Myanmar Artemisinin Monotherapy Replacement Malaria Project (AMTR) Independent Evaluation

Working Paper 1 – March 2015

Sensitivity analysis of the calculation of Disability Adjusted Life Years (DALY) averted in the context of the AMTR project

Initial Findings from the AMTR Project

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ABSTRACT

As a part of the independent evaluation of the Artemisinin Monotherapy Replacement (AMTR) Project in Myanmar, implemented by Population Services International (PSI) and co-funded by the UK Department for International Development (DFID), the Bill and Melinda Gates Foundation (BMGF), and Good Ventures, a sensitivity analysis of the estimated disability-adjusted life years (DALYs) averted by the project was undertaken. The purpose of the work was to create discussion and awareness about the limitations of the DALY as an impact assessment tool in general and specifically in the context of the project evaluation.

Analysis was done in two major steps:

1. A basic DALY model was constructed, which was similar, but not identical, to what was applied for the AMTR business case in order to be used for a sensitivity and scenario analysis of the major input variables; and
2. Probabilistic models were used (in the statistical software package R) to further explore the range of uncertainty; impact of calculation method; and sensitivity of key input variables in a baseline (no Artemisinin-based Combination Therapy [ACT]) and full scale-up scenario.

Findings from the sensitivity analysis can be summarized as follows:

- The recreated calculations using the AMTR DALY model resulted in 160,712 DALYs averted cumulatively as compared to the 161,420 in the PSI proposal.
- In addition to malaria mortality, ACT coverage proved to be one of the most sensitive variables in the one-way sensitivity analysis using the AMTR DALY model. It showed that DALYs averted in Myanmar would reduce to just over 20,000 if effective ACT coverage was reduced to 10%.
- The probabilistic model suggests a cumulative value of approximately 125,000 DALYs averted with a 50% credibility interval of 70,000-170,000.
- In addition to a high level of uncertainty around the DALY estimates, the modelling also showed significant influence of whether or not age-weighting and/or discounting is used; reducing the contribution of a single infant death from 82.5 years of life lost to 36.1 years if age-weighting and discounting is applied and to 31.3 years if only discounting is applied.
- An incidence-based, stochastic DALY estimation model provided as part of the R statistical software provides similar results, yielding approximately 50% reduction of DALYs accrued per year in Myanmar in full ACT scale-up, which would also result in slightly lower overall DALYs averted compared to the original AMTR calculations.
- This model also suggests that the duration of disease, malaria incidence, and mortality are the most sensitive variables for the DALY estimation in the full ACT scale-up scenario.

The following major conclusions can be presented from this work:

- ACT coverage, malaria incidence, and mortality are among the most influential variables in the determination of the number of DALYs averted within Myanmar by the AMTR project. However, it appears most likely that the DALYs averted within Myanmar will be significantly lower than the 161,000 estimated for the end of the project as mentioned in the proposal.

- Given the significant impact that the methodological approach has on the resulting DALYs averted a careful discussion of the importance and/or role of a DALYs averted estimation and – in case of inclusion – consideration of which methodology should be applied (e.g. age-weighting and/or discounting, comparison to a treatment with zero or non-zero effect) should precede the end-of project evaluation.

ABBREVIATIONS AND ACRONYMS

ACT	Artemisinin-based Combination Therapy
AMT	Artemisinin Monotherapy
AMTR	Artemisinin Monotherapy Replacement (project)
BMGF	Bill and Melinda Gates Foundation
DALY	Disability-Adjusted Life Years Lost
DFID	(UK) Department for International Development
HALE	Health-Adjusted Life Expectancy
HALY	Health-Adjusted Life Years
PSI	Population Services International
PYLL	Potential Years of Life Lost
QALY	Quality-Adjusted Life Years
RDT	Rapid Diagnostic Test
WHO	World Health Organization
YLD	Years Lost to Disability
YLL	Years of Life Lost

1. BACKGROUND

In recent years it has been found that the *Plasmodium falciparum (P. falciparum)* malaria parasite has developed resistance to derivatives of artemisinin in Southeast Asia. Artemisinin is typically used in combination with other anti-malarials (as Artemisinin-based Combination Therapy [ACT]) and is currently the most efficient treatment for malaria [1]. Given the history of the emergence of anti-malarial drug resistance in this area and how easily this resistance spreads to all other malaria-endemic areas, particularly Africa with its 'lion's share' of *P. falciparum* attributable morbidity and mortality, the international community has become aware of the urgent need to support countries in the Greater Mekong Region in controlling and eventually eliminating malaria caused by *P. falciparum*. It is expected that these efforts will result in the containment of the threat of artemisinin resistance.

The private sector plays a significant role in the provision of anti-malarials in many countries in the Greater Mekong Region. As a result, activities have now been extended outside of interventions implemented by the public sector to support efforts to contain artemisinin resistance. For example, in 2010 it was estimated that approximately 60% of anti-malarial drugs were sourced from the commercial market in Myanmar. A very high proportion of these medicines were Artemisinin-based Monotherapy (AMT) given in insufficient doses rather than quality ACTs. It is believed that the use of AMT favours the emergence of drug resistance due to the increase in drug pressure and survival of resistant parasite strains. In order to address this issue, the UK government through its Department for International Development (DFID) and the Bill and Melinda Gates Foundation (BMGF) financed a project, with the support of Good Ventures, to replace AMT with quality assured ACT in the private sector in Myanmar through the international NGO Population Services International (PSI). The implementation of this project (Artemisinin Monotherapy Replacement Project (AMTR) as it is called in short) began in March 2012 and is expected to run until March 2016.

In order to allow an objective external assessment of the AMTR project, DFID commissioned an independent project which started its monitoring and evaluation (M&E) activities in June 2013 with the development of the evaluation framework, an initial assessment, and work plan development. As part of this independent evaluation, the team is developing a series of case studies and working papers that are meant to complement the AMTR project by highlighting critical issues, summarizing lessons learnt, and addressing issues relevant to the evaluation. While the case studies are addressing a broader audience interested in public health matters, the working papers are designed for a more technical audience.

This working paper addresses issues related to the use of disability-adjusted life years (DALYs); not only as a part of the AMTR project evaluation but also as a tool to assess and compare the impact of a project or intervention and its value for money in general. Conclusions reached in this working paper were based on a sensitivity analysis undertaken on DALY estimations very similar to those initially used by PSI and DFID during the AMTR project design. The analysis conducted determined which variables influence the resulting DALY outcome the most. The working paper also looks at the use of the DALY in public health and the issues that are being discussed concerning its

interpretation. The paper concludes with a discussion of what the findings might imply for the project evaluation.

