Simulation of the costs and consequences of potential vaccines for Plasmodium falciparum malaria

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Summary

Malaria is one of the major public health problems for low income countries, a major global health priority, and it has also a dramatic economic impact. Funding for malaria control is on the rise and both international donors and governments of malaria endemic countries need tools and evidence to assess which are the best and most efficient strategies to control malaria.

Standard tools traditionally used to assess the public health and economic impact of malaria control interventions, such as efficacy trials and static cost-effectiveness analyses, capture only short term effects. They fail to take into account long term and dynamic effects due to the complex dynamic of malaria, and to the interactions between intervention effectiveness and health systems.

This thesis is part of a wider research project, conducted by the Swiss Tropical Institute, aimed at developing integrated mathematical models for predicting the epidemiologic and economic effects of malaria control interventions. The thesis specifically combines innovative mathematical models of malaria epidemiology with innovative modeling of the health system and of the costs and effects of malaria control interventions. These approaches are applied to simulate the epidemiological impact and the cost-effectiveness of hypothetical malaria vaccines.

Chapter 1 describes why malaria is a public health priority, the increasing relevance of conducting economic analyses in the health sector, the economic evaluation framework, and the economic consequences of malaria.

Chapter 2 presents an approach to dynamically modeling the case management of malaria in Sub-Saharan Africa.

Chapter 3 describes an approach to costing the delivery of a hypothetical malaria vaccine through the Expanded Programme on Immunization (EPI), on the basis of the information available on the likely characteristics of the vaccine most advanced in development. The results show that, although the vaccine price determines most of the total delivery costs, other costs are relevant and should be taken into account before planning its inclusion into the EPI.

Chapter 4 and 5 combine modeling of malaria transmission and control with predictions of parasitologic and clinical outcomes, to assess the epidemiological effects and the potential short and long term cost-effectiveness of a pre-erythrocytic vaccine delivered via the EPI. The results suggest a significant impact on morbidity and mortality for a range of assumptions about the vaccine characteristics, but only

small effects on transmission intensities. They also suggest that at moderate to low vaccine prices, a pre-erythrocytic vaccine providing partial protection, and delivered via the EPI, may be a cost-effective intervention in countries where malaria is endemic.

Chapter 6 simulates the cost-effectiveness of three different vaccine types: Pre-erythrocytic vaccines (PEV), Blood stage vaccines (BSV), mosquito-stage transmission-blocking vaccines (MSTBV), and combinations of these, each delivered via a range of delivery modalities (EPI, EPI with booster, and mass vaccination combined with EPI). The simulations presented in this Chapter show that PEV are more effective and cost-effective in low transmission settings. In contrast to PEV, BSV are predicted to be more effective and cost-effective at higher transmission settings than low transmission. Combinations of BSV and PEV are predicted to be more efficient than PEV, in particular in moderate to high transmission settings, but compared to BSV, combinations are more cost-effective in mostly moderate to low transmission settings. Combinations of MSTBV and PEV or PEV and BSV do not increase the effectiveness or the cost-effectiveness compared to PEV and BSV alone when delivered through the EPI. However, when applied with EPI and mass vaccinations, combinations with MSTBV provide substantial incremental health benefits at low incremental costs in all transmission settings. This highlights the importance of developing other vaccine candidates as they have potential to facilitate a PEV/BSV combination vaccine to be more beneficial. Chapter 6 simulations indicate that the transmission setting and the vaccine delivery modality adopted are important determinants of the cost-effectiveness of malaria vaccines. Alternative vaccine delivery modalities to the EPI may sometimes, but not always, be more cost-effective than the EPI. In general, at moderate vaccine prices, most vaccines and delivery modalities simulated are likely to present cost-effectiveness ratios, which compare favorably with those of other malaria interventions.

Chapter 7 discusses the implications of approaches and results presented in the thesis, their limitations and potentials. The approach used in this research represents the first attempt to develop dynamic models of malaria transmission and disease to evaluate the cost-effectiveness of malaria control interventions. Combining advanced stochastic simulation modeling of malaria epidemiology with health system dynamic modeling is a crucial innovation proposed by the approaches presented in this thesis. In fact, while it is well known that the interactions between malaria and health systems take place under temporal and spatial heterogeneity, integration of health system metrics in epidemiological modeling is rarely done. The cost-effectiveness

analyses are based on an approach to model the health system characteristics of the settings where a new intervention, such as a malaria vaccine, will be implemented, The rationale of this approach rests on: a) the need to capture the long term health and economic impact due to the interactions between malaria control interventions and the health system - e.g. the impact on the health system of variations in transmission intensity due to an intervention; b) the recognition that policy makers are more interested in cost-effectiveness predictions that are specifically tailored to their health system context rather than on a hypothetical one.

The approaches developed provide a platform that could be used to model the effects of integrated strategies for malaria control. The increase in computer power available makes possible simulating complex scenarios with several dimensions/variables in a relatively short time. This, coupled with the increasing availability of information on malaria endemic countries health systems, should be exploited to further modeling health system dynamics, which is fundamental to assess integrated malaria control strategies.

The models and the approaches presented could be applied to inform decisions at several levels. Further applications might include simulating the epidemiology, the costs and consequences of packages of interventions, allowing estimating both effectiveness and (technical and allocative) efficiency. This would, thus, help policy makers to determine which intervention or, most likely, which package of interventions, might be most effective and efficient in a particular area. Additionally, it would be possible to simulate the implications of coverage extension of malaria control interventions, and of different strategies and service delivery modalities that can reach the poorest.

The approaches developed could also allow identification of areas where intensified malaria control is the only feasible option, areas where malaria elimination is more likely to be achieved, the incremental cost-effectiveness of proceeding to elimination once a high level of control has been achieved, the optimal transmission levels at which to change strategy, and, in principle, economies of scope and or synergies in effectiveness and cost-effectiveness of new strategies. These are all research areas that have been identified as fundamental in the research agenda to be set up following the recent call for malaria elimination.

Zusammenfassung

Malaria ist eines der grösseren gesundheitlichen Probleme für Länder mit niedrigem Einkommen. Auf Grund der grossen wirtschaftlichen und Krankheitsbedingten Auswirkungen kommt der Prävention und der Behandlung der Malaria eine hohe Priorität zu. In den vergangenen Jahren hat die Verfügbarkeit von finanziellen Mitteln zur Malariabekämpfung zugenommen. Sowohl internationale Geldgeber wie auch die Regierungen der betroffenenen Länder benötigen Werkzeuge und wissenschaftliche Belege um entscheiden zu können, welches die besten und effizientesten Strategien zur Malariabekämpfung sind. Standardverfahren zur Beurteilung der gesundheitlichen und wirtschaftlichen Auswirkungen von Malariainterventionen, wie zum Beispiel Wirksamkeitsstudien und Kosten-Nutzen-Analysen, können nur Fragen nach den kurzfristigen Auswirkungen beantworten. Langfristigen und dynamischen Effekten wird hierbei jedoch nicht berücksichtigt. Solche können auftreten als Folge der komplexen Dynamik der Malaria oder der Wechselwirkungen zwischen Gesundheitssystemen und Wirksamkeit von Interventionen.

Diese Dissertation ist Teil eines grösseren Forschungsprojektes am Schweizerischen Tropeninstitut, welches zum Ziel hat mathematische Modelle zu entwickeln, um die epidemiologischen und wirtschaftlichen Auswirkungen von Malariainterventionen vorherzusagen. Die vorgelegte Arbeit kombiniert spezifisch innovative mathematische Modelle der Malariaepidemiologie und deren Interaktionen mit Gesundheitssystemen sowie Kosten und Auswirkungen von Malariabekämpfungsstrategien. Diese Ansätze werden kombiniert um die epidemiologischen Auswirkungen und die Kostenwirksamkeit von hypothetischen Malariaimpfungen zu simulieren.

Kapitel 1 erklärt weshalb Malaria eine Priorität ist im öffentlichen Gesundheitswesen, beschreibt die wachsende Relevanz ökonomischer Analysen im Gesundheitsbereich, umrahmt die Methoden ökonomischer Auswertung, und erläutert die wirtschaftlichen Konsequenzen der Malaria.

Kapitel 2 präsentiert einen Ansatz zur dynamischen Modellierung des Fallbehandlung in Subsahara- Afrika. Kapitel 3 beschreibt einen Ansatz zur Ermittlung der Kosten einer hypothetischen Malariaimpfung die durch ein nationales Impfprogramm („Expanded Programme on Immunization“ (EPI)) eingesetzt wird. Dieser Ansatz basiert auf den verfügbaren Informationen über die zu erwartenden Eigenschaften gegenwärtig am weitesten entwickelten Impfung. Die Resultate zeigen, dass, obwohl

der Preis des Impfstoffes den grössten Anteil an den Gesamtkosten eines Impfprogramms stellen, andere Faktoren relevant sind und berücksichtigt werden sollten vor der Aufnahme einer Impfung in ein Impfprogramm.

Kapitel 4 und 5 kombinieren die Modellierung von Malariaübertragung und -kontrolle mit Vorhersagen der klinischen Folgen, mit dem Ziel einer Beurteilung der epidemiologischen Konsequenzen und möglicher kurz- und langzeit-Kosteneffizienz einer prä-erythrozytischen Impfung („pre-erythrocytic vaccine"), wenn diese durch ein nationales Impfprogramm verabreicht wird. Die Resultate zeigen - über einen grossen Bereich von Annahmen bezüglich der Eigenschaften einer Impfung - einen grossen Effekt auf Morbidität und Mortalität, jedoch nur kleine Effekte auf die Transmissionsstärke. Im weiteren legen die Resultate nahe, dass bei mittlerem bis tiefem Impfstoffpreis eine teilwirksame, prä-erythrozytische Impfung, verteilt über ein Impfprogramm, durchaus eine kosteneffiziente Intervention sein kann in malaria-endemischen Ländern.

Kapitel 6 simuliert die Kosteneffizienz dreier verschiedener Impfungstypen: „Pre-erytrhocytic vaccines" (PEV), „Blood stage vaccines" (BSV), „mosquito-stage-transmission-blocking vaccines" (MSTBV), und Kombinationen derselben, ausgeliefert über eine Anzahl verschiedener Verteilungsmodalitäten (EPI, EPI mit „booster", und Massenimpfprogramm in Kombination mit EPI). Die Simulationen, welche in diesem Kapitel präsentiert werden, zeigen, dass PEV's am wirksamsten und kosteneffizientesten bei niederer Transmissionsstärke sind. Im Gegensatz zu PEV's sind BSV's laut den Resultaten wirksamer und kosteneffizienter in Situationen mit höherer Transmission. Kombinationen von BSV und PEV sind laut den Vorhersagen wirksamer und kosteneffizienter als PEV alleine, besonders bei mittlerer bis hoher Transmission. Im Vergleich zu BSV sind sie jedoch am kosteneffizientesten bei mittlerer bis schwacher Transmission. Kombinationen von MSTBV und PEV oder PEV und BSV erhöhen weder Wirksamkeit noch Kosteneffizienz im Vergleich zu PEV und BSV alleine, wenn verteilt via nationalem Impfprogramm. Wenn jedoch Kombinationen mit MSTBV gleichzeitig via Impfprogramm und Massenimpfung benützt werden, zeigt sich ein beträchtlicher inkrementeller gesundheitlicher Gewinn bei minimalen zusätzlichen Kosten, was für alle Transmissionsszenarien gilt. Dies unterstreicht, wie wichtig es ist, andere Impfstoffkandidaten weiterzuentwickeln, da diese das Potential haben, einer PEV/BSV-Kombination zu grösserer Wirksamkeit zu verhelfen. Die Simulationen in Kapitel 6 zeigen, dass Transmissionsstärke und Auslieferungsmodalität wichtige Determinanten sind für die Kosteneffizienz einer Malariaimpfung. Alternative Auslieferungsmodalitäten können - aber müssen nicht -

kosteneffizienter sein als EPI. Im Allgemeinen schneiden die meisten Impfungstypen und Auslieferungsmodalitäten bei mässigen Impfstoffpreisen gut ab im Vergleich zu anderen Malariainterventionen.

Kapitel 7 diskutiert die in der Dissertation präsentierten Ansätze und Resultate im Hinblick auf ihre mögliche Implikationen und Auswirkungen. Der in dieser Forschungsarbeit gewählte Ansatz repräsentiert den ersten Versuch, dynamische Modelle der Übertragung von und Erkrankung an Malaria zu entwickeln, um damit die Kosteneffizienz von Malariainterventionen zu evaluieren. Stochastische Modellierung der Malariaepidemiologie in Kombination mit dynamischer Modellierung von Gesundheitssystemen stellt eine wichtige Innovation der in der Dissertation vorgestellten Ansätze dar. Tatsächlich wurde eine Integration von Messung von Gesundheitssystemen und epidemiologischen Modellen bis anhin selten versucht, obwohl es hinreichend bekannt ist, dass Interaktionen zwischen der Epidemiologie der Malaria und den Gesundheitssystemen stattfinden, und zudem eine räumliche und zeitliche Heterogenität aufweisen. Die Kosteneffizienzanalysen basieren auf einer Methode, welche versucht die Eigenschaften der Gesundheitssysteme in Gebieten zu modellieren, wo eine neue Intervention, wie z.B. eine Malariaimpfung, angewandt werden würde. Dieses Vorgehen beruht auf der Einsicht, dass a) es notwendig ist, langfristige Einflüsse auf Gesundheit und Ökonomie als Folge von Wechselwirkungen zwischen Malariabekämpfungsmassnahmen und dem Gesundheitssystem zu prognostizieren (z.b. den Einfluss von Veränderungen in der Übertragungsstärke – als Folge einer Intervention - auf die Gesundheitssysteme); b) dass politische Entscheidungsträger stärkeres Interesse an Kosteneffizienzvorhersagen haben, wenn diese speziell auf die jeweilige Situation zugeschnitten sind.

Die erarbeiteten Vorgehensweisen könnten verwendet werden um die Effekte von integrierten Malariabekämpfungsstrategien abzuschätzen. Die Zunahme an verfügbarer Rechenkraft macht es möglich, komplexe Szenarien mit vielen Variablen/Dimensionen in relativ kurzer Zeit zu simulieren. Diese Möglichkeit sollte, zusammen mit der zunehmenden Verfügbarkeit von Informationen über die Gesundheitssysteme in malariaendemischen Ländern, genutzt werden, um dynamische Modelle von Gesundheitssystemen weiterzuentwickeln. Dies ist von grosser Wichtigkeit im Hinblick auf die Beurteilung von integrierten Malariabekämpfungsstrategien.

Die präsentierten Methoden und Modelle könnten angewandt werden um Entscheidungsprozesse auf verschiedenen Ebenen zu unterstützen. Als weitere

Anwendung wäre es zudem möglich, die Epidemiologie, Kosten und Konsequenzen ganzer Interventionspakete zu simulieren, was eine Abschätzung sowohl von Effektivität wie auch (technischer und allokativer) Effizienz ermöglichen würde. Dies würde es dann für politische Entscheidungsträger möglich machen, zu beurteilen, welche Massnahmen (oder welches Massnahmenpaket) am wirksamsten und effizientesten wären in einem spezifischen Gebiet. Zusätzlich wäre es möglich die Auswirkungen einer Erweiterung des Abdeckungsgrades von Interventionen zu simulieren, wie auch die Auswirkungen von verschiedenen Versorgungsmodalitäten um die Ärmsten zu erreichen.

Eine weitere Anwendung der entwickelten Methoden wäre die Identifikation von Gebieten wo eine intensivierte Malariakontrolle die einzig vernünftige Option darstellt im Vergleich zu Gebieten, wo eine Eliminierung eher machbar erschiene, die Ermittlung der inkrementellen Kosteneffizienz des Fortschreitens zu einer Elimination nachdem ein hohes Mass an Kontrolle bereits erreicht ist, die Ermittlung der optimalen Übertragungsintensität für einen Strategiewechsel, und, grundsätzlich, die Identifikation von Verbundeffekten und Synergien in Wirksamkeit und Kosteneffizienz von neuen Strategien. All diesen Aspekten wird innerhalb der Forschungsagenda basierend auf dem im Jahre 2008 erfolgten Aufruf zur Ausrottung der Malaria, eine grosse Priorität eingeräumt.

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Chapter 1: Introduction

Malaria is one of the major public health problems for low income countries, a major global health priority, and it has also a dramatic economic impact. Funding for malaria control is on the rise and both international donors and governments of malaria endemic countries need tools and evidence to assess which are the best and most efficient strategies to control malaria. Predictive models are therefore needed for assessing the public health and economic consequences of adopting one or a combination of malaria control interventions in a given setting. This is not easy due to the complex dynamics of malaria and of health systems, particularly regarding the long term effects of malaria control interventions.

This chapter, after a brief description of malaria and of the strategies to control it, provides an introduction to the rationale of health economics and economic evaluation of health programs. It then analyzes what is currently known about the macro and micro economic consequences of malaria. Lastly, it describes the rationale of the thesis and its overall and the specific objectives.

1.1 Malaria

Malaria is an infection due to a protozoa transmitted to humans through a mosquito bite. Human malaria is caused by four species of Plasmodium: *P. Falciparum, P. Vivax, P. Ovale, P. Malaria,* although almost all deaths are caused by *P. Falciparum.*

Despite significant measurement problems[1], it is estimated that 3.2 billion people live in areas of risk[2] in 109 countries, and that in 2006 there were around 250 million malaria episodes (range 189-327) worldwide, causing around one million deaths, mostly of children under 5 years[2 3].

In Sub Saharan Africa (SSA), where malaria is one of the major causes of death, it accounts for 7.2% of total death and for 8.2% of the total *burden of disease (DALYs* - Table 1.1). Malaria is also a cause of increase in all cause mortality rates as it is a co-cause of maternal anemia during pregnancy, of low birth weight, and early births, that cause 75,000-200,000 deaths of children per year only in SSA[4] as well as severe child pneumonia.

A few decades ago malaria was eliminated in many parts of the world with efficacious anti-malaria drugs and other preventive strategies such as the extensive use of spraying - DDT (Dichlorodiphenyltrichloroethane). Afterwards, the

development of resistance to malaria drugs and, probably, the restricted use of DDT caused, in the poorest countries, a rapid increase in malaria morbidity and mortality rates also in zones where malaria had disappeared[5].

Table 0.1 Deaths and DALYs (per 1000) – total and attributable to Malaria, year 2004

	Population		*Total Deaths (1)*		*Deaths Malaria (2)*		*(2)/(1)*	*Total DALYs (3)*		*DALYs Malaria (4)*		*(4)/(3)*
WHO Regions	N (000)	%	N (000)	%	N (000)	%	%	N (000)	%	N (000)	%	%
Africa	737536	11%	11248	19%	806	91%	7.2%	376525	24.7%	30928	91%	8.2%
Sub-Saharan Africa	750833	12%	11683	20%	842	95%	7.2%	391416	25.7%	32202	95%	8.2%
The Americas	874380	14%	6158	10%	2	0%	0.0%	143233	9.4%	89	0%	0.1%
Eastern Mediterranean	519688	8%	4306	7%	39	4%	0.9%	141993	9.3%	1412	4%	1.0%
Europe	883311	14%	9493	16%	0	0%	0.0%	151461	9.9%	4	0%	0.0%
South-East Asia	1671904	26%	15279	26%	36	4%	0.2%	442979	29.1%	1341	4%	0.3%
Western Pacific	1738457	27%	12191	21%	5	1%	0.0%	264772	17.4%	169	0%	0.1%
World	6436826	100%	58772	100%	889	100%	1.5%	1523259	100.0%	33976	100%	2.2%

Source: Global Burden of disease update 2008 - Disease and injury regional estimates for 2004.
http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html

1.2. Strategies and policies to control Malaria

Malaria can be fought through integrated strategies of prevention and treatment that are available (known) and often would represent cost-effective interventions for malaria endemic countries. Prevention strategies such as Insecticide Treated bed-Nets (ITNs) are efficacious in reducing mortality, as is the prevention and management of malaria in pregnancy, the pharmacological treatment with Artemisinin-based combination therapies (ACTs), and the improvement of epidemic response in emergencies[2].

Nevertheless, the burden of malaria remained high due to a combination of factors including the growth of parasite and vector resistance to the current anti-malarial drugs and insecticides, the weakening of traditional malaria control programs and of primary health services in many areas where malaria is endemic.

1.2.1 Preventing malaria

Using ITNs is one of the most efficacious strategies to prevent morbidity and mortality due to malaria[6 7], and it is also highly cost-effective with cost-effectiveness ratios comparable to those of measles vaccine in terms of cost per death or per Disability Adjusted Life Year (DALY) averted[8 9].

ITNs have a protective effect on both individuals using them and the community. Despite the progress made in the last few years (ITNs sold in the last few years grew by five/six times and annual production of ITNs almost tripled from 30 million in 2004 to 95 million in 2007, and is estimated to reach 110 million in 2008[10]) in the surveyed African countries (18) the World Malaria Report 2008 found that only 23% of children sleep under an ITN[2]. Furthermore, although malaria is more prevalent in rural areas and among the poorest, the use of ITNs tends to be more on urban areas and in better off households. In the last few years, many countries implemented ITNs programs aimed at increasing the use of ITNs, through free distributions or at subsidized prices for target groups such as pregnant women and children under 5 years old. For instance, the coverage of ITNs in children under 5 increased dramatically in countries such as Eritrea (63%) and Malawi (36%)[11], while some social marketing and free distribution programs targeted to specific population groups, temporarily reduced inequalities in ITNs coverage between rural and urban areas in Ghana, Nigeria and Togo[11].

Indoor residual spraying (IRS) is the application of long-lasting insecticide on the walls of dwellings and it is effective mainly against indoor-biting mosquito vectors. It has been shown to be effective in reducing incidence of malaria in large scale programs in various parts of Africa, the Americas, and Europe[12]. IRS is used in various regions particularly in foci of high seasonal malaria transmission but only in a few countries a large proportion of households are covered.

Larviciding is the application of chemical insecticides to (all or targeted) mosquito breeding sites. The insecticide is not effective for as long as with IRS or ITNs, it presents operational difficulties, and it must be applied during periods of peak target mosquito activity (usually at night). Larviciding is mainly indicated for urban areas, refugee camps, and industrial and development projects [13].

Intermittent preventive treatment in pregnancy (IPTp) consist of two curative doses of antimalaria treatment during pregnancy and it is recommended in areas with high and stable transmission of *P.Falciparun* malaria. It is used in 33 African countries as a national policy[2]. Intermittent preventive treatment in infants (IPTi) consists of giving infants treatment doses during vaccination or well-baby visits to health clinics, and there is growing evidence of efficacy in reducing malaria episodes and anemia.

