
| Number of days spent in a village for CE               | 1     | Day        |
| Staff involved in CE                                   |       |            |
| Team leader                                            | 0     | Person     |
| Program manager assistant                              | 1     | Person     |
| Helpers/CHWs/ volunteers                               | 2     | Person     |
| Equipment                                              |       |            |

CHW, community health worker; MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction; DHA, dihydroartemisin; PQP, piperaquine phosphate
| Parameter                                                                 | Value | Unit   |
|--------------------------------------------------------------------------|-------|--------|
| Equipment cost per village for one community engagement activity         | 0     | US$    |
| **Consumables**                                                          |       |        |
| Consumables cost per village for community engagement                    | 18    | US$    |
| **Incentives**                                                           |       |        |
| Refreshment costs per village during community engagement activity        | 19    | US$    |
| Costs of community incentives                                            | 4 828 | US$    |
| Number of villages provide with community incentives                      | 3     | Village|
| Out of all villages, the percentage of villages visited for community    | 22    | Percentage|
| engagement                                                               |       |        |
| **Training**                                                             |       |        |
| Number of training sessions for CE activities                             | 7     | Session|
| Number of participants for CE training                                    | 10    | Person |
| Number of trainers for CE training                                       | 2     | Person |
| Duration of a training session for CE activities                          | 2     | Day    |
| **Parameters specific to uPCR**                                          |       |        |
| Percentage of villages surveyed to identify villages for MDA             | 22    | Percentage|
| **Personnel**                                                            |       |        |
| Number of days spent in a village for MDA activity to identify MDA       | 1     | Day    |
| team leader/program manager/supervisor                                   | 0     | Person |
| Program manager's assistant/logistics assistant                          | 2     | Person |
| Laboratory staff                                                         | 0     | Person |
| Helper/CHW                                                               | 2     | Person |
| **Incentives**                                                           |       |        |
| The incentive for a participant to donate blood                           | 1     | US$    |
| Equipment                                                                |       |        |
| The equipment cost per village for mass blood survey activities           | 5     | US$    |
| **Consumables**                                                          |       |        |

CHW, community health worker; MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction; DHA, dihydroartemisinin; PQP, piperaquine phosphate
| Parameter                                                | Value | Unit   |
|---------------------------------------------------------|-------|--------|
| Consumables costs for uPCR tests                        | 1     | US$    |
| uPCR analysis cost per test                             | 25    | US$    |
| Training                                                |       |        |
| Number of training sessions for the uPCR method          | 8     | Session|
| Number of participants for uPCR training                 | 15    | Person |
| Number of trainers for uPCR training                     | 2     | Person |
| Duration of a training session for uPCR                  | 2     | Day    |
| Monitoring and supervision                               |       |        |
| Number of trips for monitoring uPCR activity             | 1     | Trip   |
| Number of days spent monitoring uPCR activity            | 5     | Day    |
| Parameters for mass drug administration                  |       |        |
| Percentage of villages offered MDA activity              | 21    | Percentage |
| Number of MDA rounds in a year                           | 3     | Round |
| Average population coverage for MDA in a round           | 85    | Percentage |
| Personnel                                               |       |        |
| Number of days spent in a village for MDA activity       | 7     | Days   |
| Incentives                                              |       |        |
| The incentive for one participant in a round of MDA activity (US$) | 1 | US$ |
| Travel                                                  |       |        |
| Number of trips to a village for MDA activity (1 round)  | 1     | Trip   |
| Number of trips for car rental during MDA activity (1 round) | 15 | Trips |
| Equipment                                               |       |        |
| Equipment cost per village for MDA activity             | 25    | US$    |
| Consumables                                             |       |        |
| Consumables cost per village for MDA activity           | 20    | US$    |
| Cost of DHA + PQP, blister pack child                   | 0.93  | US$    |