2. THE DALY AND ITS USE IN PUBLIC HEALTH

For many years economists and public health experts have struggled to find and agree on a composite metric that expresses the importance or impact of a disease in a given society or environment in a single figure. Many methodologies and metrics[1] have been developed to describe disease burden due to both mortality and morbidity; to allow priorities to be set for interventions; and to link in cost effectiveness or value for money across diseases, regions and/or disciplines. Among the measures explored were the 'potential years of life lost' (PYLL) that would only look at the mortality aspect, as well as metrics that include quality aspects of life before death: 'quality adjusted life years' (QALY), 'health adjusted life years' (HALY), and 'health adjusted life expectancy' (HALE) [2,3]. The 'disability-adjusted life years' (DALY), however, is the metric that has prevailed and established itself in international global health policy and practice. The DALY was developed in the early 1990s as part of the World Bank and WHO burden of disease project [4-5] and it continues to be used widely in the public health sector.

The concept of the DALY is to present a single indicator of health status that allows a standardized and simple way to:

- Aid in setting health services and research priorities;
- Aid in identifying disadvantaged groups and targeting of health interventions; and
- Provide a comparable measure of output for interventions, programmes and sector evaluation and planning [4].

The DALY is composed of two elements, namely:

1. Life time lost due to premature death, expressed as years of lost life (YLL); and
2. Time spent with a disability due to that disease or disease group, expressed as years lost to disability (YLD) [3, 4].

The years of lost life are estimated from the age of death and a standard table of life expectancy, while the years lost to disability are calculated based on the years lived with a disability weighted to reflect the reduction in functional capacity of the individual [3,4]. Prior to the summation of the components that yield a DALY value, years lost are adjusted using a set of 'value choices' [4] which "weight time lived at different ages and different time periods differently (through age-weighting and discounting respectively)" [2].

The proponents of the DALY have argued that this system is fair since it allows like-with-like comparison and makes the social values that invariably enter into the prioritisation of funding or programming explicit and open to adjustment as part of a consensus process [5]. Indeed, the disability weights used have been adjusted over time [6] as has the way the DALYs are calculated [7]. However, critics of the DALY have argued that, "the conceptual and technical basis for DALYs is flawed and that the assumptions and value judgements underlying it are open to serious question" [2]. In their argument they distinguish between the two principle uses of the DALY, the measurement of the 'burden of disease'

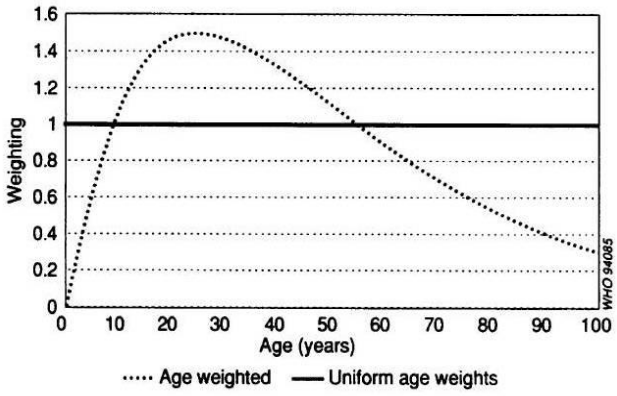
[1] Among the measures explored were the 'potential years of life lost' (PYLL) that would only look at the mortality aspect, as well as metrics that include quality aspects of life before death: 'quality adjusted life years' (QALY), 'health adjusted life years' (HALY), and 'health adjusted life expectancy' (HALE) [2,3]

and allocation of resources. These are further discussed below:

1. The DALY claims to represent the overall 'burden' of disease or health conditions while actually only being an "aggregate quantity of ill-health" [2]. To assess the 'true' burden to society, other factors would have to be taken into account in addition to merely age and sex, such as support through public services, private incomes and family or friends. This would then better incorporate the circumstances of individuals experiencing ill health and the way they are able to cope with it, and would therefore better reflect the actual 'burden' of illness [2]. When this principle is applied to the resource allocation task, it implies that dimensions such as income and socio-economic status are important criteria allowing, for example, a higher resource allocation to vulnerable or difficult to reach groups irrespective of their quantitative contribution to ill health. The DALY framework, in failing to include such dimensions, is considered inadequate.

2. The age-weighting assigns different relative values to the time lost through disability or premature death based on age (see Figure 1) with the peak value at 24.5 years. While this is thought to "capture different social roles at different ages" [4], critics argue that this approach is not only arbitrary, as it would not equally apply to different social groups or societies, but it also implies that for a health condition of constant duration more DALYs would be averted in treating a young adult than an infant. Taking these factors into consideration and if minimizing aggregate DALYs is the criterion for resource allocation as suggested, the resulting outcomes are inequitable and ethically unacceptable. The same argument is made for discounting which similarly values time lost less if it occurs at young or old age. Consequently, these critics feel that "in measuring an individual's contribution to the burden of disease, age and time period are irrelevant distinctions to make [2].

Figure 1: Age-weighting function as presented in the original DALY presentation by Murray [4]



The other issues being discussed pertaining to the use of the DALY metric, are the strengths and limitations of having a single comparative measure and the use of standard disability weights and life tables across all countries and settings. On the one hand this approach strengthens the DALY as a tool to serve as the measure for its first application in 1994 for the global burden of disease study [4,5]. However on the other hand, its use can distort reality if the local parameters deviate significantly from the generalized global parameters. For example, life expectancy in many developing countries is significantly lower than the global average and by applying the latter implicitly assumes that if only ill-health issues were to be addressed, life expectancy would automatically reach levels of developed countries [2] despite the fact that there are many other influences on life

expectancy other than health. Similarly, by comparing DALYs averted or cost per DALY averted using such standardized parameters across countries, an easy and seemingly better comparison is obtained. However, the comparison of the DALYs averted is based on the assumptions made by the model. In the case of the Myanmar AMTR project, would the DALYs averted based on an estimate of malaria in children under 5 (which can easily be compared to any country in Africa), actually give us a realistic picture of the impact if most of the malaria disability and deaths actually occurred in adults?

Finally, there is also uncertainty around the DALY estimates to be considered [8]. These can be divided into four major pillars [9]:

1. Variability in sampling data that goes into the estimate;
2. Variability between the different methods used to calculate the DALY;
3. Uncertainty in the extrapolation of results; and
4. Uncertainty on generalising the results to other populations.

The first two are directly related to the estimation of the DALY. One of the basic approaches to do this is conducting a sensitivity analysis where one or more alternative assumptions are used to estimate the DALY without, however, taking into account the actual probability of these assumptions [8]. Alternatively, probabilistic models can be used that frequently apply Monte Carlo simulations[2] to obtain a realistic picture of the probability of certain results and their range [8]. Although the use of some level of sensitivity analysis is recommended as the standard procedure to use DALYs for cost-effectiveness analysis [3], this is not always the case in public health debates where the complexities that a simple metric, such as the DALY is attempting to summarise, sometimes tend to be forgotten, and the limitations that such a simplification invariably has.