Currently, vaccines for malaria are under development although no completely effective vaccine is yet available. The vaccine that is most advanced in clinical development is RTS,S/AS02A. This is a pre-erythrocytic vaccine specific to *P falciparum*, which aims to kill the parasites before they enter the red blood cells. A recent study followed 2000 Mozambican children and demonstrated reduction in the infection risk of approximately 45%[14]. The vaccine has also shown to be safe and partially effective in infants[15], the age group that will most likely be targeted by a vaccine campaign. Other vaccines currently under development target either the blood stages of the parasite or the stages that are transmitted to the next host by a mosquito[16].

1.2.2 Treating malaria

Malaria differs from many other infectious diseases in many respects, including the fact that early treatment is much more important than for other diseases such as, for instance, tuberculosis. It is thus not only important the availability of efficacious drugs but also the health system capability to respond rapidly to the disease. For a long time efficacious anti-malaria drugs were available and inexpensive. Over time the growing resistance to chloroquine, the inexpensive and most used antimalarial drug, and to sulfadoxine-pyrimethamine, an alternative drug to chloroquine, became the major obstacle to the treatment of malaria. The alternative to these drugs are the new combination therapies, such as the various ACTs that proved to be efficacious.

In most of the countries where information is available, at least 50% of fever episodes in children are treated with antimalarial drugs. For instance, between 1998 and 2004 the median proportion of children under 5 years old treated with antimalarial drugs reported in the 35 available studies was 49.6% (range 3.0-68.8%) of which 95% with chloroquine, while most of treatments were not within 24 hours from the first fever and/or it was with inadequate dosages[11]. As a consequence, the actual access to efficacious treatments against malaria is likely to be much lower. The only realistic alternative is thus to increase the use of ACTs, and many countries are pursuing this direction.

In 2008 all except four countries and territories worldwide had adopted ACT as first line drug for *P. falciparum*, while a number (22) of countries had adopted home management as main strategy to control malaria in children under 5 years old[2]. This strategy includes a training program for mothers, the provision of pre-packaged drugs needed to guarantee early treatments to children in rural areas with low access to health facilities. Unfortunately, ACT use faces three main problems: the still relatively high production costs (between 10-20 times that of chloroquine); the limitations in production capacity due mainly to the lack of derivatives of Artemisia; the short shelf live and a complex dosage regimen.

1.3 Health economics and the economic evaluation framework

Economics is the study of how individuals and societies choose to allocate scarce resources (i.e. all basic inputs to production such as time, abilities, capital, and natural resources) among competing alternative uses, and how to distribute the products from these resources. The rationale of economics is based on the concepts of scarcity - meaning that there are not enough resources to satisfy all demands and needs -, efficiency, and on that of opportunity costs.

In economics, efficiency is defined in two ways: allocative efficiency, when resources are allocated between objectives to produce the greatest gain to society (i.e. doing the right things); technical efficiency, when the goal is to maximise the achievements of a given objective within a given budget (i.e. doing things right).

An opportunity cost is the cost of something in terms of an opportunity foregone (and the benefits that could be received from that opportunity), or the most valuable foregone alternative. It need not be assessed in monetary terms, but rather, in terms of anything that is of value to the person or persons doing the assessment.

The key principle of economics is searching to maximize efficiency, considering also equity. Although economics can inform decisions on the unavoidable trade-offs between equity and efficiency, this is in the domain of politics, since it relates to the values of societies.

Economics is thus aimed at answering three related "fundamental economic questions":

- The first is which goods (and services) a given society should produce? This question is related to the concepts of allocative efficiency.

- The second is how to produce the goods and services chosen? This question is related to the concept of technical efficiency.
- The third is for whom to produce the goods (and services)? This question is related to the concept of equity – i.e. who benefits from the use of the goods and services produced.

Health economics, being an application of economics to the health sector, is the study of how scarce resources are allocated among alternative uses for the care of illness and the promotion, maintenance, and improvement of health. Health economics investigates how health, health care and its related services, their costs and benefits and health itself are distributed among individuals and groups in society. In the last few decades, health economics has become increasingly relevant for a number or reasons.

First, the size of the contribution of the health sector to the overall economy is increasing:

- The health sector contributes a growing share of Gross Domestic Product (GDP) in all countries[17] (e.g. in 1929 in USA it accounted for 3.5% of GDP, in 1965 for 5.9%, now around 16%) – health expenditure is increasing rapidly in both high income (HICs) and low income countries (LICs[1]) - global health spending in 2002 was $3.2 trillion , around 10% of global GDP[18].
- The health sector has a growing importance in personal spending in both high and low income countries. Financial barriers to health care access are a major problem in many countries, especially the poorest ones. Globally it is estimated that around 150 million people suffer financial catastrophe annually because they pay for health services[19].

Secondly, there is a positive correlation between health and economic development. Investing in health improves economic performance and vice versa. As shown by the Commission on Macroeconomics and Health (CMH) [20]: *"Poverty and ill-health are closely linked [..] Health is a cornerstone of economic growth and social development; [..] Economic growth is not a precondition for real improvements in health; […] Increased investment in health would translate into hundreds of billions of dollars per year of additional income"*. The capability of developing countries to invest in health is limited. In 2002 only 12% of the

[1] According to the classification of the World Bank, low income countries are those with 2007 GNI per capita less that US$935, middle income countries are those with GNI per capita between US$ 936 and 11,455 (lower income US$ 936-3,705, upper middle income US$ 3,706-11,455), high income countries are those with GNI per capita of US$11,456 or more (http://web.worldbank.org)

global health expenditure was spent in LICs and Middle Income Countries (MICs). HICs spend 100 times more on health per capita (population-weighted) than LICs (30 times if one adjusts for cost of living differences). In 2007, in 64 WHO member states the total health expenditure was lower than US$50 per person per year and in 30 states it was lower than US$20[21]. Additionally, in LICs and MICs there is limited capacity to mobilize public resources for health. The public share of total health expenditure is 29% in LICs, 42% in lower MICs, 56% in upper MICs, 65% in HICs[18 22].

1.3.1 The economic evaluation framework

Economic evaluation is a systematic and transparent framework for assessing efficiency of programs. The basic task of economic evaluations is to identify, measure, value, and compare the costs and consequences of alternatives being considered.

Traditionally economic evaluations of health care programs have taken the form of cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). In CEA the cost per unit of health effects (i.e. life-years) gained by the adoption of the programme is estimated. In CUA health effects are measured in terms of utility, in order to combine in a single measure the different health benefits according to individuals' judgement.

CEA compares health intervention costs, measured in terms of the value of resources used to deliver them, and their benefits in terms of units of health outcomes estimating thus the cost-effectiveness ratio (CER) of an intervention as the costs and units of health benefit, the more efficient alternative being that with the lower CER. Depending on the comparison undertaken, the result may be an average cost-effectiveness ratio or an incremental cost-effectiveness ratio. The former compares total costs and total benefits, starting from zero, whereas the latter compares additional costs and additional benefits, starting from the current or some other level of coverage of an intervention.

CEA allows comparisons throughout the health sector and not only for the same health outcome. It does not allow comparison to non health outcomes unless these outcomes can be incorporated into costs. The main difference between CBA and the other techniques is that the former places monetary values on both the inputs (costs) and outcomes (benefits) of the activity/intervention being evaluated, while the latter provides monetary measures of only the costs.

Since the late 1960s, when economic evaluations began to be used in cost-benefit analysis of development projects by the World Bank, guidelines have been developed[23-25] defining the basic economic evaluation framework[26-31]. Several economic evaluation guidelines have been produced for evaluating health interventions, and costing guidelines or contributions to methodology which further detail specific applications of costing[32-34]. A seminal work by Drummond et al in 1987 defined a commonly agreed economic evaluation framework for health care programmes[35]. Also, the 1996 textbook "Cost-effectiveness analysis in health and medicine" by Gold et al was an important contribution to the application of economic evaluation to the field of health[36]. In the mid-1990s two important sets of journal publications were published based on these two textbooks, whose aim was to set norms and standards for economic submissions to academic journals[37-40].

More recently, the World Health Organization (WHO) has published its own guideline, which describes what is termed 'generalized cost-effectiveness analysis' – a common approach for the global application of CEA[41 42]. Generalized CEA is essentially the application of CEA to a wide range of interventions to provide general information on the relative costs and health benefits of different interventions in the absence of local decision constraints. Generalized CEAs require thus the evaluation of a set of interventions with respect to the counterfactual of the null set of the related interventions. Such relative cost-effectiveness, is meant to be a useful reference point for evaluating the directions for enhancing allocative efficiency in a variety of settings[43]. This approach has been applied by a WHO project, Choosing Interventions that are Cost Effective (WHO-CHOICE) assembling regional and country specific databases on the costs, impact on population health and cost-effectiveness of key health interventions[44].

In addition to these sets of general economic evaluation guidelines, several disease-specific or setting-specific CEA guidelines have been produced for conduct of CEA in resource-poor settings, covering diarrhea diseases[45] immunization[46], HIV/AIDS[47 48], tuberculosis[49], safe blood services[50], primary health care generally[51], and more recently bed-nets for malaria[52].

While several excellent guidelines have been elaborated, for the purposes of describing the general economic evaluation framework, the Drummond et al 10-point checklist is still the most useful[35 53]. This checklist, summarized in Table 1.2, elaborates the ten essential questions that should be answerable when reading a health economic evaluation study.

Economic evaluations are increasingly adopted to inform decision making in the health sector. However, this is only one of the many criteria for setting priorities and even in HICs, where evidence of cost-effectiveness of health intervention is more available than in LICs and MICs, the impact of CEA on priority setting is still limited though growing[54-58]. In a number of countries CEA are required for interventions to be included in the reimbursed benefit package such as for instance in England, and in the Netherlands and Australia for new drugs, and for labeling claims in the US Food and Drug Administration.

Regarding LICs and MICs related health problems, economic evaluations were used by the World Bank World Development Report "Investing in Health" back in 1993. More recently it was adopted by the Disease Control Priority Project, by the Global Forum for Health Research, and the WHO Commission on Macroeconomics and Health.

At national level, some LIC or MIC used cost-effectiveness data to inform decisions on the packages of essential care (e.g. Bangladesh, Mexico) and an important experience at district level in Tanzania (the Tanzania Essential Health Interventions Project -TEHIP) showed that it is possible to improve health outcomes re-allocating funds to cost-effective interventions that address the greatest contributors to burden of disease[59].

Table 0.2 The economic evaluation framework as captured by the Drummond et al 10-point checklist

#	***Drummond et al 10-point checklist***
1	Was a well-defined question posed in answerable form?
2	Was a comprehensive description of the competing alternatives given?
3	Was the effectiveness of the programmes or services established?
4	Were all the important and relevant costs and consequences for each alternative identified?
5	Were costs and consequences measured accurately in appropriate physical units?
6	Were costs and consequences valued credibly?
7	Were costs and consequences adjusted for differential timing?
8	Was an incremental analysis of costs and consequences of alternative performed?
9	Was allowance made for uncertainty in the estimates of costs and consequences?
10	Did the presentation and discussion of study results include all issues of concern to users?

Source: [53]

1.4. The economic costs of Malaria

The costs of malaria can be distinguished in direct and indirect costs. Direct costs are those incurred by health systems and sick individuals (and their families) to pay for interventions to prevent and cure malaria. A mild episode of malaria requires, usually, a drug treatment and an outpatient visit, while an episode of severe malaria requires an hospital admission and acute care treatment. Moreover, in LICs a malaria episode can lead to major costs for the families of patients due to the *user fees* paid to access health services, to the costs of transportation to health facilities, and, in case of hospitalization, to that incurred for staying overnight outside home for a few days.

Indirect costs of malaria are due to the reduced productivity of individuals caused by the disease and can be distinguished in two categories: those due to the fact that sick adults, or parents of sick children, cannot carry out their usual work, losing income and therefore not contributing to wealth production of their country; those due to premature mortality that shorten the time these individuals contribute to the economic development of their society.

The economic consequences of malaria on society have been analyzed by both microeconomic studies, aggregating estimates of costs per malaria case, and by macroeconomic studies estimating the impact of the disease on economic growth of the countries where it is more prevalent.

1.4.1 The macroeconomic impact of Malaria

The countries where malaria is endemic are amongst the poorest of the world, as shown by a study estimating that 58% of malaria cases are among the poorest 20% of world population[60]. The GDP per capita – adjusted for purchasing power parity– of the countries with more malaria is, on average, a fifth of that of the countries where malaria is not endemic[61].

Malaria affects the macroeconomic performances of endemic countries also contributing to the low attractiveness of foreign investments, hindering the development of human capital, and inducing large scale effects that can inhibit economic development.

The quantitative measurement of the relationship between malaria and economic development of countries is, however, very complex. Nevertheless, recent econometric studies, using cross country data, showed that malaria is a determinant of economic growth and development in the long term[61] [62]. According to these studies, the yearly growth rate of GDP per capita of malaria endemic countries is

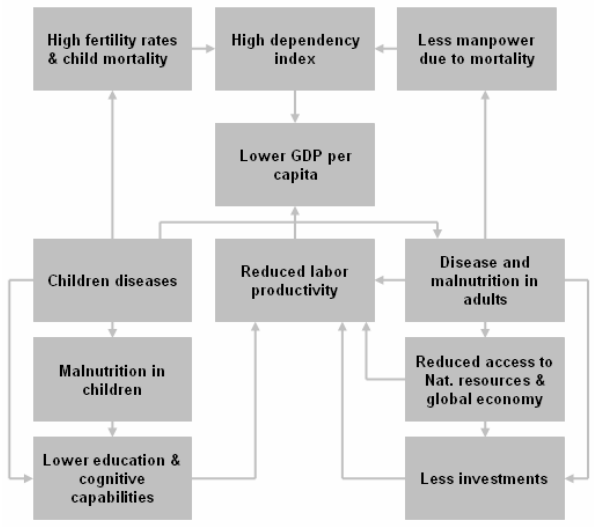
lower by 0.25-1.3% compared to that of countries without malaria, controlling for the impact of other factors that affect economic growth such as saving rates, political and economic institutions, education levels etc. These studies show also that over a period of 25 years these differential growth rates can account for almost half of the GDP per capita of LICs.

Nevertheless, macroeconomic studies do not provide any indication on the mechanisms through which economic growth is affected by malaria. Some of these mechanisms are however indirectly known (Figure 1.1). For instance, the deaths of millions of children in SSA cause, indirectly, an increase in fertility rates and large households, with negative consequences on available investments in education and health protection per child.

Moreover, malaria affects mainly infants and young children and those that survive can incur in long term consequences in the physical, mental, and learning and earning potentials. It has been shown, for instance, that between 10% and 50% of the school days lost due to health reasons in SSA are due to malaria[63], with negative consequences on school failure and drop out rates, and on school performances.

In endemic countries, foreign investments are scarce and there are numerous examples of foreign investor hardships due to health emergencies. For instance, in an aluminum plant built in Mozambique by a British company, with an investment of US$1.4 billion, the first two years there have been 7000 cases of malaria among the personnel and 13 deaths of expatriate personnel due to malaria related causes[63].

Figure 0.1 Relationship between Health and GDP (adapted from[64])



1.4.2 The microeconomic impact of Malaria

Many microeconomic studies showed that malaria is cause of significant costs for patients, in particular for the poorest households. Direct costs to prevent and cure malaria, can account up to a relevant part of the yearly income of poor households. For instance, in Malawi, the total annual cost of malaria per household was US$ 40 in 2003, around 7% of households income[65], while in Kenya it was around 9-18% of annual income of a group of farmers, and in Nigeria it was around 7-13%[66]. Other studies conducted in Africa a few years ago – in Burkina Faso, Chad, Congo, Rwanda – estimated that, in 1987, the cost of a malaria case was US$ 9.87, of which US$ 1.83 for direct costs and US$ 8.06 for indirect costs (including those due to morbidity and mortality). In 1987 values the total economic costs was US$ 0.8 billions and accounted for 0.6% of GDP of SSA countries, while another study updated these figures to around 1% of GDP[67].

The monthly per capita expenditure to prevent malaria was US$ 0.05 in rural area of Malawi[65] and US$ 2.1 in some urban areas in Cameroon (equivalent to US$ 0.24 - $ US$15 per households)[68], while the expenditure to treat malaria was US$0.41 in Malawi[65] and US$ 3.88 in Cameroon (equivalent to US$1.88-US$26 per household)[68]; in Malawi direct costs of treating malaria were around 28% of the income of the poorest households and around 2% of the other households.

Indirect costs of malaria are harder to estimate, due both to methodological problems and to a lack of accurate information on the consequences of malaria on productivity of people living in malaria endemic areas. The studies that attempted to measure indirect costs of malaria, estimated a cost per episode between US$0.68 for children under 10 in Malawi[65] and US$23 for adults in Ethiopia[69].

The aggregate estimates (at national level) of microeconomic studies are, however, lower than those obtained by macroeconomic studies. This is the reason why some economists argue that part of the costs of malaria are not accounted in microeconomic studies, as they do not capture the negative externalities that make the overall impact of malaria greater than the sum of the impact on each individual and household[63]. However, even if these studies report lower costs than those based on macroeconomic approaches, they still show that the costs of malaria is high in particular for poorest households, accounting for a significant proportion of their income.

1.4.3 The impact of Malaria on health systems

The weaknesses of health systems contribute to the costs of malaria incurred by patients. This is shown by the fact that most malaria episodes are treated at home through the private purchase of anti-malaria drugs (e.g. a study estimated that in Ghana only one fifth of fever episodes were treated in health facilities[70]).

Notwithstanding, malaria has an important impact on health systems of malaria endemic countries, even if there is a lack of solid detailed data on public expenditure for preventing and treating malaria. However, it is possible to evaluate the impact of malaria on health systems in relative terms. In malaria endemic countries, it is estimated that, on average, around 25-35% of outpatient visits are due to malaria (clinically diagnosed) both on children under five years old and in other age groups. In malaria endemic countries, between 20% and 40% of hospital admissions are caused by malaria[4]. Due to the high fatality rates, mainly caused by late access to health care, to inappropriate clinical management or to a lack of efficacious drugs, malaria is also one of the major causes of mortality in hospitals.

1.4.4 Cost-effectiveness of malaria control strategies

The reasons of the failures to control malaria are also related to the fact that over 90% of the burden of disease is in low income countries, with inefficient health systems and significant barriers (financial and otherwise) to access to preventive strategies and to efficacious treatments. ACTs costs around US$1-2 per course (but it can reach up to US$10 in the private sector) although it is anticipated that prices will decrease in the near future to less than US$1. An ITN costs on average US$2.5-4 while Long Lasting ITNs can be even more expensive. Although these are very low figures for HICs, for most people leaving in malaria endemic countries these are unaffordable, and most governments of these countries do not have enough financial resources to provide universal access to these interventions (Table 1.3).

Although there is no cost-effectiveness threshold that can be considered definitive for priority setting in the health sector, there are rule of thumbs that can be used to take more informed decisions. For instance, WHO defined a health intervention in low income countries to be "*Highly attractive"* when the cost per DALY averted is lower than US$25-30 and *"attractive"* when it is lower than US$ 150[41].

In the last two decades, extensive evidence showed that most interventions to control malaria, in endemic countries, are cost-effective (Table 1.4 reports the results of a sample of cost-effectiveness studies).

For instance a comprehensive study evaluated the cost-effectiveness of a number of malaria preventive and treatment strategies in SSA, estimating that in countries with a GDP per capita lower than US$315, with a high and moderate malaria transmission (such as Malawi, Mozambique, and Tanzania) the cost per DALY averted of preventive strategies was between US$3 and US$93, that of improving case management between US$ 3 and US$8[2]; in countries with GDP per capita between US$315 and US$1000 (such as, for instance, Benin, Ghana, and Zimbabwe) cost-effectiveness ratios were only slightly higher and lower than US$ 150 per DALY averted, while preventive strategies in countries with GDP per capita higher than US$1000, and thus most likely to be able to afford the costs of these interventions, such as Botswana and South Africa, were in some cases higher than US$ 150 per DALY averted[8 71]. The Disease Control Priority Project second edition conducted a modeling study with secondary data and estimated cost-effectiveness ratios for ITNs IRS, and IPTp. For ITNs the costs per DALY averted was US$ 11 (90% range US$ 5-21) for ITNs treated with Deltamethrin, and US12 (90% range US$ 6-31) for ITNs treated with Permethrin; for IRS the cost per DALY averted was US$ 9 and 24 depending on the insecticide used and the number of rounds; for IPT the (incremental) cost per DALY averted was US$ 13 (90% range US$ 9-21)[72].

WHO conducted a study in 2005 to determine the generalized cost effectiveness of a number of malaria control strategies in SSA countries estimating average cost-effectiveness ratios ranging from US$9 per DALY averted, achieving 90% coverage of case management with ACT, to US$ 41 per DALY averted with a combined strategy including Indoor residual spraying plus ITNs, plus case management with ACT (95% coverage)[73].

A study conducted a few years ago (in 1999) in Brazil[74], estimated the cost-effectiveness of an IRS program to be around US$ 132 per DALY averted, improving case management allowing early treatment of malaria had a cost per DALY averted of US$ 17, while a combination of the two programs had a cost per DALY averted of US$67[3]. Another example is in a highly endemic South African district, where IRS and ACT were introduced, leading to a 89% reduction in both hospital admissions for malaria and mortality with an 80% reduction in health expenditure attributable to malaria[75].

[2] Value in US$ of 1995.
[3] In US$ of 1995.