CHW, community health worker; MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction; DHA, dihydroartemisinin; PQP, piperaquine phosphate
| Parameter                                           | Value | Unit   |
|-----------------------------------------------------|-------|--------|
| Cost of DHA + PQP, blister pack youth               | 1.46  | US$    |
| Cost of DHA + PQP, blister pack adult               | 1.98  | US$    |
| Cost of primaquine base 7.5 mg tablet                | 0.01  | US$    |
| Cost of medicine for the treatment of side-effects   | 39    | US$    |
| Antimalarial drug wastage                           | 5     | Percentage |

**Training**

| Parameter                                           | Value | Unit   |
|-----------------------------------------------------|-------|--------|
| Number of training sessions for MDA                 | 8     | Session |
| Number of participants for MDA training             | 10    | Person |
| Number of trainers for MDA training                 | 3     | Person |
| Duration of a training session for MDA              | 3     | Day    |

**Monitoring and supervision**

| Parameter                                           | Value | Unit |
|-----------------------------------------------------|-------|------|
| Number of monitoring trips for MDA (1 round)        | 1     | Trip |
| Duration of monitoring trips for MDA (1 round)      | 10    | Day  |

CHW, community health worker; MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction; DHA, dihydroartemisinin; PQP, piperaquine phosphate

**Discussion**

The malaria map is shrinking in both Kayin State [23] and the whole of Myanmar [25]. Myanmar has set a goal to interrupt transmission and eliminate *P. falciparum* malaria from the entire country by 2025 [26]. Malaria elimination requires a substantial level of investment, especially for detecting and responding to small numbers of remaining malaria cases [27]. Which malaria intervention packages to use and the resources needed to eliminate this disease nationally and sub-nationally is a challenging question for a developing country that largely relies on external funding to achieve this goal.

Malaria case management and intensive vector control are core interventions in malaria control, but achieving elimination goals is likely to require other population wide measures, particularly in the context of increasing multi-drug resistant malaria. A population-wide, medicine-based strategy, such as MDA, can accelerate the reduction in transmission [28]. Several targeted MDA projects have been conducted in the GMS, including in Kayin State [13], and have been shown to reduce the incidence and prevalence of malaria [14, 29]. The implementation of targeted MDA, however, requires a significant investment in terms of resources and time to mobilise the targeted villages. The higher cost relative to standard approaches
to malaria control and elimination was considered an acceptable given the risk of multi-drug resistance and the measures deemed necessary to address this.

The cost of identifying target villages was the largest contributor in this cost analysis. When the prevalence of malaria is declining, its management is focused on subclinical infection. In low transmission settings, asymptomatic infection dynamics should be adequately identified using highly sensitive diagnostic methods. Molecular techniques are more sensitive than other diagnostic methods. The detection limit of PCR is approximately 22 parasites per mL. METF used high-volume uPCR to identify villages to target for MDA. An alternative assay to uPCR, such as RNA or ELISA, would reduce the cost of the prevalence survey while maintaining sufficient sensitivity [30].

Studies on the cost of deploying malaria MDA are limited, with one study examining the delivery costs of MDA in two island settings and an emergency setting [16]. The average cost per person reached for three rounds of MDA conducted in Comoros, Vanuatu and Sierra Leone were estimated at US$ 42·39, 17·85 and 3·93, respectively. These costs were higher than our estimated cost per person reached for three rounds of targeted MDA. Recently published article evaluated the cost-effectiveness of focal MDA and MDA in Zambia [31] estimated the cost per person reached for MDA was 9·42, which was also higher than our estimate costs of MDA.

In Southeast Asia, only two countries have been declared malaria-free, the Maldives (2015) and Sri Lanka (2016). Both are likely to have benefitted from their geographical isolation. Looking back on the success story in Sri Lanka, it took decades of effort with a multidimensional approach that included combined vector control, case management and disease surveillance. A genomic epidemiology study that collected data from 2008 to 2018 [32] revealed that the spread of multi-drug resistant *P. falciparum* malaria in GMS countries was accelerating, highlighting the urgent need to adopt an effective strategy to eliminate malaria. Recently published studies [9, 13, 29, 33] suggest that targeted/focal MDA with a high degree of community participation can rapidly reduce malaria infections to zero when used in conjunction with intensive vector control and standard case management. There was no significant increase in any of the genetic markers for resistance after MDA [29]. The components necessary for a successful integrated malaria elimination strategy are predicted to be highly dependent on the setting [34], and Myanmar is expected to require MDA or other more intensive interventions.