In spite of all the debate and potential criticism, the DALY has become the most commonly used measure of the global 'burden of disease', even though significant changes have been made over time, including the most recent estimation of DALYs without age-weighting and discounting [7]. DALYs also feature highly in the assessments of support to developing countries provided by the UK government through DFID [10], and are a critical aspect of project business cases and evaluations.

[2] Monte Carlo experiments are a broad class of computational algorithms that rely on repeated random sampling to obtain numerical results. Typically one runs simulations many times over in order to obtain the distribution of an unknown probabilistic entity. The name comes from the resemblance of the technique to the act of playing and recording results in a casino. (https://en.wikipedia.org/wiki/Monte_Carlo_method)

3. DALY ESTIMATES FOR THE AMTR PROJECT AND THE PSI APPROACH

The estimation of DALYs averted is a significant aspect of the PSI proposal to DFID and BMGF (Annex P) as well as the DFID business case.

Two separate aspects were considered:

1. DALYs averted within Myanmar through direct project impact; and
2. DALYs averted globally by stopping the spread of resistance to Africa.

The major results presented are the following:

Expected DALY averted in Myanmar: 161,420
Expected DALY averted in Africa: 6,225,910
Cost per DALY averted in Myanmar: US$195.99
Cost per DALY averted globally: US$4.95

In addition, the DFID business case estimates that at least 223,776 DALYs averted needed to be reached in order to meet the WHO guidance of US$ 150/DALY averted for a recommended intervention.

The DALY estimations for the AMTR project were done using the standard PSI ACT DALY model, in use at the time of proposal writing, as a starting point. This model does not include ACT coverage but rather calculates the DALY per ACT treatment course given and then applies this rate to the number of ACT courses expected to be delivered or actually delivered. The DALY per ACT course in turn is obtained in two steps:

- Calculation of the number of malaria cases treated per ACT course as

*(1 – wastage) * adherence rate * clinical efficacy of ACT * diagnostic specificity (proportion of fever cases confirmed as malaria)*

- Calculation of the Years of Life Lost (YLL) per ACT as

*Malaria cases treated per ACT course issued * case fatality rate * discounted life years lost to malaria*

The model was originally developed to capture the DALY averted per ACT course in children 0-4 years and used an average age at death of that age group in the specific country and a standard life expectancy of 81.5 years. In view of the differing malaria epidemiology in Myanmar the DALY estimate for children under 5 was reduced by 44% to adjust for the main burden among older age groups. To arrive at the final number of DALYs averted expected from the AMTR project, i.e. applying the DALY averted per ACT course to the number of expected ACT treatments delivered, PSI made a number of additional adjustments[3]

- To ensure that DALYs averted were only applied to confirmed cases;
- To include an estimated decline in malaria incidence during the project durations based on the MARC plan related activities;
- To take into account that a partial course will have a lower effect (by 45%) due to recrudescence; and
- To factor in a lower proportion of full courses given outside the primary target area of AMTR interventions.

Since then PSI has changed their methodology to calculate DALYs averted associated with their products. The new model still calculates DALY per ACT course as principle output but uses the Lives Saved Tool (LiST)[4] to estimate the deaths averted per ACT course which is then converted to DALY per ACT course. The country specific settings in LiST include population size, malaria mortality, and effectiveness. As per the previous approach, this model only considers children 0-4 years.

[3] See Annex P of AMTR proposal for details
[4] http://livessavedtool.org

4. SENSITIVITY ANALYSIS

For this working paper we have focused only on a sensitivity analysis of the in-country DALYs averted by the AMTR project to show and discuss the range of results that could be obtained by a similar basic approach as used in the project. The value of discussing aspects of the potential (but difficult to quantify) global impact of the AMTR project in preventing the spread of artemisinin resistance to Africa will be part of the final, independent project evaluation.

4.1. Methodology

In order to address the potential sensitivity of DALY averted calculations to the various assumptions and parameters, several approaches to sensitivity analysis have been adopted and implemented. These include:

- One-way sensitivity and scenario analysis;
- Probabilistic sensitivity analysis using a DALY model similar, but not identical to that used by PSI to calculate deaths and DALYs averted by ACT distribution; and
- Utilizing DALY methods which include or exclude discounting.

Although the original estimations for the AMTR project were done over a three year schedule, we have used the updated project duration of four years. However, since the additional year is gained through a 'no-cost extension' this does not impact the overall cost per DALY averted.

4.1.1. The AMTR DALY calculation model

As previously mentioned, the PSI DALY model does not include ACT coverage as an input but only calculates the DALY averted per ACT course and then multiplies this with the planned or actual ACT distributed, i.e. the ACT coverage or estimated ACT doses delivered is applied *post hoc*. Since such a model would not allow estimating the impact of coverage on the DALY outcome, a basic DALY model was created that is not identical to the PSI model used for the AMTR project, but similar enough for the purposes of this analysis. The model was termed the AMTR DALY model and calculated as follows:

$$DeathsAverted = BaselineMortality \times \frac{ACTeffectiveness \times (Coverage_2 - Coverage_1)}{(1 - (ACTeffectiveness * Coverage_1))}$$

DALYs Averted are then calculated based on the following steps:

$$YLL = DeathsAverted \times YLLperDeath$$

$$YLD = YLL \times YLDperYLL \times YLDfraction$$

$$DALYsAverted = YLL + YLD$$

The terms used in equations listed above are defined below:

- *BaselineMortality* – number of deaths in the population at risk due to malaria
- *ACTeffectiveness* – effectiveness of ACTs to prevent mortality if received
- $Coverage_2$ – coverage at the second time point
- $Coverage_1$ – coverage at the time that baseline mortality is estimated
- *YLL* – years of life lost which are averted due to the change in coverage of ACTs
- *YLL per death* – expected additional years of life that would have been lived by a person who died due to malaria. In the case of the PSI model this is restricted to children under five and a life expectancy at the time of death is assumed to be 82.5 years
- *YLD* – years of (healthy) life lost to disability averted by the change in ACT coverage. It is calculated by applying a

ratio of YLL:YLD from the Global Burden of Disease study [4], then assuming that only a portion of these (50% - the *YLDfraction*) are actually averted because treatment is not immediately applied after symptom onset, and thus multiplying the YLL first by *YLDperYLL* and then by the *YLDfraction*[5]

The YLD and YLL are summed to a number of total DALYs estimated to be averted due to the change in ACT coverage from Time Point 1 (baseline) to Time Point 2. These are finally related to the total number of ACTs which were delivered, to calculate the following relative measures:

- Deaths averted per ACT course; and
- DALYs averted per ACT course.