Table 0.3 Health expenditure in lowest income countries

Health expenditure in lowest income countries (average GDP per capita 450 US$)	**%/$**
Total health expenditure (% GDP)	4,8%
Per capita health expenditure ($)	23,2
Public health expenditure (% GDP)	1,2%
Public health expenditure (% of total health expenditure)	26,6%

Source: World Bank

Table 0.4 Cost-effectiveness ratios reported in a sample of studies on Malaria control strategies

Prevention	***Country***	***Cost per death averted (US$***	***Cost per DALY averted (US$)***	***Source***
Bed-nets	Gambia	219 (167–243)	9 (9–14)	[76]
		494 (326–805)	21	[77]
		829 (447–2117)	(14–35)	[78]
	SSA		4–10	[8]
	SSA		11-17 (5-31	[72]
Bed-nets and ITNs	Ghana	2112 (992–2289)	77 (37–84)	[79]
	Kenya	2958 (2838–3120)		[80]
	Africa		10–118	[81]
	SSA	788-2926	13-89	[9]
ITN and chemioprophilaxis	The Gambia	300 (246–333)	13 (13–20)	[76]
Chemioprophilaxi in children	The Gambia	167		[82]
Antenatal chemioprophilaxi with chloroquine	Malawi	950 (317–951)		[83]
IPTp (SP)	SSA		14–93	[8]
	SSA		13 (9-21	[72]
	Malawi	81 (79–352)		[83]
IRS	SSA		4–29	[8]
	SSA		12-24 (5-34)	[72]
	SSA		16–58	[8]
	SSA	3,933-4,357	119-132	[9]
Larviciding i	Zambia (1929-1950)	858	22–591	[84]
IPTi	Tanzania and Mozambique		Tanzania: 3.7-7.9 (1.6-27) Mozambique: 8.3-11.2 (3.3-92)	[85]
Treatment and combination strategies				
Drug treatment	Africa	0.20–6		[86]
Improvement in compliance	SSA		2–8	[8]
Case detection, drug treatment and IRS	Nepal	109–17,650	12–1803	[87]
Early treatment	Brasil	677 (271–1355)	17	[74 88]
IRS, source reduction, and improvement in early diagnosis and case management	Brasil	2596 (1093–5193)	67	[74]
IRS and source reduction (larviciding)	Brasile	5072 (785-10427)	132	[74]
Improvement of case management	SSA		1–3	[8]

1.5 Rationale of the thesis

The impact of malaria control interventions has been generally inferred from intervention efficacy trial results, which assess only the short-term effects using well controlled delivery systems. However, the long term effectiveness of implemented malaria control interventions will be reduced because of less than perfect access, compliance, targeting accuracy, and patient adherence. There will also be longer term dynamic effects (feed backs) due to changes in the immune status of the population, and benefits due to herd immunity and community effects of vector control. Cost-effectiveness studies are generally based on short-terms effectiveness estimates. Models for the cost-effectiveness of disease control strategies and also those of malaria control interventions, generally assume the incidence of illness and transmission dynamics to be independent of the prevailing case management system[36] [53]. Decision trees typically start with the observation of an illness episode and consider how the episode is managed subsequently, but do not consider whether case management itself affects the incidence of the disease. With infectious diseases such as malaria, this approach ignores the feedback that may arise from an effective case management system, which in turn reduces the frequency of infection, and thus impacts transmission dynamics. When the infection has a long time course, which may encompass several illness episodes, treatment may also reduce the subsequent burden of disease independently of its effect on transmission. In the case of malaria, untreated *P.falciparum* infections can persist for many months, during which clinical attacks recur at irregular intervals[89]. Conventional cost-effectiveness analyses of malaria control interventions do not consider these effects.

Malaria control interventions, such as source reduction by means of environmental management, increasing the coverage of ITNs, IRS, and potentially the introduction of a malaria vaccine, modify the demands on the health system, and thus affect both immediate direct impact and longer-term indirect effects of case management. This applies even when the intervention, such as vaccination, does not directly modify case management. It follows that predictions of the impact of preventative and curative interventions against malaria should take into account these dynamic effects.

1.6 Objectives of the thesis

This thesis is part of a larger research project aimed at:

- developing models for the natural history and epidemiology of *P. falciparum* malaria;
- developing models for malaria control interventions in the health system;
- predicting the epidemiology and the cost-effectiveness of malaria control interventions.

The thesis is focused on four specific objectives:

- The first is developing an innovative approach to dynamically model the costs and effects of case management of *P. falciparum* malaria in SSA. This model is integrated into a model for the clinical epidemiology and natural history of *P. falciparum* malaria (Chapter 2).

- The second is developing an approach to costing the delivery of a malaria vaccine through the Expanded Program on Immunization (EPI), presenting the predicted cost per dose delivered and the cost per fully immunized child (FIC), which are key inputs to the cost-effectiveness analysis (Chapter 3).

- The third is predicting the epidemiological impact and modeling the cost-effectiveness of introducing a pre-erythrocytic malaria vaccine into the EPI schedule in SSA under a range of health system scenarios, conditions, and assumptions (Chapter 4 and 5). The epidemiological impact and the cost-effectiveness estimates are based on the approaches developed in the first two objectives (Chapter 2 and 3).

- The fourth is simulating the likely cost-effectiveness of three different malaria vaccine types - pre-erythrocytic vaccines, blood stage vaccines, mosquito-stage transmission-blocking vaccines, and combinations of these – under a range of health system delivery modalities - EPI, EPI with booster, and mass vaccination combined with EPI - (Chapter 6).

1.7 References

1. de Savigny D, Binka F. Monitoring future impact on malaria burden in sub-saharan Africa. *Am.J Trop Med Hyg* 2004;71(2 Suppl):224-231.

2. World Health Organization. World Malaria Report 2008, 2008.

3. Snow R, Guerra C, Noor A, Myint H, Hay S. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature* 2005;434(7030):214-217.

4. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates of the causes of death in children. *Lancet* 2005;365(9465):1147-1152.

5. Olliaro P, Cattani J, Wirth D. Malaria, the submerged disease. *JAMA* 1996;275(3):230-233.

6. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane.Database.Syst.Rev.* 2004(2):CD000363.

7. Phillips-Howard P, Nahlen B, Kolczak MS, Hightower AW, ter Kuile F, Alaii JA, et al. Efficacy of permethrin-treated bed nets in the prevention of mortality in young children in an area of high perennial malaria transmission in western Kenya. *Am J Trop Med Hyg* 2003;68 (Suppl. 4):23-29.

8. Goodman CA, Coleman PG, Mills A. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999;354(9176):378-385.

9. Yukich JO Lengeler C Tediosi F BNMJCDSWJJCLMREMMDWVGTZMG. Costs and consequences of large-scale vector control for malaria. *Malar J.* 2008;Dec 17;7:258.

10. UNICEF. Malaria and children: Progress in intervention coverage. . New York: UNICEF, 2007.

11. World Health Organisation. World Malaria Report. Roll Back Malaria, WHO, Unicef http://www.who.it, 2005., 2005.

12. Lengeler C, Sharp B. Indoor Residual Spraying and Insecticide-Treated Nets. *Reducing Malaria's Burden. Evidence of Effectiveness for Decision Makers*: Global Health Council, 2003:17-24.

13. Najera JA Zaim M. Malaria Vector Control: Decision Making Criteria and Procedures for Judicious Use of Insecticides. In: WHO/CDS/WHOPES/2002.5, editor. Geneva: World Health Organization., 2002.

14. Pedro L Alonso JSJJAALEMJMIMBSCGMEQBPAOO-AMM. Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomised controlled trial. *The Lancet* 2004;Volume 364, Number 9443:1411-20.

15. Aponte JJ AP, Renom M, Mandomando I, Bassat Q, Sacarlal J, Manaca MN, Lafuente S, Barbosa A, Leach A, Lievens M, Vekemans J, Sigauque B, Dubois MC, Demoitié MA, Sillman M, Savarese B, McNeil JG, Macete E, Ballou WR, Cohen J, Alonso PL. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. *Lancet. 2007* 2007;Nov 3;370(9598):1543-51. Epub 2007 Oct 18. .

16. Ballou WR, Arevalo-Herrera M, Carucci D, Richie TL, Corradin G, Diggs C, et al. Update on the clinical development of candidate malaria vaccines. *Am.J Trop Med Hyg* 2004;71 (2 Suppl)(2 Suppl):239-247.

17. Hsiao WC. Why Is A Systemic View Of Health Financing Necessary? . *HEALTH A F FA I R S* 2007; Vo l u m e 2 6 , Nu m b e r 4.

18. Gottret P Schieber G. Health financing revised: A practitioner's guide. . In: Bank TIBfRaDTW, editor. Washington DC, 2006.

19. Xu K Evans DB Carrin G Aguilar-Rivera AM Musgrove P Evans T. Protecting households from catastrophic health spending. . *Health Aff (Millwood).* 2007;Jul-Aug;26(4):972-83.

20. Sachs JD. Macroeconomics and health: investing in health for economic development. Geneva Commission on Macroeconomics and Health, WHO 2001.

21. World Health Organisation. WHO, Fact sheet, Spending on Health: a global overview. http://www.who.int/mediacentre/factsheets/fs319/en/index.html (accessed May 11th 2009).

22. World Health Organization. Fact sheet. Spending on health: a global overview. http://www.who.int, 2008.

23. Little IMD, Mirrlees JA. *Manual of Industrial Project Analysis in Developing Countries*. OECD, Paris, 1969.

24. Dasgupta P. An analysis of two approaches to project evaluation in developing countries. *Industrialization and Productivity Bulletin, UNIDO* 1970;15.

25. United Nations Industrial Development O. *Guidelines for project evaluation*. New York: United Nations, 1972.

26. Layard R. *Cost Benefit Analysis*: Harmondsworth: Penguin., 1972.

27. Mishan E. *Cost Benefit Analysis.* . London: 2nd edition. Allen and Unwin., 1075.

28. Sugden R, Williams A. *Principles of practical cost-benefit analysis*: Oxford University Press, 1978.

29. Pearce D Nash C. *The Social Appraisal of Projects: A Text in Cost Benefit Analysis.* . Hounslow and London: Macmillan., 1981.

30. Curry S Weiss J. *Project analysis in developing countries.* : MacMillan., 1993.

31. Little I Mirrlees J. The costs and benefits of analysis: project planning and appraisal twenty years on, in Cost-benefit analysis, R. Layard and S. Glaister, Editors. 1994, Cambridge University Press., 1994.

32. Adam T Evans D Murray C. Econometric estimation of country-specific hospital costs. . *Cost-effectiveness and Resource Allocation,*.

33. Hutton G Baltussen R. Cost valuation in resource-poor settings. . *Health Policy and Planning,* 2005;20(4): p. 252-259.

34. Johns B, Baltussen R, Hutubessy R. Programme costs in the economic evaluation of health interventions. *Cost.Eff.Resour.Alloc.* 2003;1(1):1.

35. Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*: Oxford University Press. First Edition, 1987.

36. Gold MR, Gold SR, Weinstein MC. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press, 1996.

37. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic sumissions to the BMJ *British Medical Journal* 1996;313(3 August):275-283.

38. Weinstein M, Siegel J, Gold M, Kamlet M, Russell L. Recommendations of the panel of cost-effectiveness in medicine. *Journal of the American Medical Association* 1996;276(15):1253-1341.

39. Russell LG Siegel MR Daniels JN Weinstein M ftPOC-EiHaM. The role of cost-effectivenes in health and medicine. . *Journal of the AMerican Medical Association,* 1996;276(15): p. 1172-7.

40. Siegel J Weinstein M Russell L Gold M. Recommendations for reporting cost-effectiveness analyses. . *Journal of the American Medical Association,* 1996;276(15): p. 1339-41.

41. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, et al. *Making choices in health: WHO guide to cost-effectiveness analysis*: World Health Organization, Geneva, 2003.

42. Baltussen R. The economic foundations of Generalized CEA. GPE discussion paper, World Health Organization, 2002.

43. Murray CJ Evans DB Acharya A Baltussen RM. Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ.* 2000;Apr;9(3):235-51.

44. World Health Organisation. WHO-CHOICE, Choosing Interventions that are Cost Effective. http://www.who.int/choice/en/.

45. World Health Organization. . Estimating costs for cost-effectiveness analysis: Guidelines for managers of diarrhoeal disease control programmes. , 1988.

46. Organization WH. Expanded Programme on Immunization: Costing Guidelines. , 1979.

47. Pepperall J MA, Vaughan P, Watts C and Zwi A. Costing guidelines for HIV/AIDS prevention strategies. London School of Hygiene and Tropical Medicine., 1994.

48. Kumaranayake L PJ, Goodman H, Mills A and Walker D. Costing guidelines for HIV/AIDS prevention strategies. A companion volume to 'Cost analysis in primary health care: a training tool for programme managers'. . *London: Health Economics and Financing Programme, London School of Hygiene and Tropical Medicine.*, 2000.

49. Sawert H. Cost analysis and cost containment in tuberculosis programmes: The case of Malawi. Global Tuberculosis Programme, World Health Organization., 1996.

50. World Health Organization. Safe blood and blood products: costing blood transfusion services., 1998.

51. Creese A and Parker D. Cost analysis in primary health care: a training manual for programme managers. 1994, Geneva: World Health Organization., 1994.

52. Kolaczinski JH Hanson K. Costing the distribution of insecticide-treated nets: a review of cost and cost-effectiveness studies to provide guidance on standardization of costing methodology. *Malaria Journal* 2006;5:37.

53. Drummond M, O'Brien BJ, Stoddart GL, Torrance G. *Methods for the economic evaluation of health care programmes*. New York: Oxford University Press. Second edition, 1997.

54. Gabbay J le May A. Evidence Based Guidelines or Collectively Constructed 'Mindlines?' Ethnographic Study of Knowledge

Management in Primary Care. *British Medical Journal* 2004;329 (7473): 1013.

55. Glick H Polsky D Schulman K. *Trial-Based Economic Evaluations: An Overview of Design and Analysis.*, 2001.

56. Hoffmann C, B. A. Stoykova, J. Nixon, J.M. Glanville, K.Misso, M. F., Drummond. Do Health-Care Decision Makers Find Economic Evaluations Useful? The Findings of Focus Group Research in U.K.Health Authorities. *Value Health 5 (2): 71–78.* 2002.

57. McDaid D, R. Cookson, and ASTEC Group. . "Evaluating Health Care Interventions in the European Union. *Health Policy 63 (2): 133–39.* 2003.

58. Sheldon TA, N. Cullum, D. Dawson, A. Lankshear, K. Lowson, I. Watt,, others a. What's the Evidence That NICE Guidance Has Been Implemented? Results from a National Evaluation Using Time Series Analysis, Audit of Patients' Notes, and Interviews. *British Medical Journal* 2004;329 (7473): 999.

59. de Savigny D Kasale H Mbuya C Reid G. *Fixing Health Systems. 2nd edition*, 2008.

60. Barat L PN, Basu S. . Do Malaria control interventons reach the poor? A view through the equity lens. . *Am J Trop Med Hyg.* ;Aug;71(2 Suppl):174-8., 2004.

61. Gallup JL, Sachs J. The economic burden of malaria. *Am J Trop Med Hyg* 2001;64(1-2 Suppl):85-96.

62. McCarthy D WH, Wu Y. . Malaria and Growth. . *Policy Research Working Paper 2303. Washington DC; World Bank., 2000.*, 2000.

63. Sachs J, Malaney P. The economic and social burden of malaria. *Nature* 2002;415(6872):680-685.

64. Breman JG, Alilio MS, Mills A. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. *Am J Trop Med Hyg* 2004;71 (2 Suppl)(2 Suppl):1-15.

65. Ettling M MD, Schultz LJ, Chitsulo L. . Economic impact of malaria in Malawian households. . *Trop Med Parasitol. Mar;45(1):74-9., 1994.*

66. Leighton C FR. Economic impacts of Malaria in Kenya and Nigeria. . *Bethesda, MD: Abt Associates. 1993.*

67. Shepard DS EM, Brinkmann U, Sauerborn R,. The economic cost of malaria in Africa. . *Trop Med Parasitol.*;Sep;42(3):199-203. Review, 1991.

68. Desfontaine M GH, Goghomu A, Kouka-Bemba D, Carnevale P. Evaluation of practices and costs of antivectorial control at the family level in central Africa. . *Yaounde City (March 1988) Bull Soc Pathol Exot Filiales; 82(4):558-65. French. 1989.*

69. Cropper ML HM, Poulos C, Whittington D. . The value of Preventing Malaria in Tembien, Ethiopia. . In: Working Paper WDTWB, editor, 1999.

70. Agyepong I KKJ. Providing practical estimates of the malaria burden for health planners in resource poor communities. . *Am J Trop Med Hyg.* . 2004;Aug;71(2 Suppl):162-7.

71. Goodman C CPMA. Economic Analysis of Malaria Control in Sub-Saharan Africa. Global Forum for Health Research, May 2000.

72. Breman JG Mills A Snow BW Mulligan JA Lengeler C Mendis K Sharp B Morel C Marchesini P White NJ Steketee RW Doumbo OK. Conquering Malaria. *Disease Control Priorities in developing countries.*, 2007.

73. Morel CM, Lauer JA, Evans DB. Cost effectiveness analysis of strategies to combat malaria in developing countries. *BMJ* 2005;331 1299.

74. Akhavan D MP, Abrantes A, Gusmao R. Cost-effective malaria control in Brazil: Cost-effectiveness of a malaria control program in the Amazon Basin of Brazil, 1988-1996. . *Social Science and Medicine*;49:1385-1399. 1999.

75. Muheki C MD, Barnes K. Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. . *Tropical Medicine and International Health,* 2004;9(9): p. 959-966.

76. Picard J AM, Alonso PL, Armstrong Schellenberg JR, Greenwood BM, Mills A. . A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. Costst-effectiveness of bed net impregnation alone or combined with chemoprophylaxis in preventing mortality and morbidity from malaria in Gambian children. . *Transactions of the Royal Society of Tropical Medicine and Hygiene, 2:53-57.* 1993.

77. Aikins MK F-RJ, D'Alessandro U, Langerock P, Cham K, New L, Bennett S, Greenwood B, Mills A. . The Gambian National Impregnated Bednet programme:Costs, consequences and net cost-effectiveness. . *Social Science and Medicine* 2004;46(2):181-191.

78. Graves PM. Comparison of the cost-effectiveness of vaccines and insecticide impregnation of mosquito nets for the prevention of malaria. . *Annals of Tropical Medicine and Parasitology.* 1988; 92(4):399-410.

79. Binka F, Mensah OA, Mills A. The cost-effectiveness of permethrin impregnated bednets in preventing child mortality in Kassena-Nankana district of Northern Ghana. *Health Policy* 1997;41(3):229-239.

80. Some ES. Optimizing the community effectiveness of insecticide-impregnated bednets used for malaria control in coastal Kenya: Implications of perceptions, programme organization, compliance, and costs. . In: PhD Thesis DoEaPH, London School of Hygiene and Tropical Medicine, University of London., 1999., editor.

81. Evans DB AG, Kirigia J. Should governments subsidize the use of insecticide-impregnated mosquito nets in Africa? Implications of a costeffectiveness analysis. . *Health Policy and Planning, 12(2):107-114.* 1997.

82. Picard J MA, Greenwood B. The cost-effectiveness of chemoprophylaxis with Maloprim administered by primary health care workers in preventing death from malaria amongst rural Gambian children aged less than five years old. . *Transactions of the Royal Society of Tropical Medicine and Hygiene, 86(6):580-581.*, 1992.

83. Schultz LJ SR, Chitsulo L, Macheso A, Kazembe P, Wirima J. Evaluation of maternal practices, efficacy, and costeffectiveness of alternative antimalarial regimens for use in pregnancy: chloroquine and sulfadoxine-pyrimethamine. . *American Journal of Tropical Medicine and Hygiene,* 1996;55(1 Suppl):87-94.

84. Utzinger J, Tozan Y, Singer B. Efficacy and cost-effectiveness of environmental management for malaria control. *Trop Med Int Health* 2001;6(9):677-687.

85. Hutton G Schellenberg D Tediosi F Macete E et al. Cost-effectiveness of malaria intermittent preventive treatment in infants (IPTi) in Mozambique and the United Republic of Tanzania. *Bull World Health Organ* 2009;87:123–129 | doi:10.2471/BLT.08.051961.

86. Sudre P BJ, McFarland D, Koplan JP. . Treatment of chloroquine-resistant malaria in African children: a cost-effectiveness analysis. . *International Journal of Epidemiology,* 1992;21(1):146-154.

87. Mills A. Is malaria control a priority? Evidence from Nepal. . *Health Economics,* 1993;2(4):333-347., 1993.

88. Akhavan D MP, Abrantes A, d'A Gusmao R. Cost-effective malaria control in Brazil: Cost-effectiveness of a malaria control program in the Amazon Basin of Brazil, 1988-1996. Social Science and Medicine, 49:1385-1399. 1999.

89. Collins WE, Jeffery GM. A retrospective examination of the patterns of recrudescence in patients infected with Plasmodium falciparum *Am.J Trop Med Hyg* 1999;61(1 Suppl):44-48.

Chapter 2: An approach to model the costs and effects of case management of plasmodium falciparum malaria in Sub-Saharan Africa

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Abstract

An important shortcoming of existing methods for estimating the cost-effectiveness of malaria control interventions is that the incidence of illness and transmission dynamics are assumed to be independent of the case management system. We have developed a model for case management and integrated it into a stochastic simulation of *Plasmodium falciparum* malaria dynamics. This allows us to predict the incidence of clinical episodes and of mortality while incorporating effects of case management on persistence of parasites and transmission. We make predictions for a range of different transmission intensities in sub-Saharan Africa and simulate a range of case management scenarios with different coverage rates. The model predicts that high treatment rates have a proportionately greater epidemiologic impact at low transmission levels. Further development is needed for models for health seeking behavior and referral patterns. The current model is a first step towards useful predictions of the epidemiologic and economic consequences of introducing and/or scaling-up of malaria control interventions.

2.1 Introduction

Models for the cost-effectiveness of different disease control strategies generally, and malaria control interventions in particular, usually assume the incidence of illness and transmission dynamics to be independent of the prevailing case management system.[1,2] Decision trees typically start with the observation of an illness episode and consider how the episode is managed subsequently, but do not consider whether management itself affects the incidence of the disease. With infectious diseases such as malaria, this approach ignores the feedback that may arise from an effective case management system, which in turn reduces the frequency of infection, and hence impacts transmission dynamics.

Models for nosocomial infections and those recently developed to simulate the SARS epidemic[3,4] provide examples of approaches in which the operation of the health system interacts in a dynamic fashion with the biology of the infecting organism. In these models, prompt treatment of infections reduces epidemic spread, and thus results in both reductions in the subsequent burden of disease and in the requirements for treatment of secondary cases.

When the infection has a long time course, which may encompass several illness episodes, treatment may also reduce the subsequent burden of disease independently of its effect on transmission. In the case of malaria, untreated *Plasmodium falciparum* infections can persist for many months, during which clinical attacks recur at irregular intervals.[5] One of the current mainstays of malaria control is access to early

diagnosis and effective treatment.[6] Prompt and effective treatment not only reduces the reservoir hosts who are infective to mosquitoes, but also prevents recurrences. Longitudinal studies of malaria in endemic populations frequently record declines in incidence over time. A major reason for this is likely to be that study participants receive more frequent treatment and this reduces the incidence of subsequent malaria fever attacks, irrespective of any effect on transmission. Conventional cost-effectiveness analysis of treatment does not consider these effects.

Malaria control interventions, such as source reduction by means of environmental management, increasing the coverage of insecticide-treated nets (ITNs), indoor residual spraying, and (potentially) the introduction of a malaria vaccine, modify the demands on the health system, and hence affect both immediate direct impact and longer-term indirect effects of case management. This applies even when the intervention, such as vaccination, does not directly modify case management. It follows that prediction of the impact of preventative and curative interventions against malaria must take into account these dynamic effects.

This paper presents a first attempt to develop a dynamic model including case management of *P. falciparum* malaria in a typical setting of sub-Saharan Africa. It has been integrated into a model for the clinical epidemiology and natural history of *P. falciparum* malaria.[7] We compare the outcomes of different case management regimens in settings of different transmission intensities.