Policymakers must therefore consider a trade-off between investing in rapid elimination strategies that might stave off the threat of resurging drug resistant malaria, or slower (and cheaper) elimination strategies. GMS countries need to buy time to halt the spread of multi-drug resistant malaria while new antimalarial are developed. This analysis provides the added cost of targeted MDA to rapidly eliminate malaria on top of existing malaria surveillance and control costs. We estimated the programmatic cost of targeted MDA in Kayin State using financial data from the METF implementation, and developed a malaria mass intervention costing tool to support policy decisions towards *P. falciparum* malaria elimination in other settings. The key features of this costing tool are its ease of use, the flexibility to
explore different targeting strategies, and the cost predictions for any single malaria intervention or package of interventions.

The costing tool was designed based on the targeted MDA initiative in Myanmar; nonetheless, the tool can also be used to predict programmatic costs in other GMS countries, by adjusting the unit costs of resources and the proportion of villages undergoing interventions. For example, the tool could be deployed in other regions in Myanmar, such as Chin state, where *P. falciparum* malaria incidence and mortality is high in comparison with other regions [25]. The added benefit, beyond addressing the multi-drug resistance issue, would be the additional lives saved by accelerating elimination to a date earlier than 2030. Table 1 allows the exploration of the cost implications of delivering this programme in a higher prevalence setting, which would probably mean a higher number of villages fulfilling the conditions for being designated a hotspot. Table 2 allows the exploration of the trade-off between costs and the use of cheaper alternative screening options.

There are several limitations to this cost analysis. Different teams providing MDA include staff members of differing levels of seniority, so there may be some variations in estimating staff costs. However, this variation between MDA teams is negligible. As the percentage of villages provided with MDA increases, programme managers have the option of training more staff or using their existing team for an extended period. In our cost estimation, we used the same team to provide MDA. Cost variations may result if a programme manager makes the trade-off of recruiting more staff to complete MDA in less time. The targeted MDA initiative in this cost analysis was operated by a Thailand-based organisation. Therefore, staff compensation and travel costs to access the villages were based on staff travelling from the Thai side, so some cost variations will be seen if villages were accessed from the Myanmar side. However, this variation would be minimal, since most of the costs were incurred within the country.

Our costing model can predict the costs of a particular malaria elimination package design, but cannot make any assurances on the likelihood of success of such a package in achieving elimination elsewhere. It is designed to be used in concert with detailed knowledge of the target area and/or with mathematical models that can simulate the impact of various strategy designs on the prevalence and incidence of malaria [34].

**Conclusions**

This cost analysis quantifies the costs of accelerating *P. falciparum* malaria elimination. Such cost analysis makes a useful contribution to determine the level of resources required to clear the residual malaria parasite reservoir. It also provides a framework for projecting the cost of similar programmes in settings with different epidemiology and/or the exploration of the cost of alternative designs. The study demonstrated the use of financial data from MDA research to project the programmatic implementation cost of MDA with a different number of targeted villages.

**Abbreviations**
MDA: Mass drug administration
GMS: Greater Mekong Subregion
WHO: World Health Organization
METF: Malaria Elimination Task Force
uPCR: ultrasensitive polymerase chain reaction
US$: United States dollars
RDT: rapid diagnosis test
CE: community engagement
ELISA: Enzyme-linked Immunosorbent Assay
CHW: community health worker
DHA: dihydroartemisinin
PQP: piperaquine phosphate

**Declarations**

**Availability of data and materials**

The datasets used and/or analysed during this cost analysis are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

Ethical approval was granted by the Faculty of Tropical Medicine, Mahidol University, Thailand (TM-ORS 021/2018). Permission to conduct the study was obtained from the Malaria Elimination Task Force. We collected only secondary data from the Finance department.