The model then calculates the number of deaths potentially averted by a scale-up to an anticipated coverage, and the number of ACT courses required to achieve this scale-up by the following relationship:

$$
\begin{aligned}
&ACTs \\
&= MI_{U5} \times ACT_{wastage} \\
&\times ACT_{misuse} \\
&\times (Coverage_2 - Coverage_1) \\
&\times PopulationSize
\end{aligned}
$$

In using the equation above *ACTs* are the total courses of ACTs required to achieve scale up assuming:

- MI_{U5} – malaria incidence among the under-five population
- $ACT_{wastage}$ – one plus the wastage rate of ACTs
- ACT_{misuse} – one plus the fraction of malaria negative patients given ACTs
- *Coverage* indicators – those assumed before and after intervention
- *PopulationSize* – number of persons in the population considered (ordered to be on the same scale as the malaria incidence estimate).

This formula is used to estimate the number of DALYs or deaths averted per ACT course distributed.

4.1.2. Assumptions and alternatives to the AMTR DALY model

Typically, all relative costs or resources to affect evaluations and models will require a number of assumptions or have alternative approaches. Even when the models are appropriate and well parameterised, there are often alternative approaches or parameterisations which could have been applied. Whether the approach or parameters chosen are appropriate will depend ultimately on the question that the assessment is meant to answer. The consequence of a broad applicability of a modelled scenario is that it is less able to accurately estimate the numbers of DALYs averted in a specific setting than it is to provide 'fair' comparisons of the impacts of ACT scale up in settings, e.g. ranging from Asia to the Americas and Africa. This is exemplified by the use of a general life table across all malaria settings. The main assumptions of the AMTR model can be broken down to two main groups, parameter estimates and model structural assumptions.

Parameter Estimates

All model parameters including the baseline mortality, ACT effectiveness, ACT wastage, life expectancy, and others may be subject to measurement error and bias. Furthermore, some assumptions for parameter estimates in the AMTR model are taken from global data

[5] The PSI calculations for the AMTR proposal set the YLD to 0 arguing that ACTs treat malaria but do not prevent it. We did not follow this argument in our AMTR model. However, the YLD component is very small for malaria and does not significantly impact on the outcome

(such as the GBD study for the YLD: YLL ratio, the effectiveness estimates for ACTs at mortality prevention and life expectancy). While all estimates, including global ones, are subject to measurement error (composed of precision and bias errors), global estimates may also be improper for use in a specific location.

Structural Assumptions

The AMTR model presented here makes a number of structural assumptions which could have an effect on the outcomes of the model as well as the ability to compare those outcomes to other estimates of the DALYs averted by the scale up of ACTs. There are several major assumptions which include but are not limited to:

- The model assumes a constant age of death and that ACT scale up will not affect malaria transmission;
- The model calculates YLL in the DALY calculation using an approach that does not include age-weighting. This has been hotly debated in the past but is currently general practice in Global Burden of Disease calculations;
- The model relies on a linear, non-dynamic model of malaria incidence and mortality. This formulation is more akin to a chronic disease than an infectious disease with complicated temporal dynamics and non-linearity. In other words, the model assumes that in the absence of changes in ACT intervention coverage, malaria mortality will be exactly the same in each time period, and the level in the previous time period has no 'carry over' effects in upcoming time periods. It also assumes that malaria incidence will remain constant regardless of ACT intervention level (or any other factors); and
- The model calculates YLD by applying a simple ratio to the YLL based on the GBD study rather than directly from a model of malaria incidence.

  For the purpose of DALY calculations, several of the assumptions relating to parameter estimates and structural uncertainty might be thought to be particularly relevant in assessing uncertainty or biasing in comparisons to other estimates of DALYs averted due to ACT scale up.

4.1.3. Approaches to assessing assumptions and conducting sensitivity analysis

We have taken several approaches to the assessment of the sensitivity of outputs to assumptions in model structure and parameter estimates inherent in the AMTR DALY model:

1. A one way sensitivity analysis and scenario analysis of the AMTR DALY model was conducted to show how parameter estimates can affect the overall outputs of the model. Parameters investigated include life expectancy at age of death, ACT effectiveness, ACT wastage, ACT misuse, baseline mortality and under five malaria incidence.
2. In order to address parameter uncertainty in the DALY analysis, but keeping the same model structure as used by PSI, we developed a Monte-Carlo simulation model which can accept a range of input values for the parameter estimates and then simulate outcomes using random, but plausible variations in these parameters. We utilized this model to construct credibility intervals around the mean estimates of ACT courses, deaths averted, DALYs averted, and the deaths averted and DALYs averted per ACT course ratios presented by the AMTR project.

3. We examined the impact of applying age-weighting, discounting and alternative life-tables on the estimates of YLL following a child death.
4. We applied the package 'DALY' in the R software (http://www.r-project.org) to conduct additional Monte-Carlo simulations of DALYs averted, and conducted a sensitivity analysis of an alternative model formulation to calculate DALYs averted.

4.2. Findings

4.2.1. One-way sensitivity analysis and scenarios

In order to recreate as closely as possible the expected number of DALYs averted by the PSI programme in Myanmar as reported in their proposal (Annex P), a scenario of malaria incidence, malaria mortality, ACT coverage, ACT effectiveness, ACT wastage, ACT misuse and life expectancy at age of death was constructed. The main variables and their parameterizations are presented in Table 1 showing that the three variables that were varied over time were incidence, mortality and ACT coverage.

Table 1 Base Case scenario inputs to AMTR DALY model

Parameter	Baseline	Year 1	Year 2	Year 3	Year 4
Malaria Incidence (Cases/person/year)	0.232	0.212	0.191	0.172	0.15
Malaria Mortality (deaths/100,000*)	10	9.1	8.2	7.4	6.5
ACT coverage	0%	35%	89%	90%	90%
ACT effectiveness	84%	84%	84%	84%	84%
ACT wastage	10%	10%	10%	10%	10%
ACT misuse	15%	15%	15%	15%	15%
Population Size	10,000,000	10,000,000	10,000,000	10,000,000	10,000,000
Life expectancy at age of death in years	82.5	82.5	82.5	82.5	82.5

* *assuming baseline ACT coverage*

This resulted in estimates of the four key outcomes as shown in Table 2. The overall projected DALYs averted over the time of the project were 160,712 which is very close to the discounted rate of 161,420 reported by PSI and reasonably close to the undiscounted value of 172,281. The DALY averted per ACT course were 0.0238 compared to 0.0196 for the original AMTR proposal based on the 8.8 million ACT expected to be distributed and the undiscounted DALYs averted. It must be kept in mind, however, that even though the results are similar, the way in which they were arrived at differed somewhat.