2.2 Materials and methods

Epidemiologic model. The epidemiologic model is a stochastic individual-based simulation of *P. falciparum* malaria in endemic settings that uses a 5-day time step. The primary input is the pattern of the entomologic inoculation rate (EIR) in the absence of malaria control interventions, with separate values of the EIR specified for each of the 73 5-day periods during the year.[7,8] For the present analyses we simulate populations of 100,000 individuals, with an approximately stationary age distribution matching that of the demographic surveillance site in Kilombero, Tanzania, 1997-1999.[19]

For every individual in the simulated population each discrete *P. falciparum* infection is characterized by a simulated duration and parasite density at each 5-day time point.[9] The host acquires immunity as a function of exposure and this in turn modifies the parasite density, and infectivity to mosquitoes[10,11] at subsequent time-points. At

each time point, a clinical event, either uncomplicated clinical malaria, severe malaria, or death from either malaria or other causes, may occur. Probabilities for occurrence of these events depend on the parasite density, recent exposure and age-dependent co-morbidity. They have been determined by functions that have been fitted to field data across a wide range of transmission settings.[12-14] In addition, the prevalence of anemia (hemoglobin levels below 8 g/dL) is assigned at the population rather than the individual level, as a function of simulated age and parasite prevalence.[15]

Clinical events. There are five different entry points into the case management tree: (i) no event, (ii) uncomplicated malaria, (iii) severe malaria, (iv) indirect malaria death, and (v) non-malaria death or out-migration. They are defined as follows:

1. *No event*, includes asymptomatic malaria infections. In this case the simulated individual continues to the next time point, with the natural history of *P. falciparum* infections unmodified by the case management model.

2. *Uncomplicated clinical malaria* comprises *P. falciparum* infections that may be treated either at home or in peripheral health facilities. The model assumes that the risk of uncomplicated clinical malaria depends on whether the parasite density exceeds a critical threshold, which in turn is a function of past exposure.[13] The case management implications of uncomplicated clinical malaria further depend on whether the host has recently been treated for malaria. Two possibilities were considered, as follows:

(A.) *An uncomplicated clinical malaria* in the absence of recent treatment. This is defined by no treatment over the previous 30 days (6 time points). The decision tree pathways for this scenario are depicted in Figure 2.1a. They include (i) entry into the formal health care system and receiving the first-line drug, (ii) self-treatment at home with the recommended first-line drug or (iii) absence of malaria treatment-seeking.

(B.) *An uncomplicated clinical malaria* episode that occurs despite recent treatment history. Figure 2.1b shows the decision tree pathways for this scenario. An uncomplicated malaria case that was treated in the past 30 days is assumed to either seek care or not. If care is sought, it is assumed to take place in the formal health care system, with treatment being based on the second-line drug. We do not consider the possibility that patients self-treat following drug failure, because this would very likely involve ineffective retreatment with the first-line drug, with no epidemiological consequences.

3. Severe malaria episodes are those clinical malaria episodes that are life-threatening if they are left untreated. We consider severe malaria episodes as those events that would have led to an admission diagnosis of severe malaria, had the patient presented to a health facility.[12] The current model assumes that a severe malaria case can either be treated as an in-patient or not be treated at all. In the former case it is assumed that compliance is 100%. There are three possible clinical outcomes for treatment of a severe malaria episode, namely (i) death, (ii) recovery with neurological sequelae, or (iii) full recovery (Figure 2.1c).

4. Indirect malaria death considers those deaths that would not have occurred in the absence of prior malaria exposure but which do not meet the criteria for severe malaria.[12]

5. *Non-malaria death and out-migration* correspond to events that occur independently of the parasitologic status of the host. These events are simulated in order to maintain the correct age-structure of the simulated population.

When more than one simulated clinical attack occurs within 30 days of each other, these are counted as the same episode. There can thus be several treatments for one episode. The severity assigned to the episode is assigned to that of the most severe malaria attack within the 30-day period.

Each decision tree pathway predicts the outcome in terms of (i) whether or not the parasites are cleared, and (ii) the clinical outcome (i.e. death, recovery with long-term sequelae or full recovery). The epidemiologic effects of the case management depend stochastically on the values of the joint probabilities of the clinical and parasitologic outcomes, conditional on the clinical event. These conditional probabilities are computed by calculating the probabilities for each branch of the decision tree pathways (Figure 2.1). For the model of uncomplicated malaria the probabilities associated with each branch in the decision tree were obtained from the literature (Table 2.1).

For the severe malaria model, we used in-patient case fatality rates, $Q_h(a)$, from a recent study in Tanzania,[16] and estimated corresponding community case fatality rates, $Q_c(a)$. $Q_h(a)$ varies with age a, taking values from 3% to 13%. $Q_c(a)$ takes values estimated previously using our model for severe malaria and mortality assuming the two risks to be related via a constant odds ratio, φ_1, taking a value of 2.09,[12] i.e.

$$Q_c(a) = \varphi_1 Q_h(a) \frac{1 - Q_c(a)}{1 - Q_h(a)} \qquad (1)$$

We assume negligible drug-resistance to quinine, so that parasites are cleared in all hospitalized cases who survive. We assign a probability of sequelae, R_x, with a value independent of treatment (Table 2.1).

Disability adjusted life-years (DALYs). Years of life lived with disability (YLDs) are calculated using standard methods[17] on the basis of the duration of disability, and respective disability weights (Table 2.2). These weights for different malaria-attributable disease conditions have been obtained from the Global Burden of Disease (GBD) study.[18]

Years of life lost (YLLs) and DALYs (age-weighted) are calculated assuming age-specific life expectancies, based on the life-table from Butajira, Ethiopia, with an average life expectancy of 46.6 years at birth.[19] This life-table represents that of an East African setting, but is characterized by low malaria transmission. For example, it is very similar to that for Hai district, a high altitude site in Tanzania.[20]

In a first step, YLLs and DALYs are presented with no discounting. Subsequently we compare the results with those obtained using a 3% discount rate, which is the one most commonly employed in cost-effectiveness analyses.[1,2]

Table 0.1 Model inputs used for efficacy and malaria treatment seeking behavior

		Case management scenarios					Source
Symbol	***Description***	***No treat-ment***	***Reference***	***Moderate coverage***	***Complete coverage***	***Effective treatment***	
	Uncomplicated malaria						
P_u	*Probability of seeking care in the formal health sector*	*0.0*	*0.04*	*0.27*	*1.0*	*1.0*	*
P_s	*Probability of self-treatment*	*0.0*	*0.01*	*0.13*	*0.0*	*0.0*	*
P_r	*Probability of seeking out-patient care in case of treatment failure*	*0.0*	*0.04*	*0.27*	*1.0*	*1.0*	*
	Compliance						
C_u	*SP: formal health sector*	*n.a.*	*0.90*	*0.90*	*0.90*	*1.00*	[33]
C_r	*Amodiaquine*	*n.a.*	*0.45*	*0.45*	*0.45*	*1.00*	[33]
C_s	*SP: self-treatment*	*n.a.*	*0.85*	*0.85*	*n.a.*	*n.a.*	[33]
	Cure rate†						
R_u	*SP: formal health sector*	*n.a.*	*0.93*	*0.93*	*0.93*	*1.00*	[33]
R_r	*Amodiaquine*	*n.a.*	*0.85*	*0.85*	*0.85*	*1.00*	[33]
R_s	*SP: self-treatment*	*n.a.*	*0.63*	*0.63*	*n.a.*	*n.a.*	[33]
	% of non-compliers for whom treatment is effective						
R_{ns}	*SP*	*n.a.*	*0*	*0*	*n.a.*	*n.a.*	-
R_{nr}	*Amodiaquine*	*n.a.*	*0.20*	*0.20*	*n.a.*	*n.a.*	[33]
	Severe malaria						
P_h	*Probability of in-patient care*	*0.0*	*0.48*	*0.48*	*1.0*	*1.0*	[27]
R_q	*Cure rate (Quinine)*	*n.a.*	*0.998*	*0.998*	*0.998*	*0.998*	[32]
R_x	*Probability of neurological sequelae for severe episodes for age-group <5 years*‡	*0.0132*	*0.0132*	*0.0132*	*0.0132*	*0.0132*	[33,48]
	Probability of neurological sequelae for severe episodes for age-group ≥5 years‡	*0.005*	*0.005*	*0.005*	*0.005*	*0.005*	[33,48]

*The values for the reference scenario are adapted from those used in our simulation of a field trial of a malaria vaccine; those for the moderate coverage scenario are based on the data of the Tanzanian NMCP.[29] †The cure rate refers to the "adequate clinical response rate"; SP: sulphadoxine-pyrimethamine; ‡The same probabilities are used for neurological sequelae for both in-patients and non-hospitalized severe episodes; n.a.: not applicable.

Table 0.2 Disability weights and duration of disability used to calculate YLDs

Disease condition	Disability weight	Duration (years)
Untreated neurological sequelae	*0.473*	*35.4*
Neurological sequelae (treated)	*0.436*	*35.4*
Uncomplicated malaria episode	*0.211*	*0.01*
Anemia	*0.012*	*n.d.*
Low birth weight	*n.d.*	*n.d.*
Others	*n.d.*	*n.d.*

n.d. = not defined

Malaria transmission intensity. The introduction of changes in case management (or of other interventions) leads to transient behavior, which may in principle modify the level of *P. falciparum* transmission. These effects on transmission are captured in the model by the effects on infectiousness of the human population resulting from clearing parasites. The simulation model predicts for time point t the proportion, $\bar{\kappa}_m(t)$ of vectors that become infected at each feed on a human host.[10,11] We adjust this to give $\kappa_u(t) = 0.56\ \bar{\kappa}_m(t)$ to allow for the bias arising because $\bar{\kappa}_m(t)$ is estimated from artificial feed data.[10] We record the value $\kappa_u^{(0)}(t)$ that $\kappa_u(t)$ takes in the simulation of the reference scenario to which a change in the case management model has been applied, and compare this value to $\kappa_u^{(1)}(t)$, the prediction of $\kappa_u(t)$ for the same time-point in the simulation with a change in case management. The effect of the change in case management on transmission is then modeled by a change in the EIR in adults at l_v time units later ($E_{\max}(t+l_v)$), such that:

$$E_{\max}^{(1)}(t+l_v) = \frac{E_{\max}^{(0)}(t+l_v)\ \kappa_u^{(1)}(t)}{\kappa_u^{(0)}(t)} \qquad (2)$$

where l_v corresponds to the duration of the sporogonic cycle in the vector, and where $E_{\max}^{(0)}(t+l_v)/\kappa_u^{(0)}(t)$ is the overall vectorial capacity. The consequences for the infection rates follow from details of the epidemiologic model.[8]

We considered four different intensities of transmission, each with the same seasonal pattern as that in Namawala, Tanzania[21] (Table 2.3). For the reference scenario, we used an overall annual EIR of 21 infectious bites per annum which represents a typical level of transmission for a meso-endemic setting.[22,23]

Table 0.3 Scenarios modeled: health systems and transmission intensities

Transmission intensities	Annual EIR
Very low transmission	*1.3*
Low transmission	*5.2*
Reference	*21*
High transmission	*83*
Very high transmission	*329*
Health system	
No treatment	
Reference	
Moderate coverage	
60% Abuja target coverage	
Full coverage	
Effective treatment	

Health Systems. Uncomplicated malaria patients seeking formal health care in Tanzania are usually diagnosed during an out-patient visit either in a health centre, a dispensary or a hospital. A diagnostic test (normally light microscopy of finger-prick blood smears) is performed on less than 10% of treated cases.[24] Current Tanzanian national treatment guidelines recommend that an uncomplicated malaria episode be treated with sulphadoxine-pyrimethamine (SP) as the first-line drug. Amodiaquine serves as the second-line drug, and quinine is used for treatment of severe malaria.[25] Our models assume that formal-sector treatment adheres to these practices (Tables 2.4 and 2.5). We also assume that SP is used as the drug of choice for self-treatment but the efficacy is assumed lower to account for lower quality of drugs purchased in the private sector. The levels of compliance and of drug resistance that we assume are given in Table 2.1.

We evaluate the effects of different case management in our model by varying either malaria treatment seeking-behavior or availability of treatment. Table 2.3 summarizes the set of scenarios considered, which include 5 different sets of assumptions for the level of treatment:

(i) *No treatment*: in this model we assume no access to antimalarial treatments at all.

(ii) *Reference case management*: in this model we took the same probability of seeking treatment for uncomplicated malaria as in our recent simulation of a malaria vaccine trial,[26] but assume 20% of treatments to be self-treatment and 80% to use formal care. We use a value of 48% for the probability of seeking treatment for severe malaria (Table 2.1).[27,28] The treatment rates for uncomplicated episodes are

low because the model for clinical episodes was fitted to very intensive surveillance data from Senegal, which included very minor fevers that would be very unlikely to lead to treatment seeking.[13] The treatment rates were estimated by triangulating the predictions of this model for clinical episodes with health system attendance data from Manhiça, Mozambique.[26]

(iii) *Moderate coverage*: For this model we use recent data from the Tanzanian National Malaria Control Program (NMCP) of the Ministry of Health (MOH).[29] This report states that 27% of children <5 years of age were treated within 24 hours in health facilities, 13% at home and 2% at traditional healers. The remaining 58% received no treatment within 24 hours from the onset of disease.[30] We use these percentages of 27% of children receiving formal care, and 13% self-treatment for uncomplicated malaria episodes (Table 2.1). We use the same coverage of formal care for severe malaria as in the reference model. In the context of our 5 day time-step we do not distinguish in our simulations whether treatment is within 24 hours or not.

(iv) *60% Abuja target coverage:* 60% of uncomplicated episodes are treated with appropriate drug. The simulated coverage of hospital treatment for severe episodes remains at 48%.

(v) *Complete coverage:* We assume that 100% of uncomplicated clinical episodes are treated via formal-sector care. We also assume that 100% of severe malaria episodes are treated.

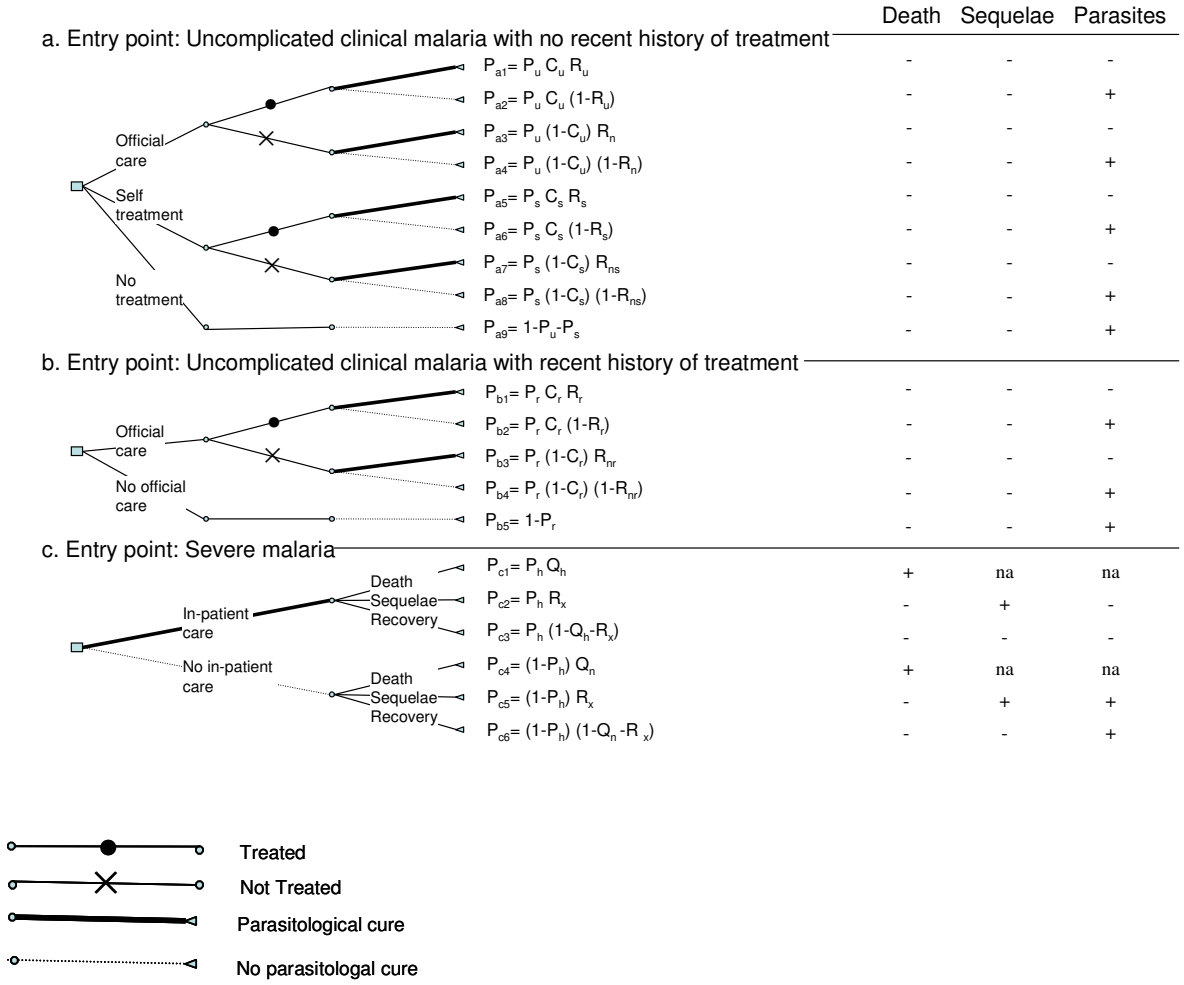
(vi) *Effective treatment:* We assume that 100% of clinical episodes are treated via formal-sector care, and furthermore that there are no treatment failures. Moreover we assume that all severe episodes receive in-patient treatment.

To explore the dynamic impact of different case management options, we ran simulations over a 90-year period at different transmission intensities under the assumptions of the reference case management scenario. The rather low level of treatment in this scenario is intended to approximate conditions prevailing in many areas studied in Africa of limited drug availability, drug resistance, and non-treatment or under-treatment of minor febrile attacks.

This defined the baseline status of the simulated populations. We then simulated the transient behavior over the next 5-, 10- and 20-year periods, for different case management scenarios, assuming the vectorial capacity for *P. falciparum* transmission to follow the same seasonal pattern as during the baseline period. We

compared outcomes with those of scenarios in which the reference case management regime continued.

Figure 0.1 Decision tree pathways



na: not applicable

Costing. Both marginal and average costs of health care were computed. The marginal cost of treatment is the additional financial or opportunity costs that is incurred when treating each additional case, but does not include the fixed cost of the infrastructure. The average costs include all those costs involved in delivering the intervention, including the use of spare capacity, and those health care resources diverted from other uses.[31]

Uncomplicated malaria: Direct costs of an uncomplicated malaria case seeking care at formal-sector facilities, C_{do}, comprise the cost of an out-patient visit, the cost of drug treatment, and other costs incurred by the patients, i.e.

$$C_{do} = D_o + V_o + H_o \qquad (3)$$

where H_o is the patient (household) cost when visiting formal-sector outpatient facilities (excluding fees) and D_o is the cost of out-patient drug treatment, and V_o is the non-drug costs of an out-patient visit. D_o is computed as:

$$D_o = D_{od} L_d (1 + W) \qquad (4)$$

where D_{od} is the cost of drug per day and L_d is the number of days of therapy. The drug regimens and hence price depend on patient age and weight (Table 2.4), with the prices, which include distribution costs to districts, corresponding to those in the medical store department catalogue[32] of the Tanzanian MOH. *W,* the % additional cost of drug wastage, takes a value of 25% throughout.[33]

The non-drug cost of an outpatient visit is computed from published data on proportions of out-patients reporting at different levels of the health system, on the proportion, p_t, of cases undergoing diagnostic tests, and on unit costs after exclusion of drug costs (Table 2.6). In the average analysis, the non-drug cost, V_{ao}, is thus given by:

$$V_{ao} = p_{hc} V_{hc} + p_h V_h + p_d V_d + p_t T . \qquad (5)$$

In the case of marginal costs there is an adjustment for the proportion of recurrent non-fixed costs, i.e.:

$$V_{mo} = V_{ao}\, p_{ro} (1 - p_{rfo}) . \qquad (6)$$

The patient (household) costs per outpatient visit, H_o, comprise travel expenses, expenses related to medical supplies H_m and non-medical supplies, H_n, such as the purchases of food and drinks or costs of spending the night away from home while seeking care[34] (Table 2.6), so that:

$$H_o = H_t + H_m + H_n \quad (7)$$

In case of self-treatment it is assumed that patients do not incur in any additional costs to purchase the drug because the drugs are likely to be purchased from a private shop close to the patient's home.