**Consent for publication**

Not applicable

**Competing interests**

None of the authors declare any competing interests.

**Funding**
The Wellcome Trust of Great Britain and the Bill and Melinda Gates Foundation supported this cost analysis. However, the funding organisations had no role in the design of the study, analysis, interpretation of data and in the writing of the manuscript.

Authors’ contributions

SSK, TD, WP, YL, LJW, and FN were involved in designing the study. SSK and TD performed the financial data collection. SSK and WP analysed the costs of targeted MDA. SSK and OC developed the costing tool. SSK, WP, RJM, and LJW wrote the original draft. All authors have read and approved the final manuscript.

Acknowledgements

We would like to thank all field staff at SMRU, who explained the nature of the MDA project to participants. English language support was provided by Adam Bodley of Impact Factor Editing.

References

1. World Health Organisation: Global Technical Strategy for Malaria, 2016-2030. 2015.
2. Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, et al. Spread of artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2014; 371(5):411-423.
3. Six Mekong Nations call for accelerated action to eliminate malaria before 2030 [https://mohs.gov.mm/Main/content/new/six-mekong-nations-call-for-accelerated-action-to-eliminate-malaria-before-2030]
4. World Health Organisation. Consideration of Mass Drug Administration for the containment of artemisinin-resistant malaria in the Greater Mekong Subregion. 2010.
5. Newby G, Hwang J, Koita K, Chen I, Greenwood B, von Seidlein L, et al. Review of mass drug administration for malaria and its operational challenges. Am J Trop Med Hyg. 2015; 93(1):125-134.
6. Morris U, Msellem MI, Mkali H, Islam A, Aydin-Schmidt B, Jovel I, et al. A cluster randomised controlled trial of two rounds of mass drug administration in Zanzibar, a malaria pre-elimination setting-high coverage and safety, but no significant impact on transmission. BMC medicine. 2018; 16(1):215.
7. Lwin KM, Imwong M, Suangkanarat P, Jeeyapant A, Vihokhern B, Wongsaen K, et al. Elimination of Plasmodium falciparum in an area of multi-drug resistance. Malar J. 2015; 14:319.
8. Adhikari B, Pell C, Phommasone K, Soundala X, Kommarasy P, Pongvongs T, et al. Elements of effective community engagement: lessons from a targeted malaria elimination study in Lao PDR (Laos). Glob Health Action. 2017; 10(1):1366136.
9. Tripura R, Peto TJ, Chea N, Chan D, Mukaka M, Sirithiranont P, et al. A Controlled Trial of Mass Drug Administration to Interrupt Transmission of Multidrug-Resistant Falciparum Malaria in Cambodian
Villages. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018; 67(6):817-826.

10. Peto TJ, Tripura R, Davoeung C, Nguon C, Nou S, Heng C, et al. Reflections on a Community Engagement Strategy for Mass Antimalarial Drug Administration in Cambodia. The American journal of tropical medicine and hygiene. 2018; 98(1):100-104.

11. Deng C, Wang Q, Zheng S, Zhou C, Gao Y, Guo J, et al. Mass Drug Administration of Artemisinin-piperaquine on High Malaria Epidemic Area. Trop Med Health. 2014; 42(2 Suppl):33-41.

12. Ali AS, Thawer NG, Khatib B, Amier HH, Shija J, Msellem M, et al. Artemisinin combination therapy mass drug administration in a setting of low malaria endemicity: programmatic coverage and adherence during an observational study in Zanzibar. Malar J. 2017; 16(1):332.

13. Landier J, Parker DM, Thu AM, Lwin KM, Delmas G, Nosten FH, et al. Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on Plasmodium falciparum malaria in Eastern Myanmar: an observational study of a regional elimination programme. Lancet. 2018; 391(10133):1916-1926.

14. von Seidlein L, Peto TJ, Landier J, Nguyen TN, Tripura R, Phommasone K, et al. The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial. PLoS Med. 2019; 16(2):e1002745.