Table 2 Outputs of the AMTR DALY model using the base scenario

Outcome	Year 1	Year 2	Year 3	Year 4	Total
Death Averted	268	613	559	491	**1,931**
DALY Averted	22,262	51,010	46,551	40,889	**160,712**
Death Averted per ACT course	0.00285	0.00285	0.00286	0.00287	**0.00286**
DALY Averted per ACT course	0.0237	0.0237	0.0238	0.0239	**0.0238**

In a one way sensitivity analysis and scenario analysis we examined the impact of changing important parameters of the model to other plausible levels. The scenario analysis consisted of both best-case and worst-case outcomes, which combine the high and low estimates of each variable. The results of this analysis are shown in the Table 3 below.

Table 3 Results of one way and scenario sensitivity analysis of the AMTR DALY model

Parameter	Base Value	Sensitivity analysis value(s)	Effect on Cumulative			
			Deaths Averted	**DALYs Averted**	**Deaths Averted per ACT course**	**DALYs Averted per ACT course**
Malaria Incidence	See Table 1	0.5 0.05 per annum	No change	No change	0.001 0.0001	0.08 0.008
Malaria Mortality	See Table 1	1/ 100,000 1/100 per annum	255 255,360	21,248 21 Million	0.000038 0.038	0.00314 3.14
ACT coverage	See Table 1	10% 100%	262 2,620	21,800 218,075	No change	No change
ACT effectiveness	84%	25% 95%	575 2,184	47,831 181,757	0.000085 0.0003	0.0071 0.0269
ACT wastage	10%	0% 50%	No change	No change	0.0003 0.00021	0.0261 0.017
ACT misuse	15%	0% 50%	No change	No change	0.0003 0.00022	0.0274 0.018
Life expectancy at age of Death	82.5 years	31.3 92.6 years	No change	60,973 178,439	No change	0.009 0.0264
Worst case	See Above	See Above	10	316	0.000002	0.00007
Best case	See Above	See Above	380,000	35 Million	0.19	17.6

The largest variations in outputs were seen for malaria mortality and ACT coverage. Particularly the latter is of interest as a reduction from 100% to only 10% resulted in merely 21,800 cumulative DALYs averted. Other variables only showed a very moderate impact of less than tenfold differences between low and high estimates and this was particularly true for ACT effectiveness, ACT

misuse and life expectancy at age of death. As could be expected, the worst and best case scenarios showed a huge variation resulting a 100,000 fold difference between lowest and highest values for DALYs averted. However, it must be kept in mind that these scenarios do not take into account the likelihood of such a constellation of values.

4.2.2. Probabilistic Sensitivity Analysis

In order to try to quantify the uncertainty in the AMTR model we also conducted a probabilistic sensitivity analysis using a Monte Carlo simulation. Table 4 below describes the input parameters to the simulation model, which was similar to the PSI model in terms of calculation structure. All uncertain parameters were drawn from triangular distributions specified by their minimum value, maximum value, and most likely value (or Mode) using the 'urtriang' function of the 'Runuran' package in R.

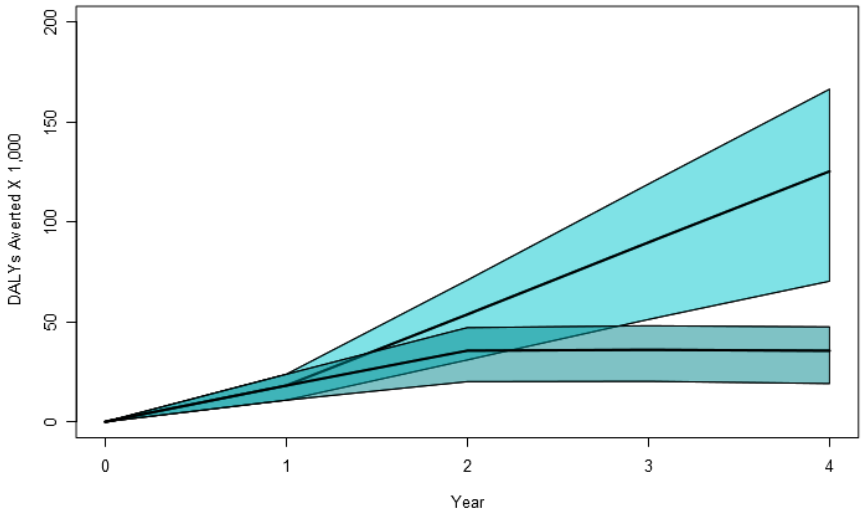
Table 4 Probabilistic Sensitivity Analysis input parameters

Parameter	Baseline	Year 1	Year 2	Year 3	Year 4
Malaria Incidence (per capita)	Min (0.05) Mode (0.232) Max (0.5)	Min (0.05) Mode (0.212) Max (0.5)	Min (0.05) Mode (0.191) Max (0.5)	Min (0.05) Mode (0.172) Max (0.5)	Min (0.05) Mode (0.150) Max (0.5)
Malaria Mortality per 10,000*	Min (0.1) Mode (1.0) Max (2.0)	Min (0.1) Mode (0.91) Max (2.0)	Min (0.1) Mode (0.82) Max (2.0)	Min (0.1) Mode (0.74) Max (2.0)	Min (0.1) Mode (0.65) Max (2.0)
ACT coverage	Min (0) Mode (0.005) Max (0.01)	Min (0.1) Mode (0.35) Max (0.5)	Min (0.1) Mode (0.89) Max (0.9)	Min (0.1) Mode (0.90) Max (0.95)	Min (0.1) Mode (0.90) Max (1.0)
ACT effectiveness		Min (0.70) Mode (0.84) Max (0.95)			
ACT wastage		Min (0.0) Mode (0.1) Max (0.5)			
ACT misuse		Min (0.0) Mode (0.15) Max (0.5)			
Life expectancy at age of death		Min (31.3) Mode (82.5) Max (91.6)			

*assuming baseline ACT coverage

Using the input parameters from Table 4, we conducted 10,000 simulations and derived 90% credibility intervals for the estimates of Deaths averted, DALYs averted, and the ratio of Death and DALY averted per ACT course over the life of the project. Figure 2 shows the annual and cumulative number of DALYs averted over the AMTR project with 50% credibility intervals. The cumulative number of DALYs averted in this model is approximately 125,000, or 35,000 less than in the PSI model.