Severe malaria: the direct health care costs of a severe malaria case C_{di} are given by:

$$C_{di} = D_i + V_i + H_i \qquad (8)$$

where V_i is the non-drug cost of in-patient care, D_i is the cost of drug treatment, and H_i is the patient (household) cost when visiting formal-sector in-patient facilities. D_i is computed by multiplying the costs by the duration for which they are incurred. During the first day of treatment the drug dosage and consequently the costs are different, so overall D_i is given by:

$$D_i = (D_{i1} + D_{i2}(L_i - 1))(1 + W) \qquad (9)$$

where D_{i1} is the cost for the first day; D_{i2} is the cost per day thereafter and L_t is the length of treatment (in days) (Table 2.6). The non-drug cost of in-patient care in the average analysis is given by:

$$V_i = V_{ai} = N_i L_i(o) \qquad (10)$$

where $L_i(o)$ is the average length of stay, which varies depending on the outcome *o,* and N_i is the in-patient cost (see Table 2.6). Correspondingly, in the marginal analysis the non drug cost is:

$$V_i = V_{mi} = N_i L_i(o)\, p_{ri}(1 - p_{fi}). \qquad (11)$$

The costs incurred by patients are the same as for an outpatient visit for the first day. For the following days of stay we include only the costs of medical and non-medical supplies (H_m and H_n respectively), so that:

$$H_i = H_t + (H_m + H_n)L_i(o). \qquad (12)$$

Table 0.4 Sulphadoxine-pyrimethamine (SP) and amodiaquine doses and costs

Regimen	Number of tablets	Cost per course in Tshs.	Cost per course in US$ 2004
Sulphadoxine-Pyrimethamine			
< 1 year (<11 kg)	*0.5*	*12.4*	*0.012*
1 to 5 years (11-19 kg)	*1*	*24.8*	*0.024*
6 to 9 years (19-30 kg)	*1.5*	*37.2*	*0.035*
10- 14 years (30-45 kg)	*2*	*49.6*	*0.047*
15 and above (> 45 kg)	*3*	*74.4*	*0.071*
Amodiaquine*			
<1 year (<11 kg)	*1.25*	*18.75*	*0.018*
1-3 years (11-15 kg)	*1.75*	*26.25*	*0.025*
4-5 years (15-19 kg)	*2.25*	*33.75*	*0.032*
6-8 years (19-25 kg)	*3*	*45*	*0.043*
9-11 years (25-36 kg)	*4.25*	*63.75*	*0.061*
12-14 years (36-50 kg)	*6.25*	*93.75*	*0.089*
15-16 years (50-60 kg)	*7.5*	*112.5*	*0.107*
17 and aboves (> 60 kg)	*8*	*120*	*0.114*

** SP is administered as a single dose; ** Amodiaquine dosage is in number of 200 mg tablets in a 3 day course. Source:*[32]

Table 0.5 IV Quinine doses and costs, by age and weight

Age and weight categories	Dose	Cost per day in Tshs.	Cost per day in US$ 2004	Cost per course in US$ 2004
Initial dose (20 mg/kg over 4 hours)				
<1 year (< 11 kg)	*180*	*54*	*0.051*	
1-3 years (11-15 kg)	*240*	*72*	*0.069*	
4-5 years (15-19 kg)	*360*	*108*	*0.103*	
6-8 years (19-25 kg)	*420*	*126*	*0.120*	
9-11 years (25-36 kg)	*600*	*180*	*0.171*	
12-14 years (36-50 kg)	*840*	*252*	*0.240*	
15-16 years (50-60 kg)	*1080*	*324*	*0.309*	
17 and above (> 60 kg)	*1200*	*360*	*0.343*	
Dose per day thereafter (10 mg/kg every 8 hours for 6 days)				
<1 year (<11 kg)	*270*	*81*	*0.077*	*0.514*
1-3 years (11-15 kg)	*360*	*108*	*0.103*	*0.686*
4-5 years (15-19 kg)	*540*	*162*	*0.154*	*1.029*
6-8 years (19-25 kg	*630*	*189*	*0.180*	*1.200*
9-11 years (25-36 kg)	*900*	*270*	*0.257*	*1.714*
12-14 years (36-50 kg)	*1260*	*378*	*0.360*	*2.400*
15-16 years (50-60 kg)	*1620*	*486*	*0.463*	*3.086*
17 and above (> 60 kg)	*1800*	*540*	*0.514*	*3.429*

Table 0.6 Health-seeking behavior and unit cost assumptions

Item	Description	Value	Source
	Household (patient costs)*		
H_t	*Travel cost (US$)*	*0.08*	[34]
H_m	*Medical supplies (US$)*	*0.03*	[34]
H_n	*Non medical supplies (US$)*	*0.19*	[34]
	Uncomplicated malaria		
p_{hc}	*% of out-patient visits that take place at health centers*	*18%*	[42]
p_d	*% of out-patient visits that take place at dispensaries*	*72%*	[42]
p_h	*% of out-patient visits that take place at hospitals*	*10%*	[42]
V_{hc}	*Cost per out-patient visits at health centers (US$)*	*1.27*	[34]
V_d	*Cost per out-patient visits at dispensaries (US$)*	*1.02*	[34]
V_h	*Cost per out-patient visits at hospitals (US$)*	*2.10*	[49]
p_t	*% diagnostic tests (proportion of patients)*	*10%*	[24]
T	*Unit cost of diagnostic test (US$)*	*0.30*	[24]
p_{ro}	*% of out-patient visit cost that are recurrent*	*69%*	[34]
p_{rfo}	*% of out-patient visit recurrent cost that are fixed*	*25%*	[33]
H_o	Average patient cost (US$)	*0.30*	[34]
	Severe malaria		
N_i	*Non-drug cost per day of stay – (US$)*		
	(capital) :	*2.30*	[50]
	(recurrent) :	*5.50*	[50]
	(total) :	*7.80*	[50]
$L_i(1)$	*Average length of stay when patient fully recovers*	*4.50*	[33]
$L_i(2)$	*Average length of stay when patient recovers with neurologic sequelae*	*10*	[33]
$L_i(3)$	*Average length of stay when patient dies*	*2*	[33]
p_{ri}	*% of in-patient costs that are recurrent*	*71%*	[48]
$\mathbf{p_{fi}}$	*% of in-patient recurrent cost that is fixed*	*50%*	[33]

*Daily average household (patient) out of pocket costs.

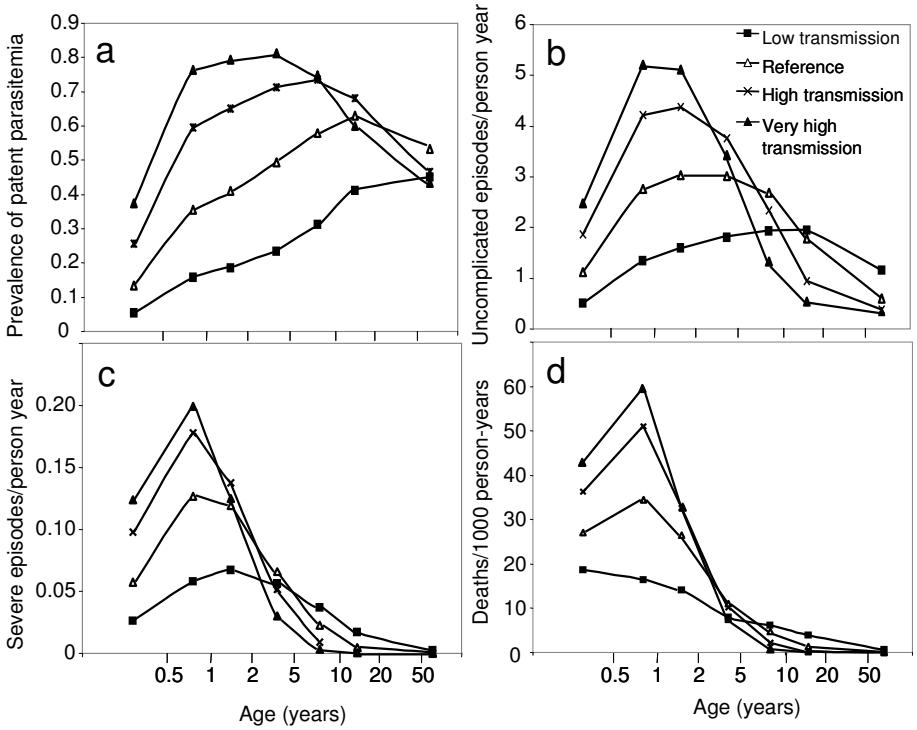
2.3 Results

The reference scenario simulation. Simulated patterns of age-prevalence and age-incidence for the reference scenario (Figure 2.2) are similar to those for typical meso-endemic settings in Africa to which the models were fitted.[9,12,13] The direct cost per capita is stable over time. The predicted infectiousness of the host population, $\bar{\kappa}_u(t)$, fluctuates seasonally around a value of approximately 3% (Figure 2.3a). Since the reference scenario uses the same transmission pattern and health system to construct the baseline population as are applied during the follow-up, there is no trend over the 20-year simulation period in these epidemiologic variables or in the treatment costs.

Over the 20-year simulation period, the total number of undiscounted DALYs lost due to malaria, in our population of 100,000 people, is approximately 481,000, corresponding to a rate of 0.24 DALYs per capita per annum. Most of these DALYs are due to mortality, so the total number of YLLs is very close to that of DALYs (Table 2.7). If YLLs and DALYs are discounted at a standard rate of 3%, the total number of DALYs is considerably lower.

The total undiscounted direct average costs to treat malaria episodes with the reference case management model, amounts to US$ 485,793 over the 20-year simulation period. This corresponds to US$ 4.86 per capita and, on average, US$ 0.24 per capita per annum (Table 2.7). Out-patient visits account for 32% of total direct costs, drug treatments of both uncomplicated and severe episodes for 7%, hospital admissions of severe episodes for 40% and patient costs for 22% (data not shown). The marginal cost, i.e. additional financial or opportunity costs that would be incurred when introducing a new control intervention, is around 58% of the average cost.

Figure 0.2 Predicted age-prevalence and age-incidence curves by transmission intensities



The reference scenario is the transmission intensity observed at Namawala divided by a factor 16; low transmission equals to Namawala transmission divided by a factor 64; high transmission is one-quarter of the Namawala transmission; very high transmission equals the transmission observed at Namawala.
a) age-prevalence curve of patent parasitemia
b) age-incidence curve of uncomplicated episodes
c) age-incidence curve of severe episodes
d) age-incidence curve of mortality

Figure 0.3. Infectivity of the human population

a) reference scenario
b) scenario assuming full treatment coverage

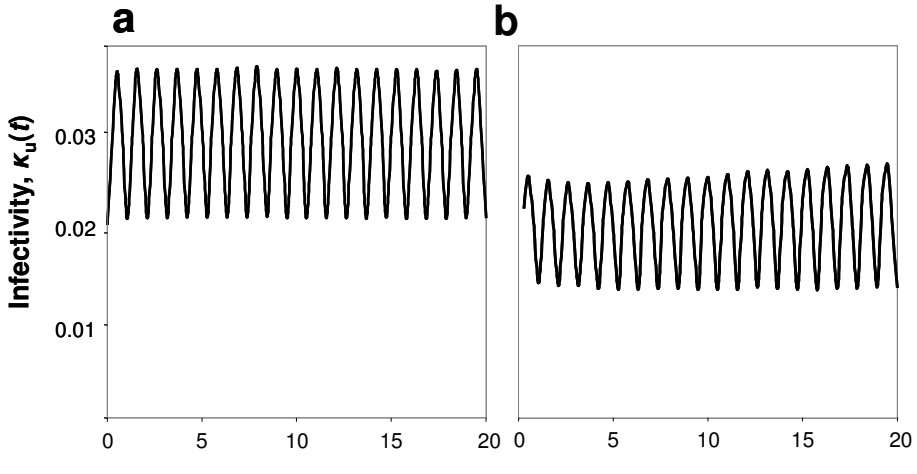


Table 0.7 YLLs*, DALYs*, and direct costs**

	Undiscounted				Discounted (3%)			
	YLL	***DALYs***	***Average costs***	***Marginal costs***	***YLL***	***DALYs***	***Average costs***	***Marginal costs***
Reference	*0.238*	*0.244*	*0.243*	*0.142*	*0.120*	*0.125*	*0.184*	*0.108*
*Moderate coverage^*	*0.217*	*0.224*	*1.066*	*0.736*	*0.112*	*0.118*	*0.809*	*0.558*
*60% Abuja target coverage^*	*0.160*	*0.165*	*1.423*	*0.946*	*0.083*	*0.087*	*1.053*	*0.70*
*Full coverage^*	*0.100*	*0.105*	*1.807*	*1.212*	*0.052*	*0.056*	*1.463*	*0.993*
*Effective treatment^*	*0.081*	*0.086*	*1.424*	*0.918*	*0.042*	*0.046*	*1.054*	*0.679*
No treatment	*0.276*	*0.276*	*-*	*-*	*0.138*	*0.143*	*-*	*-*
Very low transmission	*0.219*	*0.226*	*0.285*	*0.172*	*0.119*	*0.125*	*0.216*	*0.131*
Low transmission	*0.224*	*0.231*	*0.283*	*0.169*	*0.118*	*0.124*	*0.215*	*0.129*
High transmission	*0.242*	*0.246*	*0.204*	*0.116*	*0.120*	*0.123*	*0.155*	*0.088*
Very high transmission	*0.234*	*0.237*	*0.169*	*0.095*	*0.115*	*0.117*	*0.128*	*0.072*
Low transmission, Full coverage	*0.036*	*0.038*	*0.544*	*0.368*	*0.017*	*0.018*	*0.470*	*0.321*
High transmission, Full coverage	*0.160*	*0.165*	2.027	1.349	*0.068*	*0.072*	1.643	1.109

* lost per capita per annum due to malaria; **direct cost per capita in US$ per annum

^ at same transmission level as in the reference scenario

Effect of changing levels of access to case management. Comparison of the reference scenario with the extreme scenario with no treatment of malaria episodes (either uncomplicated or severe) revealed noticeable epidemiologic effects of treatment despite the low attendance rates for uncomplicated episodes in the reference health system. In children <10 years of age the "no treatment" scenario predicted higher prevalence of infection (Figure 2.4), a higher anemia prevalence (Figure 2.5) and a slight increase in the incidence of clinical episodes, with age patterns as shown in Figure 2.6a,b and c. There was only a small effect on the incidence of severe malaria (Figure 2.6d,e and f). Since the reference health system includes a relatively high treatment rate of severe episodes the largest differences between the "no treatment" and reference scenarios were in the mortality rates with a substantially higher mortality rate predicted with "no treatment", especially in the second half of the first year of life (Figure 2.6g,h and i).

The reference scenario is in a state of equilibrium throughout the simulation, though there is stochastic variation over time in the outputs. The "no treatment" scenario reaches a new equilibrium very quickly. Therefore, only the average prevalence over 20 years is shown for this scenario (Figure 2.4, black squares) and the effects on incidence of morbidity and mortality do not change much during the follow-up period (Figure 2.6). The total number of DALYs lost over the simulated 20-year period was 13% higher with the "no treatment" regimen than with the reference. The effect on transmission, measured by $\overline{\kappa}_u(t)$ is negligible.

The "complete coverage" model for treatment leads to a rapid decrease in transmission, as measured by $\overline{\kappa}_u(t)$ (Figure 2.3b). This stabilizes quickly at a value about 60% of that in the reference scenario, implying that treatment of all the clinical episodes (including minor episodes) can reduce the inoculation rate by about 40%. "Complete coverage" predicted very substantial decreases in prevalence of parasitemia (Figure 2.4) of anemia (Figure 2.5) and also in incidence of uncomplicated episodes (Figure 2.6), but these outcomes, reflecting the dynamics of immunity, required an extended period to reach equilibrium. Although treatment of severe episodes in the "complete coverage" health system is no different from the reference, the effects on transmission, and on persistence of parasites result in substantial reductions in incidence of severe morbidity and mortality (Figure 2.6), leading to a total number of DALYs lost over 20 years of only around 45% of those in the reference scenario (Table 2.7).

The epidemiologic effects of high treatment coverage were concentrated in the youngest age groups, resulting in a substantial shift in the age of peak incidence of uncomplicated episodes (to older ages) and of mortality (to younger ages, in which a greater proportion of the mortality is contributed by indirect deaths). The changes in the age-prevalence and age-incidence curves caused by "complete coverage" were also time-dependent so that transient effects can be seen throughout the 20-year follow-up period. As a result of the shifts in age-incidence, 10 years into the simulation an increase in incidence of clinical episodes above baseline levels is evident in individuals >10 years old (Figure 2.6b). The shifts in the peak of the incidence curves to older age-groups, accumulates over time, so that the benefit of the intensive treatment regimen decreases with time.

The distribution of direct costs is also changed as a function of treating all malaria episodes with a first-line drug. In the scenarios that we simulated there would then be little need for second-line treatment; hence many severe episodes could be prevented, which in turn reduces in-patient costs. Our model predicts that if all uncomplicated episodes were treated with the first-line drug, out-patient visit costs would account for 61% of total direct costs, drug treatments for 7%, inpatients admissions for 3% and patient costs for 30%. The total direct costs to treat all malaria episodes would be approximately 7.4-times those of the reference scenario.

The "moderate coverage" scenario predicts effects on prevalence and on the clinical outcomes (Figures 2.4, 2.5 and 2.6) more similar to those for "complete coverage" than to those for "no treatment". This is despite the assumption in the "moderate coverage" health system of treatment rates for uncomplicated episodes much less than 50% and hence much closer to those for "no treatment" than those for "complete coverage". This implies that, within our models, there is a highly non-linear relationship between health outcomes and treatment coverage for uncomplicated malaria, with a very high marginal impact of increases in coverage when it starts from a low level. This conclusion is supported by the simulation of "effective treatment" which gave very similar results to that of "complete coverage" for all the outcomes except mortality (results not shown). Mortality rates, and hence DALYs lost (Table 2.7) were reduced by the "effective treatment" health system to substantially below those with the "complete coverage" health system because all severe cases were assumed to be treated as in-patients.

Effect of transmission intensity. In higher transmission settings simulated parasite prevalence was higher, and peaked at a younger age (Figure 2.2a). The incidence of uncomplicated malaria episodes also increased with transmission intensity in young

children, but the reverse pattern was observed in older individuals (Figure 2.2b), matching the pattern to which the model was fitted.[13] The incidence of severe episodes showed a similar pattern, but with a steeper decline in incidence with age at high transmission, and consequently a crossing of the age-incidence curves at younger age (Figure 2.2c). The pattern for mortality was similar, with the mortality rate independent of transmission intensity at the age of about 3-4 years.

The average level of transmission to the vector, $\overline{\kappa}_u(t)$, was similar to that for the reference scenario for all values of EIR investigated, but the amplitude of the seasonal variation in $\overline{\kappa}_u(t)$ increased with the transmission intensity (data not shown).

The total number of YLLs and DALYs lost over the simulated 20-year period are only slightly higher in the high transmission settings when compared to areas of lower transmission intensity. The total direct costs are determined by the number of uncomplicated and severe episodes treated, which are higher than in the reference scenario in the low transmission setting and lower in the high transmission setting (Figure 2.7). These figures however depend strongly on the model predictions for rates of severe malaria in adults, of which we are highly uncertain.[12]

Changing access to case management in different malaria transmission intensity settings. The effects of an increased or decreased level of access to case management also vary according to the prevailing malaria transmission intensity (Figure 2.8). In a setting of moderate malaria transmission, treating all uncomplicated episodes over 20 years would lead to only a small difference in the total number of uncomplicated episodes, but reduces incidence of severe episodes by 49%, and the number of deaths and DALYs lost by 57% (Table 2.7).

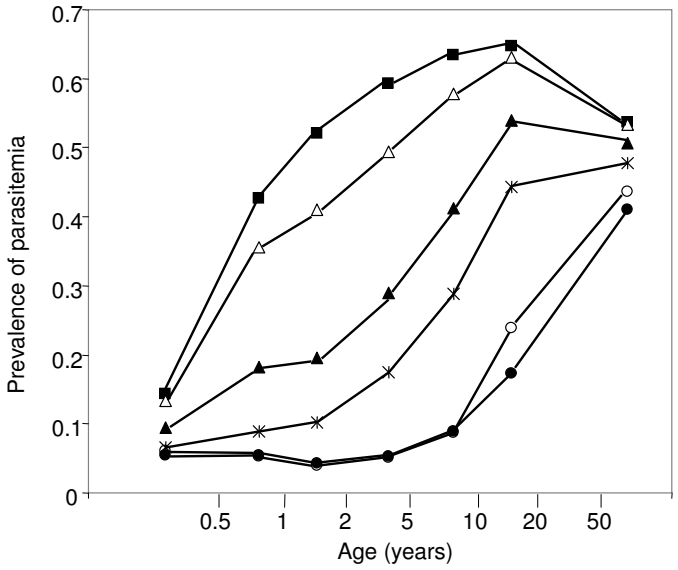
In the low transmission setting, treating all uncomplicated cases over 20 years reduces incidence of uncomplicated episodes by 71%, severe episodes by 88%, and the number of deaths and DALYs lost by 83%. In the high transmission setting complete treatment coverage would increase the total number of uncomplicated episodes over time, and would lead to a reduction of only 31% of severe episodes and DALYs lost, and 34% of the number of deaths.

Treating everyone has a much greater effect on incidence at low transmission intensities. At high transmission, a high level of coverage always appears to be beneficial in terms of reducing incidence of severe episodes and of mortality, but may even lead to an increase in incidence of uncomplicated episodes. Within the model,

this is because a very high treatment rate is associated with a reduction in exposure to asexual blood stage parasites and hence in acquired blood-stage immunity.

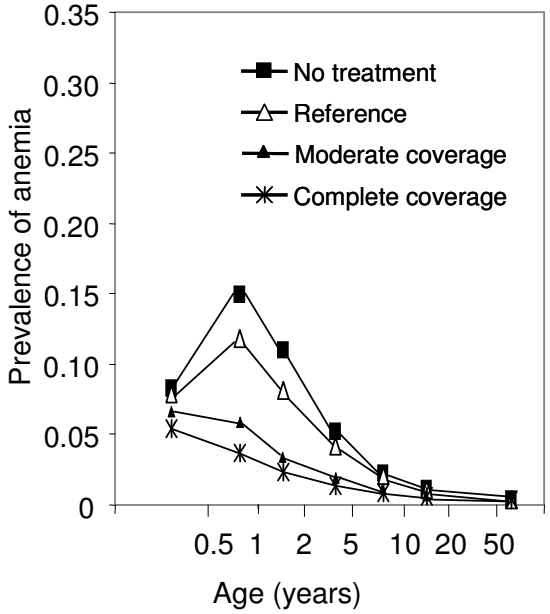
The economic implications of changing levels of access to case management also differ according to the malaria transmission intensity. Simulation over a 20-year period under the assumption of complete treatment coverage of uncomplicated malaria episodes would increase direct costs by a factor of almost 10 in a highly endemic setting, but the increase would be only 92% in low transmission settings (Table 2.7).

Figure 0.4. Age-prevalence curves of parasitemia under different case management scenarios during a simulated 20-year follow-up period



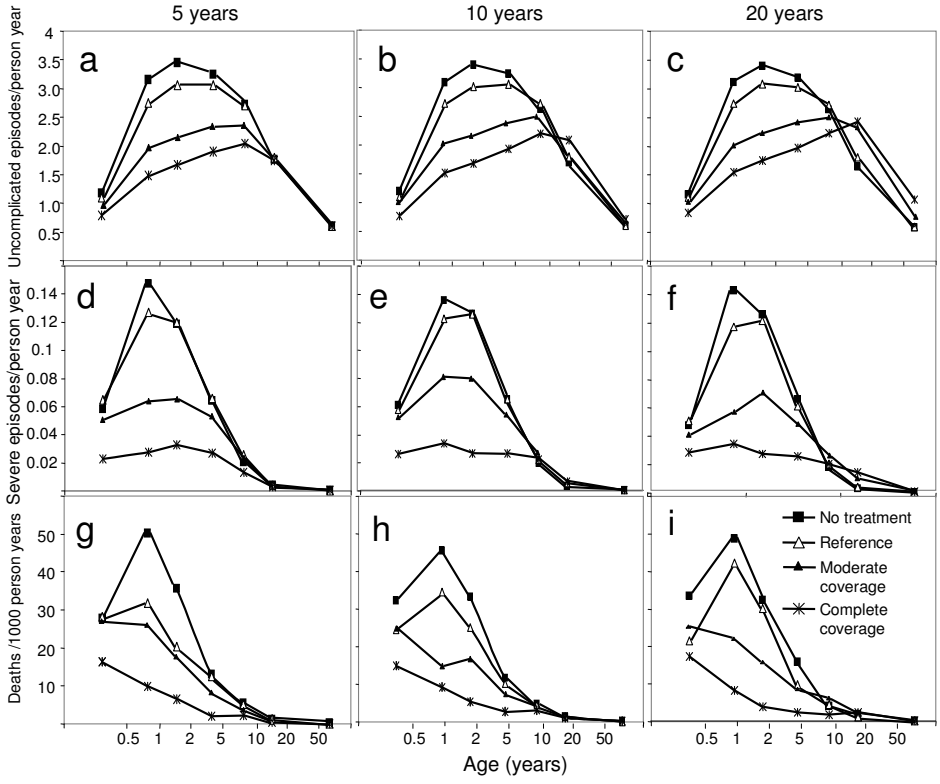
■ : No treatment; △ : Reference; ▲: Moderate coverage (1st year of follow-up); ✳ : Complete coverage (1st year of follow-up); ○ : Complete coverage (10th year of follow-up); ● : Complete coverage (20th year of follow-up);

Figure 0.5 Age-prevalence curves of anemia (Hb<8 g/dL)



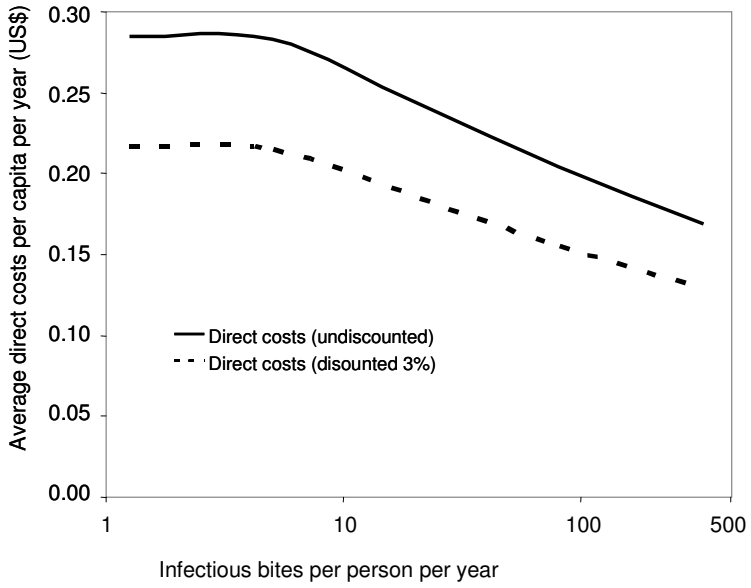
The reference scenario is the transmission intensity observed at Namawala divided by a factor 16; low transmission equals to Namawala transmission divided by a factor 64; high transmission is one-quarter of the Namawala transmission; very high transmission equals the transmission observed at Namawala.