15. White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions–a systematic review. Malar J. 2011; 10:337.

16. World Health Organisation. Review of delivery cost data on mass drug administration for malaria. 2015.

17. Turner HC, Toor J, Bettis AA, Hopkins AD, Kyaw SS, Onwujekwe O, et al. Valuing the unpaid contribution of community health volunteers to mass drug administration programs. Clin Infect Dis. 2018.

18. Turner HC, Toor J, Hollingsworth TD, Anderson RM. Economic Evaluations of Mass Drug Administration: The Importance of Economies of Scale and Scope. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018; 66(8):1298-1303.

19. UN Habitat: Climate Profile, Myanmar. 2018.

20. Jolliffe K: Ceasefires, Governance and Development: The Karen National Union in Times of Change. 2016.

21. Luxemburger C, Thwai KL, White NJ, Webster HK, Kyle DE, Maelankirri L, et al. The epidemiology of malaria in a Karen population on the western border of Thailand. Trans R Soc Trop Med Hyg. 1996; 90(2):105-111.

22. Imwong M, Nguyen TN, Tripura R, Peto TJ, Lee SJ, Lwin KM, et al. The epidemiology of subclinical malaria infections in South-East Asia: findings from cross-sectional surveys in Thailand-Myanmar border areas, Cambodia, and Vietnam. Malar J. 2015; 14:381.

23. Malaria Elimination Task Force. Activity Report Update May 2014 to December 2019. 2020.
24. Imwong M, Hanchana S, Malleret B, Renia L, Day NP, Dondorp A, et al. High-throughput ultrasensitive molecular techniques for quantifying low-density malaria parasitemias. J Clin Microbiol. 2014; 52(9):3303-3309.

25. Mu TT, Sein AA, Kyi TT, Min M, Aung NM, Anstey NM, et al. Malaria incidence in Myanmar 2005-2014: steady but fragile progress towards elimination. Malar J. 2016; 15(1):503.

26. World Health Organisation. Strategy for malaria elimination in the Greater Mekong Subregion (2015-2030). 2015.

27. Shretta R, Avancena AL, Hatefi A. The economics of malaria control and elimination: a systematic review. Malar J. 2016; 15(1):593.

28. Geneva: World Health Organisation: A framework for malaria elimination. 2017.

29. Landier J, Kajeechiwa L, Thwin MM, Parker DM, Chaumeau V, Wilaiphaingern J, et al. Safety and effectiveness of mass drug administration to accelerate elimination of artemisinin-resistant falciparum malaria: A pilot trial in four villages of Eastern Myanmar. Wellcome Open Res. 2017; 2:81.

30. Tedla M. A focus on improving molecular diagnostic approaches to malaria control and elimination in low transmission settings: Review. Parasite Epidemiol Control. 2019; 6:e00107.

31. Yukich JO, Scott C, Silumbe K, Larson BA, Bennett A, Finn TP, et al. Cost-Effectiveness of Focal Mass Drug Administration and Mass Drug Administration with Dihydroartemisinin–Piperaquine for Malaria Prevention in Southern Province, Zambia: Results of a Community-Randomized Controlled Trial. 2020.

32. Hamilton WL, Amato R, van der Pluijm RW, Jacob CG, Quang HH, Thuy-Nhien NT, et al. Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study. Lancet Infect Dis. 2019; 19(9):943-951.

33. Parker DM, Landier J, Thu AM, Lwin KM, Delmas G, Nosten FH, et al. Scale up of a Plasmodium falciparum elimination program and surveillance system in Kayin State, Myanmar. Wellcome Open Res. 2017; 2:98.

34. Gao B, Saralamba S, Lubell Y, White LJ, Dondorp AM, Aguas R. Determinants of MDA impact and designing MDAs towards malaria elimination. Elife. 2020; 9.

Figures
Figure 1

The screenshot of mass malaria intervention costing tool

![Programmatic cost of targeted MDA in Kayin State](image)

Figure 2

The total cost of targeted mass drug administration in Kayin State, based on financial data provided by the Malaria Elimination Task Force MDA, mass drug administration; uPCR, ultrasensitive polymerase chain reaction

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformation.pdf