Figure 2: Deaths and DALYs averted by the PSI programme in Myanmar

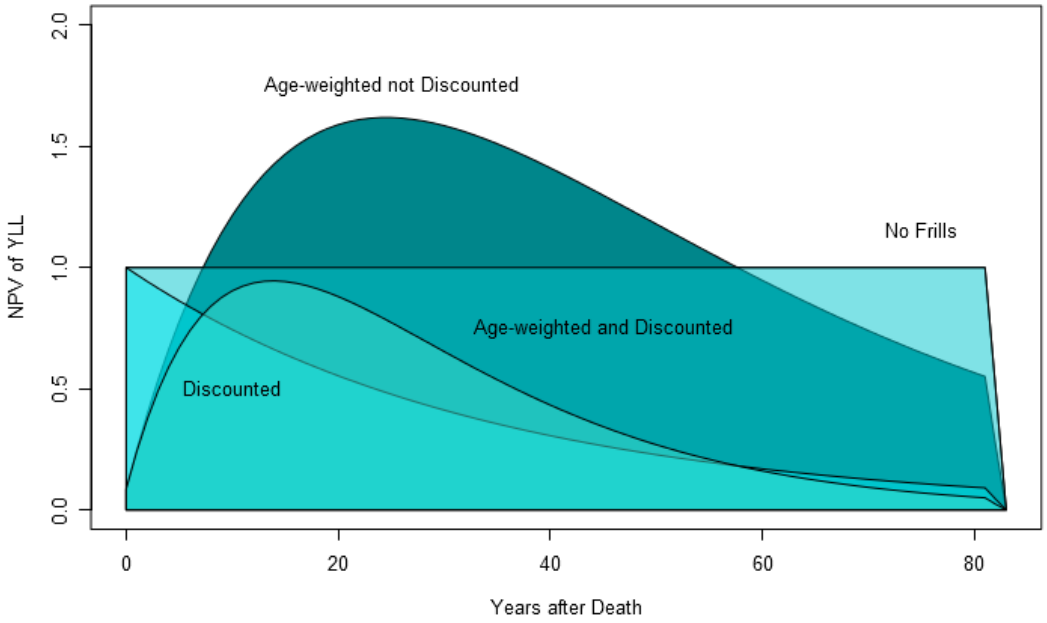


Illustrated above are the annual and cumulative DALYs estimated averted by the PSI programme based on probabilistic sensitivity analysis. The light blue shaded area represents the 50% credibility threshold for simulations of cumulative DALY impact, while the darker blue shaded area represents 50% credibility bounds for annual estimates of DALYs averted.

4.2.3. Impact of age-weighting and discounting on the YLL from one child death

In order to show the impact of using 'no-frills' DALYs (i.e. without age-weighting or discounting) on the estimates of YLL per child death, we varied the YLL from the baseline value of 82.5 years for an infant death without discounting, or age-weighting to include both age-weighting and discounting, and present the results in Figure 3. The results show the Net Present Value of the YLL per year over the entire expected lifetime of the child death. The YLL per infant death are greatly affected by the choice of DALY calculation method. In the base case the total YLL per infant death is 82.5, when age-weighting but not discounting is included, this number increases to 92.6. However, when age-weighted YLL is included and discounted at a 3% rate, the number falls to 36.1, and when age-weighting is not included but discounting is at a 3% rate, the number falls further to 31.3 YLL per infant death.

Figure 3: Net Present Value of Years of Life Lost for an infant death

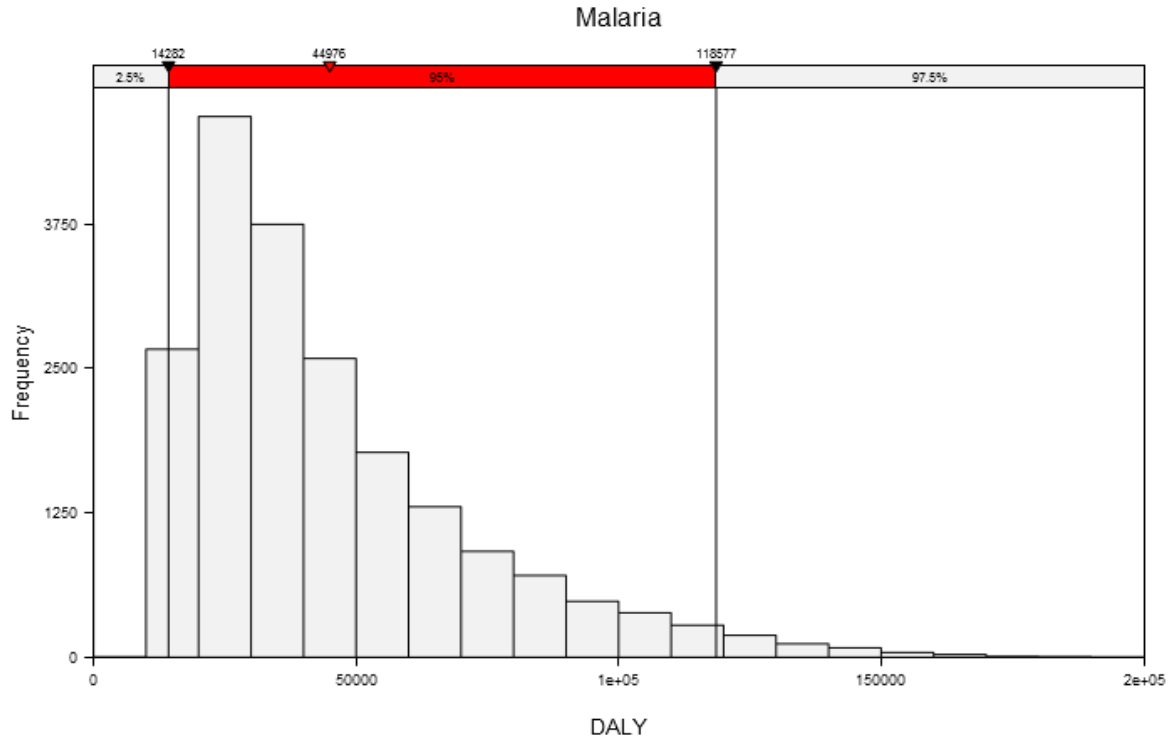


4.2.4. Estimates of DALYs averted using Incidence Based Stochastic DALY model

Many alternative impact and DALY calculation models may be used to evaluate the effectiveness of the approach being used by PSI. For the purpose of this sensitivity analysis we included a DALY averted calculation based on the 'DALY' package available in the R statistical computing software. We used the same input parameters for malaria incidence and mortality and derived weights for disability for malaria infections both treated and untreated from the Global Burden of Disease study [4]. We followed the same assumptions as the PSI model in assuming that a treated infection resulted in a reduction in YLD of 50%. We utilised ranges for parameters and input distributions similar to those used in the probabilistic sensitivity analysis above. However, since the YLD in this model is incidence based, these simulations required an additional set of parameters related to malaria incidence. These parameters were as follows: duration of malaria disease (mode (0.02 years) min (0.01 years) max (0.1 years)); disability weight of untreated malaria (Mode (0.205) min (0.1025) max (0.41)); and disability weight of treated malaria (equal to half of untreated). Additional uncertainty in the age of death and age of onset of an incident case were simulated with the following parameters: average age of death (mode (1) min (0.5) max (5)), and average age of onset of disease (mode (2.5) min (0.5) max (5)). All other parameters used the same uncertainty parameters as those in the probabilistic sensitivity analysis above. It is important to note that the DALY package in R does not support triangular distributions, and as such the Beta-Pert distribution was used to model all uncertain parameters.