Figure 0.6 Age-incidence curves under different case management scenarios at different durations of simulation during a 20-year follow-up period



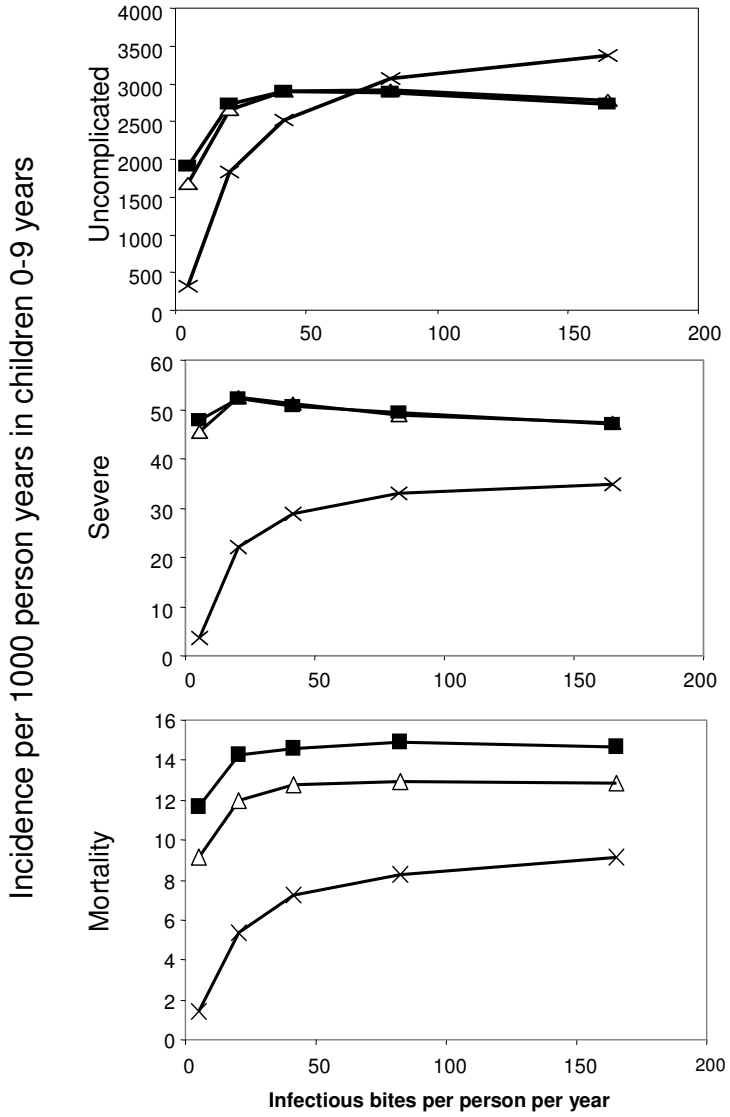
a-c) age-incidence of uncomplicated episodes; d-f) age-incidence of severe episodes; g-i) age-incidence of mortality

Figure 0.7 Direct costs in relation to transmission intensity



upper line: undiscounted; lower line: discounted.

Figure 0.8 The effect of changing case management in different transmission settings



The status of the population at baseline was defined by simulating the reference health system for 90 years for each transmission intensity. The follow-up period then ran for 20 years with the chosen health system, and the results here are the average for the 20 years. The incidence rates settled to a new level quickly. Because of the uncertainty in the rates of severe morbidity and mortality in adults we show predictions only for children <10 years of age.

■: No treatment; △ Reference case management; X Full coverage

2.4 Discussion

We present a first attempt to use a dynamic model for case-management of malaria in sub-Saharan Africa. For prediction of the effects of the case management, we considered a range of different transmission intensities characteristic for large parts of malaria-endemic Africa, and our simulations are thus likely to be of broad applicability. Lower EIRs than considered here (i.e. <5 infectious bites per person per annum) are characteristic of highly urbanized settings, the African highlands and areas located at the current distribution edges of P. falciparum transmission.[35,36] Our model needs further development and validation to make meaningful predictions for such settings.

Our modeling approach expands the scope for predictions of the epidemiologic and economic consequences of malaria interventions as a direct function of the case management. In a first step, we have simulated different rates of treatment coverage, including the most extreme scenarios of either complete lack of treatment or full coverage. These two scenarios, together with a reference scenario largely constructed from real data obtained from Tanzania, were used for simulations up to 20 years. Costs were also built into our dynamic models, which will ultimately make it possible to predict the cost-effectiveness of the case management.

Our immediate purpose is to integrate effects of case management into our dynamic models of the clinical epidemiology and natural history of *P. falciparum* malaria in a typical setting of SSA. The approach could readily be adapted to assess the costs of scaling up malaria treatment but this would entail more detailed analysis of the activities involved in scaling up malaria treatment.

Our model can be used to make predictions of the effect of introducing a new malaria control intervention (e.g. malaria vaccine) or scaling-up of existing control measures (e.g. ITNs). The former motivated the development of our modeling approach. The current model is probably better at fulfilling this objective than in capturing the impact of changes in case management, including different levels of treatment, and changes in national antimalarial drug policies. This is justified because the epidemiologic model was fitted mainly to cross-sectional data from various settings across sub-Saharan Africa. It is less able to capture longitudinal patterns within hosts, so it does not claim to incorporate realistic patterns of treatment-seeking behavior or of referral patterns. In African settings where patients have limited resources, care-

seeking patterns in general, and malaria treatment-seeking behavior in particular, are complex.[37-39]

There is a need to build on simple models of the referral system,[33] so that we become more confident of the likely impacts of changes in national antimalarial drug policies. For example, parasite resistance to SP has reached critical levels in many parts of Central and East Africa, including Tanzania[40,41] and this places a question mark against our longer-term predictions of cost-effectiveness which assume that SP treatment remains efficacious. In view of the public health, social and economic significance of SP resistance, efforts are underway in Tanzania, and elsewhere, to change national policies towards artemisinin-based combination therapy (ACT). In fact, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) has recently approved a project to switch from SP (and amodiaquine) to ACT.[42] Such a shift in drug policy is of considerable public health significance and will directly affect the case management of *P. falciparum* malaria. There is a need to adapt our model to field data from a range of different settings, and that will make it possible to explore the epidemiologic and economic consequences of the case management system under different scenarios. These should include simulation of the shift from SP to ACT, conditional on various levels of SP resistance.

Regarding the epidemiologic model, we chose to define the seasonal pattern of *P. falciparum* transmission by using data from the village of Namawala in Tanzania. The high level of transmission measured there, even in comparison to other sites in Tanzania,[22,43] made it possible to measure the intensity of transmission during the dry season. Multiplication of the Namawala rate by a constant therefore provides us with a reasonable estimate of the seasonal pattern, even for lower transmission areas where dry season transmission can usually not be measured.

Tanzania's national malaria control program reports that 75% of people live in areas of stable malaria transmission, 17% in areas of unstable transmission (duration of transmission less than one month per year), and the remaining 8% in areas of unstable transmission (highly seasonal).[30] However historic and contemporary maps of malaria endemicity for Tanzania[44,45] do not provide estimates of the inoculation rate with which to determine the distribution of EIR levels among the people within areas of stable transmission.

Our approach makes it possible to look at how such variations in transmission intensity might affect the impact of changes in the health system. However our

confidence in the present results is limited by uncertainties in our epidemiologic models (especially that for severe malaria and mortality, for which we had no data for older age groups[12]).

Increasing levels of treatment, in general shift the age-prevalence and age-incidence curves so that the peaks are in older age-groups. We developed our parasitologic model mainly using archive data that predated the widespread use of anti-malarial chemotherapy. A delayed peak in the age-prevalence curve that we attribute to this effect was already apparent in the dataset from Navrongo, Ghana[46] that we used in developing our parasitologic model.[9] The effect of treatment on reducing acquired blood-stage immunity is very uncertain, because asexual blood stage immunity is modeled as a function of both the number of distinct infections, and of the cumulative parasite load and we do not know what should be the relative contributions of these two different components of acquired immunity. The effects of cumulative parasite load are intended to simulate acquisition of immunity to antigenic variants that arise during the course of the infection.

We agree with other models for cost-effectiveness of malaria interventions in attributing most of the burden of disease to mortality rather than to disability associated with acute illness, sequelae, or anemia. Important methodological issues requiring further investigation arise in the computation of the DALYs. In African populations with high infant mortality there is generally an increase in life-expectancy during the first few years of life, and this leads to perverse outcomes in the computation of DALYs if the effect of an intervention is partly to shift mortality to older ages in childhood. For example, if life expectancy at one year is 64 years, and life expectancy at five years is 72 years, then the number of life years gained by shifting age at death would be negative: 64-72= -8. This effect is accentuated by discounting or age-weighting of the DALYs, but does not arise with the Japanese life-tables used to compute DALYs in the GBD calculations used by the World Health Organisation.[17] It is generally considered that local life-tables should be used to compute DALYs in cost-effectiveness analyses,[47] but there is a strong case for using death rates that exclude the health effect under investigation. For the present analyses we used a life table from an East African site with low malaria incidence. In these life-tables, where malaria plays only a small role, there is an increase in life-expectancy over the first few years of life.

In conclusion, we have made a first attempt to develop a modeling framework to simulate the dynamic effects of the case management of *P. falciparum* malaria across

a wide range of transmission intensities in sub-Saharan Africa. We discovered several deficiencies in our understanding of the relevant health systems. Our simulations of a range of scenarios indicate which of these uncertainties are most likely to be important for the prediction of cost-effectiveness of malaria interventions. Further development of our modeling approach offers for more realistic evaluation of the epidemiologic and economic consequences of malaria interventions. This in turn creates a sound foundation for measuring the effects of introducing new antimalarial interventions (e.g. malaria vaccines), or scaling-up those that are already known to be efficacious and cost-effective.

2.5 References

1. Gold MR, Gold SR, Weinstein MC. Cost-effectiveness in health and medicine. Oxford: Oxford University Press; 1996

2. Drummond M, O'Brien BJ, Stoddart GL, Torrance G. Methods for the economic evaluation of health care programmes. 2nd edn ed. New York: Oxford University Press. Second edition; 1997

3. Cooper B, Lipsitch M, 2004. The analysis of hospital infection data using hidden Markov models. *Biostatistics 5*: 223--237

4. Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, Gopalakrishna G, Chew SK, Tan CC, Samore MH, Fisman D, Murray M, 2003. Transmission dynamics and control of severe acute respiratory syndrome. *Science 300*: 1966--1970

5. Collins WE, Jeffery GM, 1999. A retrospective examination of the patterns of recrudescence in patients infected with *Plasmodium falciparum*. *Am J Trop Med Hyg 61*: 44--48

6. World Health Organisation, 1993. A Global Strategy for Malaria Control. Geneva, World Health Organisation.

7. Smith T, Killeen G, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M, 2006. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: Overview. *Am J Trop Med Hyg, in press*

8. Smith T, Maire N, Dietz K, Killeen GF, Vounatsou P, Molineaux L, Tanner M, 2006. Relationships between the entomological inoculation rate and the force of infection for *Plasmodium falciparum* malaria. *Am J Trop Med Hyg, in press*

9. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, Molineaux L, 2006. A model for natural immunity to asexual blood stages of *Plasmodium falciparum* in endemic areas. *Am J Trop Med Hyg, in press*

10. Killeen GF, Ross A, Smith T, 2006. Infectiousness of malaria-endemic human populations to vectors. *Am J Trop Med Hyg, in press*

11. Ross A, Killeen GF, Smith T, 2006. Relationships of host infectivity to mosquitoes and asexual parasite density in *Plasmodium falciparum*. *Am J Trop Med Hyg, in press*

12. Ross A, Maire N, Molineaux L, Smith T, 2006. An epidemiological model of severe morbidity and mortality caused by *Plasmodium falciparum*. *Am J Trop Med Hyg, in press*

13. Smith T, Ross A, Maire N, Rogier C, Trape JF, Molineaux L, 2006. An epidemiological model of the incidence of acute illness in *Plasmodium falciparum* malaria. *Am J Trop Med Hyg, in press*

14. Ross A, Smith T, 2006. The effect of malaria transmission intensity on neonatal mortality in endemic areas. *Am J Trop Med Hyg, in press*

15. Carneiro I, Smith T, Lusingu J, Malima R, Utzinger J, Drakeley C, 2006. Modeling the relationship between the population prevalence of *Plasmodium falciparum* malaria and anemia. *Am J Trop Med Hyg, in press*

16. Reyburn H, Drakeley C, Carneiro I, Jones C, Cox J, Bruce J, Riley E, Greenwood B, Whitty C. The epidemiology of severe malaria due to *Plasmodium falciparum* at different transmission intensities in NE Tanzania. LSHTM Malaria Centre Report 2002-2003. 2004:6-7.

17. Murray CJL, Lopez AD. Estimating Causes of Death: New Methods and Global and Regional Applications for 1990. In: Murray CJL, Lopez AD, eds. The Global Burden of Disease. Geneva: World Health Organisation; 1996.

18. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Harvard: Harvard University Press; 1996

19. INDEPTH Network. Model life tables for sub-Saharan Africa. Aldershot, England: Ashgate; 2004

20. INDEPTH Network. Population, health and survival at INDEPTH Sites. Ottawa: IDRC; 2002

21. Smith T, Charlwood JD, Kihonda J, Mwankusye S, Billingsley P, Meuwissen J, Lyimo E, Takken W, Teuscher T, Tanner M, 1993. Absence of seasonal variation in malaria parasitaemia in an area of intense seasonal transmission. *Acta Trop 54*: 55--72

22. Hay SI, Rogers DJ, Toomer JF, Snow R, 2000. Annual *Plasmodium falciparum* entomological inoculation rates (EIR) across Africa: literature survey, Internet access and review. *Trans R Soc Trop Med & Hyg 94*: 113--127

23. Robert V, Macintyre K, Keating J, Trape JF, Duchemin JB, Warren M, Beier JC, 2003. Malaria transmission in urban sub-Saharan Africa. *Am J Trop Med Hyg 68*: 169--176

24. National Malaria Control Program, 2004. Personal comunication.

25. Ministry of Health, 2000. National guidelines for malaria diagnosis and treatment. Malaria Control Series 2000. Ministry of Health Tanzania. Dar es Salaam, Tanzania, Ministry of Health.

26. Maire N, Aponte J, Ross A, Thompson R, Alonso P, Utzinger J, Smith T, 2006. Modeling a field trial of the RTS,S/ASO2A malaria vaccine. *Am J Trop Med Hyg, in press*

27. McCombie SC, 1996. Treatment seeking for malaria: a review of recent research. *Soc Sci Med 43*: 933--945

28. McCombie SC, 2002. Self-treatment for malaria: the evidence and methodological issues. *Health Policy Plan 17*: 333--344

29. NMCP, 2003. National Malaria Medium Term Strategic Plan 2002-2007. National Malaria Control Programme, Ministry of Health Tanzania.

30. National Malaria Control Program, 2004. Monitoring malaria situation and control activities in Tanzania 2001-2003. Health facility and community survey. National Malaria Control Programme Monitoring and Evaluation Unit. Dar es Salaam, Tanzania, National Malaria Control Program.

31. Hutton G, Tediosi F, 2006. The costs of introducing a malaria vaccine through the expanded program on immunization in Tanzania. *Am J Trop Med Hyg, in press*

32. MSD, 2004. Medical Store Department price catalogue 2004.

33. Goodman C, Coleman P, Mills A. Economic analysis of malaria control in sub-Saharan Africa. Geneva: Global Forum for Health Research; 2000

34. Adam T, Kakundwa C, Manzi F, Schellenberg JA, Mgalula L, de Savigny D, Mbuya C, Wilzynska K and the MCE team in Tanzania, 2004. Analysis report on the costs of IMCI in Tanzania. Multi-country evaluation of the Integrated Management of Childhood Illness (IMCI). World Health Organisation. Geneva, Department of Child and Adolescent Health and Development, World Health Organisation.

35. Keiser J, Utzinger J, De Castro MC, Smith TA, Tanner M, Singer B, 2004. Urbanization in sub-Saharan Africa and implication for malaria control. *Am J Trop Med Hyg 71*: 118--127

36. Zhou G, Minakawa N, Githeko AK, Yan G, 2004. Association between climate variability and malaria epidemics in the East African highlands. *Proc Natl Acad Sci U S A 101*: 2375--2380

37. Tanner M, Vlassoff C, 1998. Treatment-seeking behaviour for malaria: a typology based on endemicity and gender. *Soc Sci Med 46*: 523--532

38. Muela SH, Ribera JM, Mushi AK, Tanner M, 2002. Medical syncretism with reference to malaria in a Tanzanian community. *Soc Sci Med 55*: 403--413

39. de Savigny D, Mayombana C, Mwageni E, Masanja H, Minhaj A, Mkilindi Y, Mbuya C, Kasale H, Reid G, 2004. Care-seeking patterns for fatal malaria in Tanzania. *Malar J 3*: 27

40. Mugittu K, Ndejembi M, Malisa A, Lemnge M, Premji Z, Mwita A, Nkya W, Kataraihya J, Abdulla S, Beck HP, Mshinda H, 2004. Therapeutic efficacy of sulfadoxine-pyrimethamine and prevalence of resistance markers in Tanzania prior to revision of malaria treatment policy: *Plasmodium falciparum* dihydrofolate reductase and dihydropteroate synthase mutations in monitoring in vivo resistance. *Am J Trop Med Hyg 71*: 696--702

41. Talisuna AO, Bloland P, D'Alessandro U, 2004. History, dynamics, and public health importance of malaria parasite resistance. *Clin Microbiol Rev 17*: 235--254

42. GFATM, 2004. http://www.theglobalfund.org/search/portfolio.aspx?countryID=TNZ.

43. Drakeley C, Schellenberg D, Kihonda J, Sousa CA, Arez AP, Lopes D, Lines J, Mshinda H, Lengeler C, Armstrong SJ, Tanner M, Alonso P, 2003. An estimation of the entomological inoculation rate for Ifakara: a semi-urban area in a region of intense malaria transmission in Tanzania. *Trop Med Int Health 8*: 767--774

44. Craig M, Snow R, Le Sueur D, 1999. A climate-based distribution model of malaria transmission in sub- Saharan Africa. *Parasitol Today 15*: 105--111

45. Clyde DF, 1967. Malaria in Tanzania. London, Oxford, Oxford University Press.

46. Owusu-Agyei S, Smith T, Beck H-P, Amenga-Etego L, Felger I, 2002. Molecular epidemiology of Plasmodium falciparum infections among asymptomatic inhabitants of a holoendemic malarious area in northern Ghana. *Trop Med Int Health 7*: 421--428

47. Fox-Rushby J, Hanson K, 2001. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy Plan 16*: 326--331

48. Brewster DR, Kwiatkowski D, White NJ, 1990. Neurological sequelae of celebral malaria in children. *Lancet 336*: 1039--1043

49. Health Research for Action, 1999. Health Care Financing in Tanzania: Costing study of health services. Final Report. Volume 1Laarstraat, Belgium.

50. Alonso-Gonzalez M., Menendez C, Font F, Kahigwa E, Kimario J, Mshinda H, Tanner M, Bosch-Capblanch X, Alonso PL, 2000. Cost-effectiveness of iron supplementation and malaria chemoprophylaxis in the prevention of anaemia and malaria among Tanzanian infants. *Bull World Health Organ 78*: 97--107

Chapter 3: The costs of introducing a malaria vaccine through the Expanded Program on Immunization in Tanzania

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Abstract

This paper presents an approach to costing the delivery of a malaria vaccine through the expanded program on immunization (EPI), and presents the predicted cost per dose delivered and cost per fully immunized child (FIC) in Tanzania, which are key inputs to the cost-effectiveness analysis. The costs included in the analysis are those related to: the purchase of the vaccine taking into account the wastage rate; the costs of distributing and storing the vaccine at central, zonal, district, and facility level; those of managing the vaccination program; the costs of delivery at facility level (including personnel, syringes, safety boxes, and waste management); those of additional training of EPI personnel and of social mobilization activities. The average cost per FIC increases almost linearly from US$4.2 per FIC at a vaccine price of US$1 per dose to US$31.2 at vaccine price of US$10 per dose. The marginal cost is around 5% less than the average cost. Although the vaccine price still determines most of the total delivery costs, the analysis shows that other costs are relevant and should be taken into account before marketing the vaccine and planning its inclusion into the EPI.

3.1 Introduction

This paper presents the approach to costing the delivery of a malaria vaccine through the Expanded Program on Immunization (EPI), and presents the predicted cost per dose delivered and cost per fully immunized child in Tanzania, which are key inputs to the cost-effectiveness analysis (reported in an accompanying paper[1]).

Cost measurement is one crucial step in presenting cost-effectiveness results, costs being the numerator in the cost-effectiveness ratio, which gives crucial information on allocative efficiency in terms of the cost per health gain of a given health intervention.[2,3] The cost-effectiveness ratio is essentially calculated by dividing the net costs of a health intervention by the net health effects.

In conducting a cost study, it is essential to follow appropriate methods in order to ensure scientific quality as well as comparability with studies of other health interventions. Economic evaluation guidelines have been available since the late 1960s, in the days when cost-benefit analysis of development projects was routinely undertaken by OECD government donor agencies and the World Bank.[4,5] In these early guidelines, detailed methods were presented for cost measurement that were consistent with theories of welfare economics.[6,7] By the 1980s, economic evaluation guidelines were available for specific application in the health domain.[8-12] These early economic evaluation guidelines for health interventions, as well as later ones,[2,3,13-16] have been widely used in the health field, and are commonly referred to as the standard by which economic evaluation studies are judged.

While in the past it has been recognized that the application of economic evaluation in the health field was not standardized and suffered from lack of guidance,[17] the problem is of a different nature now that there exist an abundance of health economic evaluation guidelines, and which propose a variety of approaches. While standardization of methods has been attempted by several groups in the UK, US, and EU,[14,15,18-20] complete standardization of economic evaluation methods remains elusive.

The implication of the different approaches recommended by these guidelines is that there remains quite some discretion to the analyst in conducting and presenting a cost study. Therefore, this present study endeavors to follow closely the highest current standards for cost measurement, taking into account the weaknesses inherent in what is essentially a desk study.

Previous studies on the costs of adding interventions to the EPI

The delivery of a malaria vaccine through the EPI is a new intervention that has not been implemented or modeled anywhere in the world. Therefore, in conducting a study that measures the hypothetical cost of adding a malaria vaccine to the EPI, in a first step it is important to identify previous cost studies that have measured costs of adding other interventions to the EPI. The main aims of this literature review were to identify important costs items, to give an indication of what data are easily available for different costs of EPI, and to identify variables, factors and assumptions that need to be taken into account in developing a generalizable cost model and menu for a malaria vaccine provided within EPI, including both supply (health system) and demand (population) side variables. In particular, useful information on the main features of immunization programs, their costs, funding, and performance was obtained from the World Health Organization website on immunization financing.[21]

The review found that the costs of introducing a new vaccine are essentially a function of the cost structure of the EPI and of the particular operational conditions of the program. Among the most important determinants of the incremental costs of adding a new vaccine into EPI are the characteristics of the vaccine itself, the delivery modalities, and the capacity utilization of EPI.[22-29,29-31]

For instance, the studies on the introduction of Hepatitis B vaccine into EPI schedule showed that, at US$1 per dose, around 80% of the additional costs were due to the vaccine.[32-34] The remaining costs were mainly those of supplies, distribution system (mainly cold chain) and social mobilization. However, vaccine delivery costs vary according to the level of capacity utilization and volume of immunizations given.

Hence, the evidence shows that, although the vaccine accounts for a large part of the incremental cost of adding a new vaccine into EPI schedule, the immunization program can incur considerable additional costs and these depend heavily on the

operational conditions of the program itself. Based on these findings, it was justified to gather information on the current status of the EPI program in a malaria endemic country for the purposes of the cost-effectiveness modeling. Therefore, a method was developed to estimate the incremental cost of delivering a potential malaria vaccine through the EPI program and it was applied to collect the data needed to calculate vaccine delivery costs in one such country.

Study setting: the Expanded Program on Immunization in Tanzania

In presenting a cost-effectiveness study based on modeled data, ideally the results should reflect a specific setting. A variety of settings have been defined in previous cost-effectiveness modeling studies. For example, the comprehensive study of Goodman and others[35] stratified sub-Saharan African countries by three income levels and presented cost-effectiveness simulations for each of these.

Given the diverse characteristics of the EPI throughout Africa, such country stratification was not considered possible in this present study. Therefore, a single country, Tanzania, was chosen.

The EPI in Tanzania was established in 1974 as a vertical program and then, as part of the health sector reforms started in mid 1990s, it was integrated into the Reproductive and Child Health Unit in the directorate of Preventive Services of the Ministry of Health. Immunization services are provided by 3,544 fixed health facilities in Tanzania, both public and private for profit and non profit. 10% of these provide outreach and mobile services.[36] In Tanzania the private sector as a whole provides roughly 40% of health services. From 1996, as a consequence of the decentralization reforms, the management of day to day immunization activities at the service provisional point was left to the District and Municipal Councils.[36,37]

The recent reforms created a quasi-autonomous drug procurement agency - the Medical Store Department (MSD) - responsible for procurement, storage, and distribution (until District level) of vaccines and related equipment. Other changes introduced in the last few years include government financing of procurement of oral polio vaccine, and use of kerosene in the cold chain, the integration of kerosene and vaccine distribution, supervision and monitoring in the district health system.[37]

The vaccines provided by the Tanzanian EPI in the year 2004 include BCG (1 dose), OPV (3 doses), DPT-HPV (3 doses), tetanus toxoid (5 doses), Measles (1 dose), and Vitamin A (3 doses). In 2002 the immunization coverage at national level was 88% for BCG, 91% for OPV, 89% for DPT-HBV, 89% for measles, and 86% for tetanus toxoid to pregnant women. The drop out rate for DPT1-DPT3 was 6%. However, it should be noted that the vaccine coverage rate varies widely between EPI providers.[38]

A considerable effort was made in recent years to improve the effectiveness of the program. In 2001, EPI introduced auto-destructing syringes in place of sterilizable needles and syringes, and incinerators were constructed in all district hospitals. Incinerators are not available at health centre and dispensary level.[36] The vaccine wastage rate has been decreasing in recent years, and in 2002 it was around 5% in most regions. However, there is a wide variability among districts in wastage rates, with some of them reporting wastage rates of up to 16%.[38]

Table 3.1 presents the cost structure of EPI in Tanzania for two financial years (2000/01 and 2001/02). In 2000/01 the EPI budget in Tanzania was US$11.6 million for routine immunization services and US$3.3 million for supplementary immunization services. The program-specific spending on routine immunization service equated to about US$10.6 per DPT3 vaccinated child or US$0.33 per capita.[21] In 2001/02 the budget on routine immunization increased to US$13.6 million (a rise of 17% on 2000/01), due to new vaccine introduction and an increase in other expenditures for the program. Total expenditures in 2001/02 were close to US$18 million.

Table 3.1 also shows the cost profile of EPI program in Tanzania for the last two years available. Recurrent costs account for 67% of total cost, and non-recurrent costs for 22% (mainly cold chain equipment). Vaccines and injection supplies account for most of recurrent costs. However, note that the EPI uses and shares certain resources of the national health system, and the costs of these resources are not included in these figures. Examples include general health service personnel and managers, health facility buildings, and utilities paid for by the health system (e.g. electricity). Therefore, the costs presented in Table 3.1 do not represent the full costs of providing the EPI. In terms of EPI financing, the Tanzanian government increased its allocation for the program from 2000/01 to 2001/02, when it funded around 44% of overall financing for immunization, shown in Figure 3.1. The government pays mainly for injection supplies, salaries, transport and other recurrent costs, vehicles and cold chain equipment and some vaccines. Donors pay for vaccines, injection supplies, training, monitoring and surveillance, and for vehicles, cold chain and other capital equipment. Donors also fund supplementary immunization activities. However, according to the Financial Sustainability Plan, the Government of Tanzania is programmed to take over the funding of all vaccines in the next few years.

Tanzania's EPI has faced several problems during the last few years, which are also relevant to consider when making policy recommendations based on the findings of cost-effectiveness analysis. The main constraints to a further development of the immunization program, as perceived by EPI managers, include: inadequate funds; problems in storage of certain vaccines; delays in disbursement of funds, from both government and development partners; delays

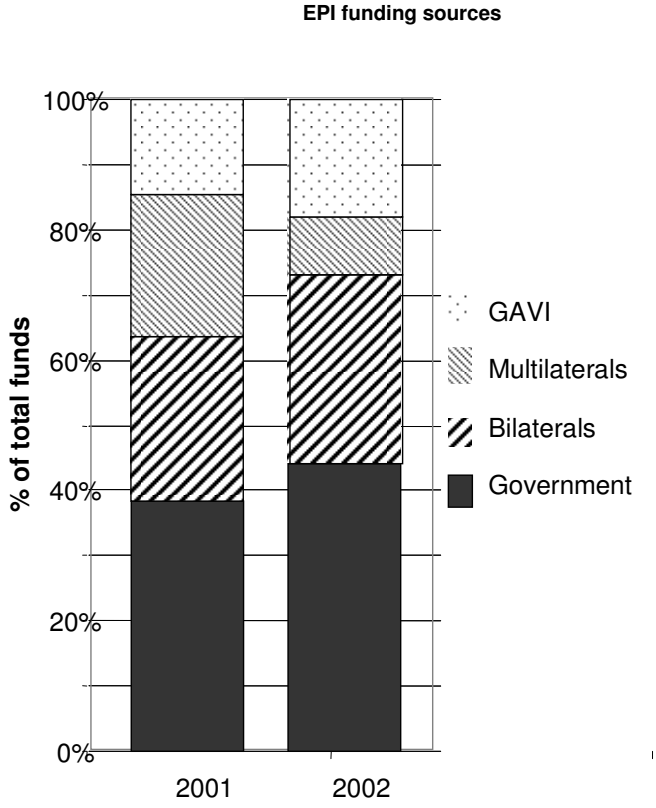
in the procurement process; inadequate refrigerators and spare cold chain capacity in some districts; shortage of cold chain equipment; and lack of adequate and qualified health staff, especially at facility level.

Table 0.1 Cost structure of EPI in Tanzania, financial years 2000/01 and 2001/02

Costs/Year	***Costs year 2000/01***	***%***	***Costs year 2001/02***	***%***
Recurrent costs (2)	*6,854,056*	*59%*	*8,981,321*	*67%*
Vaccines	*2,601,714*	*23%*	*3,310,240*	*25%*
Injection supplies	*608,931*	*5%*	*2,082,453*	*16%*
Kerosene/gas	*904,207*	*8%*	*904,207*	*7%*
Distribution of vaccines supplies	*202,247*	*2%*	*202,247*	*2%*
Personnel (per diems)	*274,285*	*2%*	*274,285*	*2%*
Transportation	*82,801*	*1%*	*85,036*	*1%*
Maintenance and overhead	*14,299*	*0%*	*7,895*	*0%*
Short – term training	*277,558*	*2%*	*301,107*	*2%*
IEC/ social mobilisation	*107,817*	*1%*	*282,100*	*2%*
Monitoring and surveillance	*1,780,197*	*15%*	*1,531,751*	*11%*
	4,704,635	*41%*	*4,399,949*	*33%*
Non recurrent costs (2)				
Transport (vehicles/bicycles)	*59,359*	*1%*	*62,921*	*1%*
Cold chain equipment	*4,645,276*	*40%*	*4,337,028*	*32%*
Total costs (1)+(2)	*11,558,691*	*100%*	*13,381,270*	*100%*
	3,312,301	*100%*	*3,199,396*	*100%*
SIA (polio and measles) (3)				
Vaccines	*1,609,752*	*49%*	*1,246,500*	*39%*
Inlection supplies	*316,653*	*10%*	*567,000*	*18%*
Per diems	*50,000*	*2%*	*50,000*	*2%*
Operational costs	*1,335,896*	*40%*	*1,335,896*	*42%*
Optional information (4)				
Shared personnel costs	*479,256*		*479,256*	
Long term training	*0*		*51,250*	
Total costs (1)+(2)+(3)+(4)	*15,350,248*		*17,111,172*	

Source: Ministry of Health, Tanzania[36]

Figure 0.1 EPI funding sources, financial years 2000/01 and 2001/02



Study aims

The aim of the present costing study is to measure the incremental costs of adding a hypothetical malaria vaccine to the EPI schedule, to enable estimation of cost-effectiveness of such a vaccine.

3.2 Methodology

Study perspective and choice of costs presented

After defining the study aims, the next step in a cost study is to choose which costs to include. The costs included in cost-effectiveness analysis depend first on the perspective of the analysis, whether it be the health care system, the patients, or society. In this study, the cost-effectiveness analysis is performed according to a societal perspective, which includes the health system, the patient, and other groups affected by the intervention (such as the larger community). Given this perspective, the costs included and measured must be relevant to the objectives of the study. In this study which examines the incremental health impact of a potential new intervention, the cost of interest is the incremental cost associated

with the intervention to achieve the health effect. Given the range of information needs of decision makers in the health sector, two types of incremental cost have been selected for measurement: marginal cost and average cost.

Marginal cost

The marginal cost consists of the additional costs that would be incurred when introducing a malaria vaccine into the EPI schedule, based on new resources that would need to be employed in the delivery of the intervention. This information is most relevant for a decision maker who has to make resource allocation decisions, based on the immediate resource impact of an intervention. Therefore, for example, when spare capacity in the health system exists, the use of that spare capacity is not included in the marginal cost analysis. However, when full capacity has been reached and new resources are needed, these are included in the marginal cost analysis.

Average cost

The average cost includes all those costs involved in delivering a health intervention, whether they are employed specially for a new intervention, whether resources are shifted away from other activities, or whether spare capacity is used. Average costing involves sharing the costs of existing capacity amongst all the interventions benefiting from those resources. The usefulness of presenting full economic cost through this analysis is that it enables comparison of intervention efficiency in the long-term, where all resources can (hypothetically) be redeployed in alternative uses. Therefore, average costs are useful for cost-effectiveness analyses for long-term planning decisions.

In both marginal and average analyses, all types of cost are included where necessary. In this analysis, for policy making reasons a distinction is made between non-recurrent (capital) cost items (defined as resources that are not wholly consumed within a one year period) and recurrent cost items (defined as items that are used up during a year).

Algorithm for calculating vaccine delivery cost

The specific characteristics of a malaria vaccine are still unknown. This analysis is based on a hypothetical vaccine that must be stored between +2°C and +8°C, it has a commercial package similar to that of DTP-HBV vaccine and it requires three doses to fully immunize a child delivered at the same time as the DTP-HBV.

The vaccine delivery cost per dose (V_d) is estimated according to the following formula:

$$V_d = P_d + D_d + S_d + M_d + E_d + T_d + Z_d \qquad (1)$$

where, P_d is the purchase cost per dose; D_d is the distribution cost per dose; S_d is the storage cost per dose; M_d is the management cost per dose; E_d is the delivery

cost per dose; T_d is the training cost per dose; and Z_d is the social mobilization cost per dose.

The variables in equation (1) are covered in detail in this paper. All variables are calculated, where relevant, under both marginal cost (MC) and average cost (AC) scenarios. The cost per Fully Immunized Child (FIC) with the vaccine is computed by multiplying V_d by three. However, the average cost per FIC is marginally greater than three times the cost per dose, due to the drop out of infants after the first dose.

To estimate the total number of doses required per year in Tanzania it is assumed that the coverage rate would be the same as that for 3 doses of DTP-HBV in the year 2003, which stood at 89%, with a drop out rate from the first to the third dose of 6%.

Net vaccine purchase cost (f.o.b.)

In the cost-effectiveness analysis different price hypotheses are used ranging from US$1.00 to US$10 per dose. No base case is presented, as it may become misleading in presenting results. Instead, cost results are presented under a number of vaccine price assumptions: US$1, US$2, US$4, US$6, US$8, and US$10. Import duties are not included, as these are not an economic cost but instead a transfer payment.

The contribution of freight costs to the price at which the country receives the vaccines (i.e. including c.i.f. – carriage, insurance and freight) essentially depends on the original price of the vaccine, the packed volume of the vaccines, and the mode of transport. For DPT-HBV the contribution of freight to the c.i.f. price is reported in MSD documents and in the GAVI Financial Sustainability Plan. However, in this analysis the price assumptions include freight costs to the port of entry.

To estimate the total vaccine cost per dose delivered it is assumed that 5% of vaccine is wasted. The purchase costs per dose of the vaccine (P_d) is computed as follows:

$$P_d = V_p(1+Q_v) \qquad (2)$$

where V_p is the vaccine price; Q_v is the wastage rate.

Storage and distribution costs

The cold chain system of EPI in Tanzania includes five operational levels each equipped with cold chain equipment as follows:[39]

- 1 central vaccine store at Medical Store Department (MSD) in Dar es Salaam;
- 8 Zonal vaccine stores at MSD;
- 15 regional vaccine stores;

- 116 district vaccine stores;
- 3,544 health facilities (dispensaries, health centers, hospitals).

All health facilities conduct immunization activities and are equipped either with a small absorption refrigerator and freezer operating on either kerosene or electricity, or with LP gas or a solar powered refrigerator.

However, the storage and distribution system is continuously undergoing changes and the MSD is restructuring the storage and distribution policy and is negotiating a new financial agreement with the Ministry of Health. Currently a new malaria vaccine would be distributed from the central MSD in Dar es Salaam to the 8 zonal stores and from these directly to Districts. The distribution from Districts to the health facilities providing immunization services is under the direct responsibility of EPI.

The new agreement between MSD and EPI includes a tariff scheme for storage of products at central and zonal level and for distribution from central stores to zonal stores and then from zonal stores to districts. The tariffs are as follows:

- For storage of cold items at the national store, Tshs 300,000/m3 (US$286) is charged per month.
- For distribution of cold chain items to all MSD zones (other than Dar South), Tshs 625,000/ m3 (US$595) is charged.
- For distribution from any MSD zonal store to all districts, Tshs 145,000/ m3 (US$138) is charged.

These new tariffs are the most reliable information currently available on the current and future cost of storage and distribution of vaccines. Therefore to estimate the incremental cost of storing and distributing the vaccine the new tariff scheme is used, assuming thus that MSD will distribute vaccine first to zonal stores and then to districts.

To estimate the incremental cost of storage and distribution of the vaccine the package volume requirement for transportation and cold chain storage at national, zonal, and at service delivery level was estimated on the basis of the WHO Guidelines for estimating costs of introducing new vaccines into the national immunization system.[40] These guidelines provide a method to estimate the total volume package required for storage and distribution of a vaccine, taking into account wastage rates, cold chain and transport grossing factors. The new tariffs defined by MSD for storage and distribution were then applied to the volume package estimated for the vaccine.

The estimated package volume per year for storage was 901 m^3, while at service delivery level it was 684 m^3. The estimated package volume for transport per year was 3,543 m^3.

MSD distributes vaccines from the central store to the 8 zonal stores and from these to district stores every three months (4 times a year). Every three months

there is thus a need to store at national, zonal, and district level one fourth (i.e. 3 months' worth) of the estimated package volume. It is assumed that MSD is able to distribute the vaccines to zonal and district stores within one month from when it receives them, and thus every three months it has to store the estimated volume package for a maximum of one month at national and zonal level.

Districts receive the vaccines every three months and distribute them to health facilities monthly. It is assumed that every three months districts have to store the estimated package volume of vaccine for a maximum of one month.

The cost of storage per vaccine dose at national level is computed according to the following formulae:

$$S_d = \frac{S_m N_m F_y}{N_{vy}} \qquad (3)$$

where S_d is the cost of storage per vaccine dose at national level; S_m is the storage cost/tariff per m^3 per month; N_m is the number of months of storage (over one year); F_y is the volume package per year for storage at all levels (per m3); and N_{vy} is the number of doses of the vaccine per year.

The storage cost at zonal and district level is assumed to be the same as that at central level. The cost of storage at facility level is computed with the same formula but the volume package required - estimated according to WHO Guidelines - is different. This is due to different grossing factors, which adjusts for the different presumed percentage use of cold chain capacity at different MSD levels. For national and provincial level the grossing factor is 2.9; whereas for district level the grossing factor is 2.2.

The cost of distribution per dose of vaccine from central to zonal stores is computed according to the following formulae:

$$D_{zd} = \frac{D_{zm} F_t \alpha}{N_{vy}} \qquad (4)$$

where $\alpha = \frac{N_{vT} - N_{vD}}{N_{vT}}$

and D_{zd} is the distribution cost from central to zonal stores per dose of vaccine; D_{zm} is the distribution cost/tariff from central to zonal stores per m^3; F_t is the estimated volume package for transport of the vaccine; N_{vT} is the total number of vaccine doses delivered in Tanzania; and N_{vD} is the total number of vaccine doses delivered in Dar es Salaam.

The adjustment factor α is included to account for the fact that the distribution from central to zonal store for the Region of Dar es Salaam should not be included. This is because the MSD does not charge EPI for vaccine supplies sent to Dar South, due to its proximity to MSD.

The cost of distribution from zonal to district stores per dose (D_{dd}) is computed according to the following formulae:

$$D_{dd} = \frac{D_{dm} F_t}{N_{vy}} \qquad (5)$$

where D_{dm} is the distribution cost/tariff from zonal to district stores per m^3. The cost of distribution of the vaccine from district to the health facilities - that is under the direct responsibility of EPI - is assumed to be the same as that from zonal to district stores. This might on the one hand overestimate distribution costs since the distance between district vaccine stores and health facilities is normally shorter than that from zonal stores to district vaccine stores, on the other hand it might not because of (dis)economies of scale of distributing less quantity of vaccine to different facilities. However, in the absence of more detailed data to confirm which cost determinant predominates, the same cost per cubic metre is assumed.

The costs of cold chain storage are mainly capital costs since cold storage mainly consists of cold rooms and refrigerators that last longer than one year. Only personnel and electricity or fuel for refrigerators are recurrent costs and these account for a marginal part of storage costs. In the absence of detailed breakdown from MSD, it is assumed that capital costs account for 80% of cold chain costs and recurrent costs the remaining 20%.

Distribution costs are both recurrent (e.g. fuel for vehicles, fares for air transport, personnel) and capital (e.g. cold boxes, costs of vehicles). Compared to the capital-recurrent breakdown of cold chain storage, fuel costs in distributing vaccines account for a more considerable proportion of total distribution costs. Therefore, it is assumed that 50% of distribution costs are capital and 50% are recurrent costs.

Management costs

A wide range of personnel are involved in delivering a new vaccine, including managers, surveillance staff, community health workers, nurses and doctors. The personnel involved in EPI are distributed throughout all the levels of the health care system – i.e. national, regional, district, and health facility.

The introduction of a new vaccine in the EPI will require additional management costs at all levels of the EPI system. It is thus assumed that all personnel of EPI at national (excluding the EPI manager), and regional level, the District Medical

Officer, the District Reproductive and Child Health Coordinators, the Medical Officers, and the Medical Records Officers would have to allocate 10% of their working time devoted to EPI. These management costs are included only in the average analysis since it is uncertain whether new personnel will be employed by EPI to manage the malaria vaccine.

Vaccine delivery costs

The costs at the point of delivery include the recurrent costs of personnel involved in EPI at facility level, of syringes, and of safety boxes, and the capital cost of waste management (other than safety boxes).

Personnel

According to interviews held with EPI at national level, the employees believe that introducing a new vaccine into EPI would not require additional personnel at facility level. The main justification given for this opinion is that EPI personnel at facility level are now integrated into the Reproductive and Child Health Unit and normally they do not dedicate 100% of their time to EPI.