Figure 4 shows the results of uncertainty in the number of DALYs annually accrued due to malaria as estimated using 10,000 Monte-Carlo simulations with the above parameterisation.

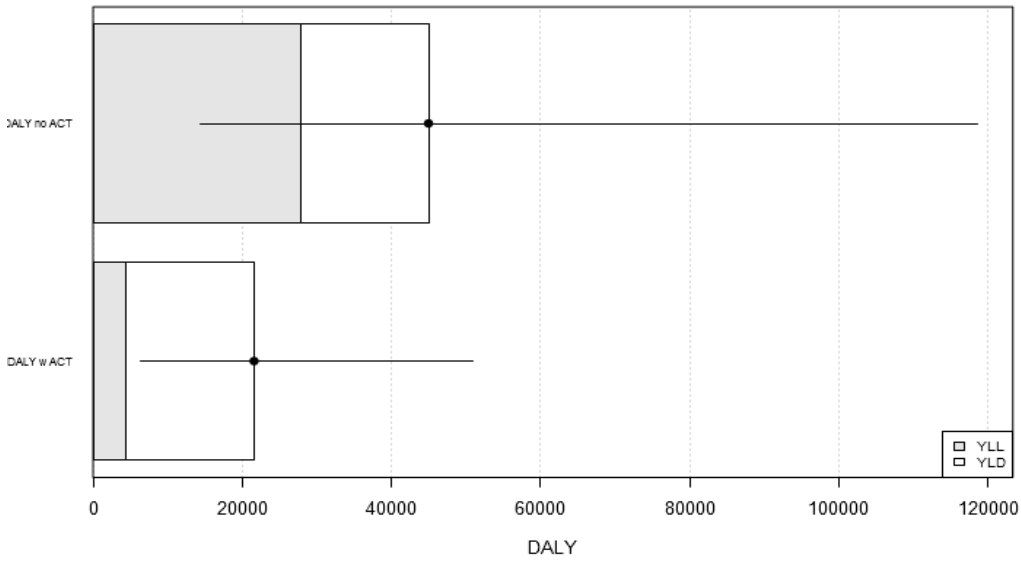
Figure 4: DALYs due to malaria in Myanmar



The bars in the Figure 4 above show the frequency of resulting DALYs averted based on 10,000 simulations. The red area on top marks the 95% confidence interval while the red triangle represents the mean. The graph shows that the mean estimate of DALYs accrued under this scenario per year was ~45,000 with a lower 95% bound of ~14,000 and an upper 95% bound of ~120,000.

In order to assess the potential for DALYs to be averted with ACT scale-up we conducted an alternative scenario using the same parameterisation as above but assuming that all malaria cases would be treated by a quality assured ACT with the same efficacy parameters described above. We also assumed that malaria mortality would be thus reduced by the full scale-up in proportion to the efficacy of the drug, but that incidence of disease would be unaffected. The following Figure 5 shows the comparison of the two scenarios (baseline and full ACT coverage) with uncertainty.

Figure 5: Comparison of DALYs under no ACTs and full scale up for one year in Myanmar

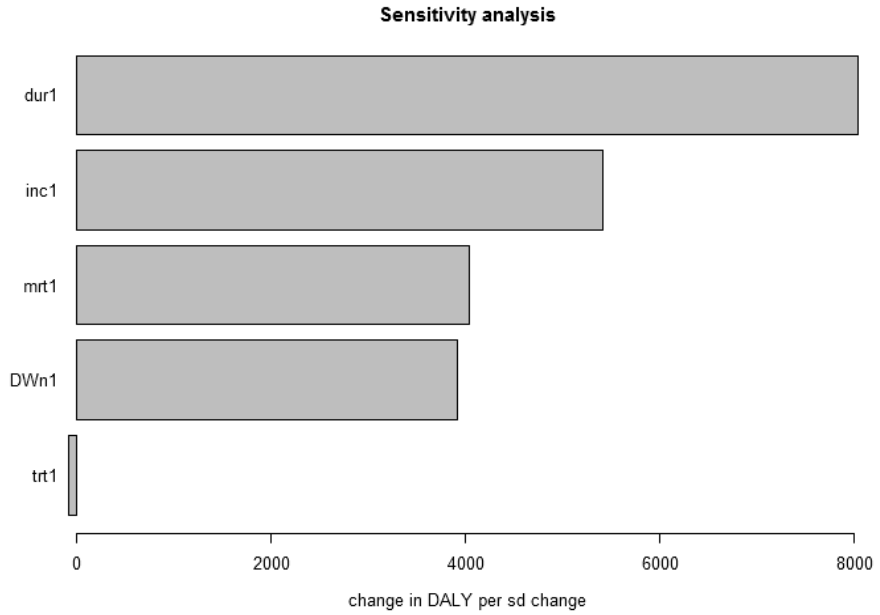


The grey area in this figure represents YLL while the white areas in the graph symbolise YLD. While the mean estimates of annual DALYs with no treatment and DALYs with ACT full scale-up are considerably reduced from ~45,000 to ~22,000, the 95% credibility intervals still overlap. Results also show that the difference is obtained through the reduction of YLL while YLD remain comparable in both scenarios, i.e. the relative contribution of YLD to the overall DALYs was much higher under ACT scale-up.

We also conducted a sensitivity analysis of determinants of variance in the alternative scenario (full ACT scale-up) to determine which of the uncertain parameters contributed most to the uncertainty in the results. The analysis was conducted using linear regression on the outputs of the simulations with standardised inputs to each simulation. Consequently, Figure 6 shows the impact of a one standard deviation change in the input parameter on the total DALYs accrued under the alternative scenario. The chart shows that duration of disease, incidence, mortality, and disability weight (untreated) variance were the primary drivers of uncertainty in this scenario.

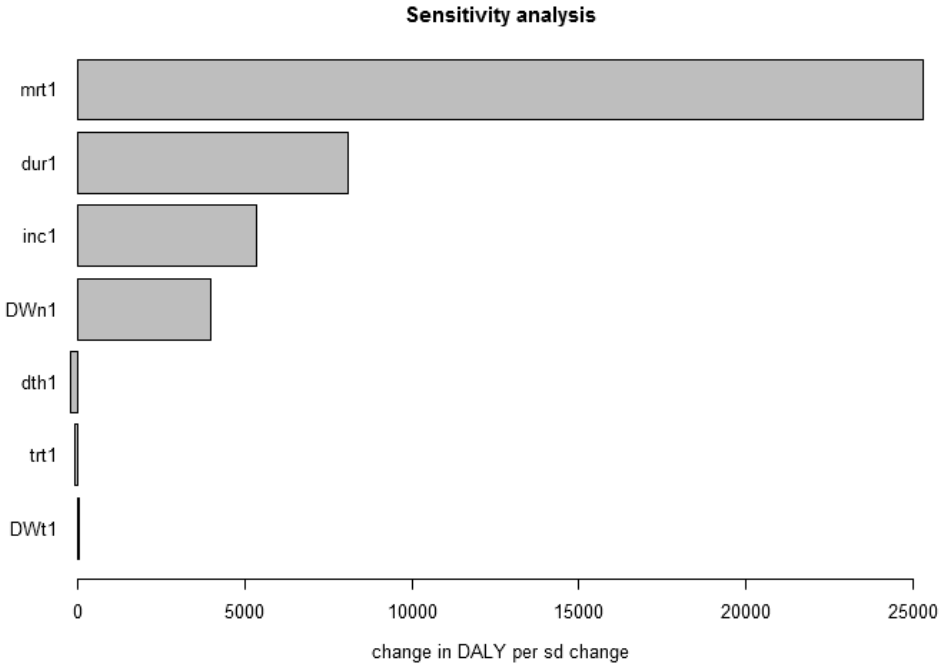
A similar analysis was conducted on the baseline scenario (no ACTs). In this case the results are slightly different and informative (Figure 7), as the primary driver of uncertainty in the DALY calculation was the mortality rate. This is justifiable given that before scale-up of ACTs the primary contribution to DALYs was due to YLL whereas, after scale-up, YLD contributed much more significantly due to the 84% reduction in mortality but a much smaller reduction (in this scenario none) in incidence and a proportionally smaller reduction in disability (see Figure 5). These calculations assume that ACTs can only prevent 50% of morbidity due to incident malaria but can prevent approximately 84% of mortality.

Figure 6: Effect of one standard deviation change in the input parameters on total DALYs accrued



This graph shows results from *after* a full ACT scale-up scenario in Myanmar. dur1= duration of disease, inc1= malaria incidence, mrt1=malaria mortality, DWn1=disability weight (untreated), trt1=ACT treatment

Figure 7: Effect of one standard deviation change in the input parameters on total DALYs accrued



This graph shows results from *before* an ACT scale-up in Myanmar. dur1= duration of disease, inc1= malaria incidence, mrt1=malaria mortality, DWn1=disability weight (untreated), DWt1=disability weights (treated), trt1=ACT treatment

5. INTERPRETATION AND CONCLUSIONS

The purpose of this sensitivity analysis was to take a closer look at the DALY calculations underlying the AMTR project approach, determine the factors that most influence the outcomes, and clarify what this could imply for the final project evaluation. The analysis focused on the uncertainty in the underlying data and calculation methods, and did not consider internal or external validity which will be part of the final project evaluation.

As a first step, a recreated model was created to estimate the DALYs averted through the AMTR project using a similar, but not identical methodology and variable parameterisation as applied in the AMTR proposal, but using the current four year project duration (following the no-cost extension) rather than the original three years. This resulted in a similar output as calculated by PSI of around 160,000 DALYs averted over the course of the project within Myanmar. In a second step, the calculations were then used to undertake sensitivity analysis of each of the main input variables. This demonstrated that ACT effectiveness, wastage or misuse, as well as life expectancy only had a moderate impact on the outcomes but that malaria morbidity and particularly ACT coverage had a significant impact. If true, ACT coverage is only 10% rather than 100%, the cumulative DALYs averted decreases to only 21,800 or 13.5% of the original estimated DALYs averted. As the evaluation team has shown in their most recent report [11], a lower than expected ACT coverage in the private sector is very likely based on current data from the PSI project. In spite of a significant reduction of AMTs, there remains a high level of undiagnosed suspected malaria cases in the private sector that are treated with non-artemisinin anti-malarials, which reduces the effective ACT coverage. Whether this situation can be improved will significantly depend on whether or not a roll-out of diagnostics with RDT can be achieved within the next year.

The second part of the working paper then uses probabilistic modelling approaches to further assess uncertainty based on 10,000 Monte Carlo simulations and initially using the same calculation approach and parameterisation as the PSI model. This resulted in slightly lower cumulative DALYs averted for the AMTR project of around 125,000 DALYs with a 50% uncertainty range of 70,000-170,000. The analysis also demonstrated how important it is for the outcome whether or not age-weighting and or discounting is applied, both of which are debatable (see section 2). In the PSI model an infant death would contribute 82.5 years of life lost in a 'no frills' approach, but only 36.1 years if age-weighted and discounted, and only 31.3 years if only discounted. This could have consequences for the final project evaluation, especially if DALY estimations are conducted that are not limited to children under five and use the actual age pattern observed in Myanmar where the majority of malaria incidence occurs in adults. Whether or not age-weights and discounting are applied would then have an even stronger impact on the outcome.

The final part of the paper then uses the "DALY" package provided in the R statistical software as an alternative method to run an incidence-based, stochastic DALY estimation, again based on 10,000 Monte Carlo simulations. These calculations suggest that the annual DALYs accrued from malaria in Myanmar would be about 45,000 with a considerable level of uncertainty (95% credibility interval 14,000-120,000), and that a full scale-up to ACT treatment would be able to reduce this by about 50%, but the 95% credibility intervals of these estimates overlap. These results would also suggest a

more modest number of DALYs averted than estimated by the initial PSI calculations for the project proposal. An interesting finding here is the observation that under full ACT scale-up the relative contribution of the disability related time lost increases significantly as mortality is more reduced than morbidity. The sensitivity analysis from this model of full ACT scale-up suggests that the duration of the disease under treatment, incidence, and mortality rates are the most influential factors for the DALY result. In the context of the rapidly declining malaria incidence rates [11], this further supports the expectation of lower DALYs averted in the context of the AMTR project than originally thought.

The following major conclusions can be presented from this work:

1. ACT coverage, malaria incidence, and mortality are among the most influential variables for the resulting number of DALYs averted within Myanmar by the AMTR project. Based on the lower estimates for these expected by the end of the project compared to the initial calculations, it appears most likely that the DALYs averted within Myanmar will be significantly lower than the 161,000 DALYs averted mentioned in the proposal.

2. Given the significant impact of the methodological approach on the resulting DALYs averted, careful discussion of the importance and/or role of a DALY averted estimation and – if this is confirmed – consideration of which methodology should be applied (e.g. age-weighting and/or discounting, comparison to a treatment with zero or non-zero effect) should precede the end-of project evaluation.

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