Based on observations of selected health facilities in Tanzania, it became apparent that there exist several ways of organizing an EPI session. In Dar es Salaam infants can get vaccination on any working day (5) of the week, while in Mtwara Region in Southern Tanzania vaccination availability varies from selected days every three months for outreach to remote villages, to two days per week for health centres.

In terms of the spare capacity of the staff to administer a new vaccine, vaccinators interviewed in general concurred that a new vaccine requiring five extra minutes per child could be accommodate without needing additional staff. However, during the health facility visits the issue of lack of skilled personnel was often raised, thus suggesting that staff are often under pressure from the volume of clients. Therefore, the impression is that EPI staff could probably accommodate a new vaccine using the current capacity but this may lower the quality of services as a whole. Hence, in order to maintain the minimum quality of services, vaccination staff will need to be strengthened in numbers, targeting those facilities that are already close to their limit in terms of proportion of working time already used.

In the marginal analysis only the incremental cost of vaccinators is included, while in the average analysis both the costs of vaccinators and that of other personnel at district and other facility level staff are included.

In the average analysis it is assumed that personnel of the districts other than vaccinators – i.e. Medical Assistants, Health Officers, and Nurses – would have to increase by 10% of their working time spent on vaccination to the malaria vaccine.

The incremental cost per dose for these personnel (I_{ld}) is computed as follows:

$$I_{ld} = \frac{W_y P_{it} P_{mv} N_p}{N_{vy}} \quad (6)$$

where W_y is the annual gross wage; P_{it} is the % of staff working time for immunization; P_{mv} is the percentage increase in EPI working time spent on malaria vaccine; and N_p is the number of personnel.

Data for the annual gross wage, the percentage of working time for immunization, and the number of personnel, come from the Ministry of Health.[36] In the marginal analysis it is assumed that these personnel have enough spare capacity to accommodate the increase in working time required by the new vaccine and thus the incremental cost is zero.

For vaccinators a cost per dose of vaccine is estimated assuming an administration time of 7 minutes, and the cost per working minute of vaccinators is computed assuming 230 working days per year and 6 productive hours per day.

The cost per dose is computed as follows:

$$L_d = \frac{W_y}{M_y} A_t \quad (7)$$

where L_d is the cost of vaccinators per dose; W_y is the annual gross wage; M_y is the total number of working minutes per year; and A_t is the vaccine administration time.

The personnel vaccine delivery cost is thus computed as follows:

Average analysis: $= L_d + I_{ld}$

Marginal analysis: $= L_d$

<u>Syringes</u>

For both marginal and average analyses, the syringe incremental cost per dose (G_d) is calculated as follows:

$$G_d = \left(N_{gd} G_i + N_{rd} G_r\right)(1 + Q_s) \quad (8)$$

where N_{gd} is the number of injection syringes per dose; G_i is the unit cost of injection syringes (freight included); N_{rd} is the number of reconstitution syringes

per dose; and G_r is the unit cost of reconstitution syringes (distribution included); Q_s is the syringe wastage rate.

The syringe wastage rate is 10% as suggested by the WHO Guidelines and confirmed by GAVI documents. The cost of syringes used is that of the MSD catalogue for year 2004 [41], while the distribution costs are assumed to be 3% per cent of the cost of syringes.

Safety boxes

Safety boxes are present at the place of vaccination, and after vaccination the used syringes are disposed immediately into these. The safety boxes incremental cost per dose (B_d) is computed as follows:

$$B_d = \frac{\left(\frac{N_s}{Y_b}\right) Q_b \, B_i}{N_{vy}} \qquad (9)$$

where N_s is the total number of syringes; Y_b is the capacity of safety boxes; Q_b is the wastage factor for safety boxes; and B_i is the unit cost of safety boxes (distribution included).

The capacity of safety boxes is 100 syringes, and the wastage rate for safety boxes used is assumed to be 11% (giving a factor of 1.11) as reported in the GAVI annual progress report.[41] The unit cost of safety boxes comes from MSD catalogue 2004 http://www.msd.or.tz/ and include 3% of distribution cost.

Waste management incremental cost per dose

The capital resources required for effective waste management should include the capital cost of incinerators and any buildings required to house them. Recurrent costs include those associated with incinerator fuel and maintenance, training, and salaries of staff. However, in Tanzania only hospitals have incinerators while in health centres and dispensaries the waste management practice is to throw the safety boxes into a deep hole and fire them with kerosene. In fact, this was confirmed in all the facilities visited by the study team.

The waste management of the malaria vaccine should be the same as that for other vaccines currently delivered through EPI, and it is unlikely that EPI would introduce different waste management practices due to a new vaccine. The cost of waste management was thus considered to be zero (except for the safety box cost, as considered above).

Training

EPI personnel will have to be trained for the administration of the new vaccine. The training on the new vaccine can either be limited to the period just before or during its introduction or can continue in successive years. In this analysis it is assumed that the training is limited to the introduction period and has duration of effect of five years, which enables an annual value for training cost to be computed.

In Tanzania training of health workers can be organized at zonal, district and facility level. When it is organized at zonal and at district level the health workers get a per diem to cover the cost of being outside the health facility. It is assumed that in the first year of vaccine introduction five days of training are provided at zonal and district level, and four days at health facilities. An ingredient approach is used to estimate the cost of training at each level.

The training at zonal level is assumed to be organized as a five days workshop in each of the eight zonal training centres, with two trainers per workshop, attended by personnel at regional and district level (i.e. not staff from health facilities), comprising one Regional Cold Chain officer, one District Cold Chain officer, one Medical records officer, one District RCH coordinator, and one Regional RCH coordinator.

The daily cost per trainers is assumed to be US$30, the overheads cost of each premises used for the training (one per zone) US$40, the per diem of personnel US$30, the transport cost per workshop per person US$4, stationary cost per person per day US$1, and tea and coffee per day US$ 2 per person.[41]

The training at district level is assumed to be attended by one person per health facility providing immunization services, and led by one trainer per district. The daily cost per trainer is assumed to be US$30, the overheads cost each premise (one per district) used for the training US$10, the per diem of personnel US$5, the transport per meeting US$2 per person, and stationary and tea & coffee costs the same as at zonal level.[36]

The training cost per dose of vaccine at zonal (T_z) and at district level (T_d) is computed according to the following formula, assuming the training has duration of effect of five years:

$$T_{z/d} = \frac{N_{tr}\left[N_{trL}\,C_L + N_a(C_a + C_{st} + C_{tea}) + N_{loc}\,C_{loc}\right] + N_a C_{tra}}{N_{vy}} \quad (10)$$

where N_{tr} is the number of days of training; N_{trL} is the number of trainers; C_L is the cost per trainer per day; N_a is the number of person attending training; C_a is the per diem of training attendants; C_{st} is the cost of stationary per person per day;

C_{tea} is the cost of tea and coffee per person per day; N_{loc} is the number of premises used for training; C_{loc} is the overheads cost of premises used for training per day; and C_{tra} is the cost of transport per person per workshop. To estimate the annual equivalent cost, equation (14) can be divided by 5.

The training at facility level is supposed to be attended by all personnel at facility level but except those that were already involved in training at district level. A trainer per health facility providing immunization services is assumed to be used, the daily cost per day of training is US$ 20 plus US$ 20 of transport cost per trainer (assuming that trainers travel only once to each facility during the 4 day training).

The total training cost at facility level (T_f) is computed according to the following formula:

$$T_f = \frac{N_{tr}(N_{trL}\, C_L) + N_f\, C_{tra}}{N_{vy}} \qquad (11)$$

where N_f is the number of facilities providing immunization services.

The total cost of training is computed as the sum of training cost at zonal, at district and at facility level:

$$T = T_z + T_d + T_f \qquad (12)$$

Social mobilization

Advocacy and social mobilization efforts are crucial for ensuring the successful introduction of a new vaccine. The introduction of the new vaccine should be followed by an increase in the social mobilization efforts.

It is assumed that in the first years after the introduction of the vaccine into EPI a substantial number of social mobilization activities will be organized. In the marginal analysis it is assumed that the budget for these social mobilization activities would be approximately equal to the current expenditure on social mobilization (Table 3.1) and it is thus estimated around US$ 300,000 per year. This scale of social mobilization is warranted by the fact that messages will need to inform the population about the characteristics of the vaccine, and the importance of continuing other preventive and curative strategies.

In the average analysis social mobilization costs are assumed to be US$ 450,000 per year. Hence the addition of US$150,000 is assumed to account for the time dedicated to social mobilization efforts by the personnel already employed by the health care system. While this amount may seem relatively small, the relatively

low unit labour cost in Tanzania explains why there is not a sharp increase in costs.

3.3 Results

Target population

In Tanzania, in 2003 the number of live births in 2003 was 1,438,000, and 1,289,000 infants survived the first year.[42] Assuming the same coverage rate reported for DTP-HBV vaccine, the total number of vaccine doses per year is estimated, assuming the same coverage rate reported for DTP-HBV vaccine, to be close to four million (Table 3.2).

Table 0.2 Target population

Population/Vaccine doses	*%*	*N*	*Source*
Target population	*100%*	*1,438,000*	[42]
Target first dose	*95%*	*1,366,100*	[36]
Target second dose	*92%*	*1,322,960*	[36]
Target third dose	*89%*	*1,279,820*	[36]
Total number of doses		*3,968,880*	

Cost per fully-immunised child (FIC)

Figure 3.2 shows the average cost per fully-immunised child at each vaccine price per dose assessed. The average cost per FIC increase almost linearly from US$4.2 per FIC at a vaccine price of US$1 per dose to US$31.2 at vaccine price of US$10 per dose.

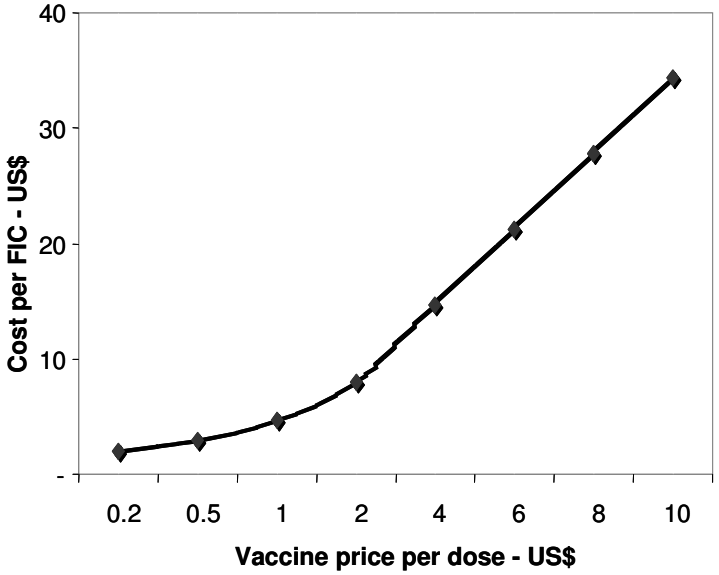
Table 3.3 presents more detailed cost data, showing that marginal costs are not considerably less than average costs. The marginal cost per dose is 6-7 US cents less than the average cost, thus making less than US$0.2 per FIC. This difference represents well under 5% difference between average and marginal cost.

Table 3.3 also presents the contribution of recurrent and non-recurrent costs to total cost. As the vaccine price increases, the non-recurrent contribution does not change, thus giving a considerably greater weight to recurrent costs at higher prices.

Table 0.3 Summary of costs at different vaccine prices per dose

Option and cost inclusion	*Recurrent / non-recurrent*	*Vaccine price assumption per dose*					
		US$ 1	US$2	US$4	US$6	US$8	US$10
Average cost	*Recurrent cost per dose*	1.41	2.41	4.41	6.41	8.41	10.41
	Non-recurrent cost per dose	0.07	0.07	0.07	0.07	0.07	0.07
	Total cost per dose	1.48	2.48	4.48	6.48	8.48	10.48
	Total cost per FIC	4.43	7.43	13.43	19.43	25.43	31.43
Marginal cost	*Recurrent cost per dose*	1.35	2.35	4.35	6.35	8.35	10.35
	Non-recurrent cost per dose	0.07	0.07	0.07	0.07	0.07	0.07
	Total cost per dose	1.41	2.41	4.41	6.41	8.41	10.41
	Total cost per FIC	4.24	7.24	13.24	19.24	25.24	31.24

Figure 0.2 Average cost per fully-immunized child



Total cost to EPI

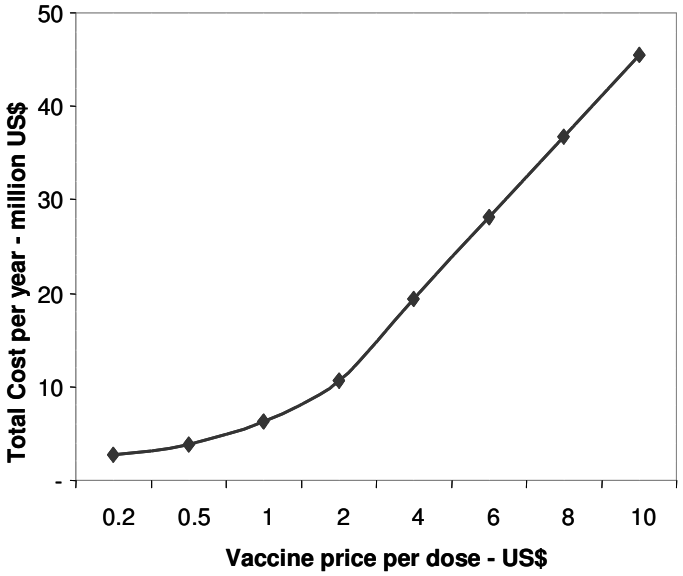
Figure 3.3 shows the marginal costs to EPI at each vaccine price per dose assessed. The marginal costs increase almost linearly from US$5.7 million at a vaccine price of US$1 per dose to US$45.3 million at a vaccine price of US$10 per dose. In this case, the marginal cost is more relevant, as this is the additional cost that EPI is likely to have to finance, on top of the current resources available and annual budget. However, the average cost is not considerably greater, somewhere in the order of US$250,000 more for all vaccine price scenarios less than 5% more than the marginal cost.

Data on the proportion of total costs made up of recurrent and capital costs are provided in the Annex tables, a distribution which is shown to vary between

vaccine price scenarios. At a vaccine price of US$1 per dose the capital costs are roughly 4% of the total cost, but this proportion declines as the vaccine price increases.

In comparison to the current budget and expenditure patterns of the EPI, these total costs represent a considerable impact on the budget if the malaria vaccine were included in the vaccination schedule (see Table 3.7 and the Annex tables). The budget for the year 2001/02 of US$17 million is little more than 3 times the cost scenario modelled at a vaccine price of US$1 per dose. At higher vaccine prices the costs of the malaria vaccine become greater than the current EPI budget, rising to three times the current budget at a vaccine price of US$10 per dose.

Figure 0.3 Marginal costs to EPI of the malaria vaccine



Components of cost

Figure 3.4 shows the percentage contribution of different cost components to total cost, at each vaccine price per dose – US$1, US$2, US$4, US$6, US$8, and US$10. It demonstrates the change in the contribution of different cost components (described in the methods section) at different vaccine prices. The conclusion is that most cost components become more and more insignificant as vaccine price increases. For example, all cost components except vaccine price and storage and distribution contribute less than 10% to total cost at vaccine prices above US$6 per dose.

Cold chain storage and distribution costs are shown in Table 3.4, and account for most of the incremental cost of the vaccine, apart from the vaccine price itself. Storage cost per dose is around US$0.03, while the cost of distributing the vaccine is US$0.08, 66% of which is accounted for by the distribution of the vaccine from central to zonal level. Storage and distribution costs are expected to be the same for both the average and marginal analysis.

Management costs are included only in the average analysis and are the same for both options. The management costs are found to be insignificant at US$ 0.0023 per dose. All of these are recurrent costs.

Vaccine delivery costs are presented in Table 3.5 and contribute US$0.22 to the average cost, and US$0.20 to the marginal cost. All these costs are recurrent costs. Figure 3.5 shows the contribution of personnel, syringes and safety boxes diagrammatically.

The training cost per dose is US$0.03 in both types of analysis, most of which are recurrent costs. Table 3.6 shows the breakdown by resource input, the main contributor (50%) being the cost of trainers. The social mobilization cost is US$0.11 per dose in the average cost analysis, and US$0.08 in the marginal cost analysis. The entire social mobilization cost is recurrent.

Figure 0.4 Storage and distribution costs

Cost item	***Cost per dose administered (US$)***
Cold Chain Storage	0.03
Recurrent	0.01
Non recurrent	0.02
Distribution	0.08
Recurrent	0.04
Non recurrent	0.04

Table 0.4Vaccine delivery costs

Cost item	Cost per dose administered (US$)	
	Average	*Marginal*
Vaccine Delivery	0.22	0.20
Recurrent		
Personnel at facility	0.08	0.06
Syringes	0.12	0.12
Safety boxes	0.03	0.03
Non recurrent	0	0

Table 0.5 Training costs

Cost item	Cost per dose administered (US$)
Training (per year)	0.03
Recurrent	
Trainers	0.015
Per diem	0.007
Stationary	0.001
Tea and coffee	0.001
Non recurrent	
Premises	0.000
Transport	0.004

Table 0.6 Contribution of cost components at different vaccine prices.

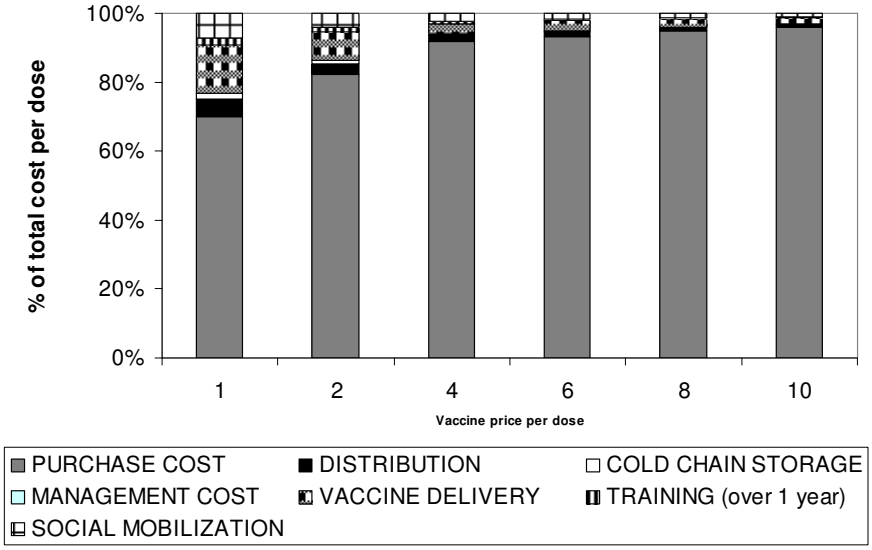
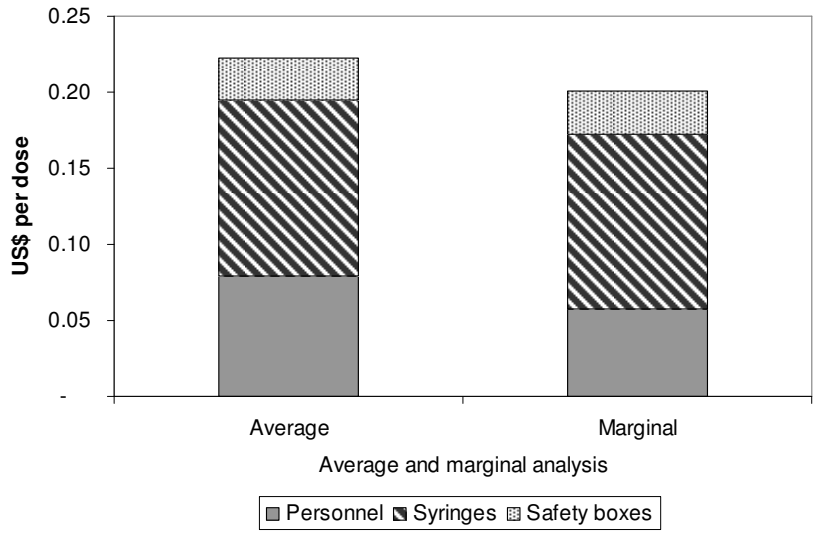


Figure 0.5 Vaccine delivery cost



3.4 Discussion

In this paper the delivery cost of a hypothetical malaria vaccine was estimated on the basis of the information currently available on the likely characteristics of the vaccine itself and on the EPI in Tanzania.

The major strength of this analysis is that it is based on information on the current features of EPI in Tanzania, using the best available data on costs and functioning of EPI, also drawing on qualitative data collected from experts from within the Tanzanian health system, and observations of health facilities by the study team. The cost of delivery is estimated assuming different vaccine price hypothesis from US$1 per dose up to US$10.

The costs included in the analysis are those related to: the purchase of the vaccine, taking into account the wastage rate; the costs of distributing and storing the vaccine at central, zonal, district, and facility level; those of managing the vaccination program; the costs of delivery at facility level (including personnel, syringes, safety boxes, and waste management); those of additional training of EPI personnel and of social mobilization activities.

Although the vaccine price still determines most of the total delivery costs, the analysis shows that other costs are relevant and should be taken into account before marketing the vaccine and planning its inclusion into the EPI. This is particularly important since new vaccines are likely to have bigger volume packages than that used in this analysis.

In fact, the vaccine delivery cost, even when the vaccine price is excluded, is relatively high and would require additional resources to be allocated to the EPI. At a vaccine price of US$1 per dose the total annual cost to EPI would be over 35% of the current budget.[36] When the vaccine price rises to US$4 per dose the total annual cost would rise to over US$ 19 million – slightly more the annual EPI budget in 2002.

It is thus important to bear in mind that for the vaccine to be delivered through EPI, some investments are required in strengthening the program. In particular, the storage capacity at central, zonal, district and facility level would need to be reinforced.

3.5 Annex

Table 0.7 Total cost of introducing the vaccine in EPI at US$1 per dose

in US$	*Incremental cost per dose administered*		*Total cost for EPI per year*	
	Average	Marginal	Average	Marginal
Purchase Cost	1.10	1.10	4'365'768	4'365'768
Distribution	0.08	0.08	322'981	322'981
Cold Chain Storage	0.03	0.03	106'688	106'688
Management Cost	0.002	0.000	9'268	-
Vaccine Delivery	0.22	0.20	882'535	795'778
Training (Over 1 Year)	0.03	0.03	117'165	117'165
Social Mobilization	0.11	0.08	450'000	300'000
Total Cost	1.58	1.51	6'254'405	6'008'379
Recurrent Costs	1.51	1.45	5'990'191	5'744'165
Non Recurrent Costs	0.07	0.07	264'214	264'214
TOTAL COST PER FIC	4.73	4.54	-	-

Table 0.8 Total cost of introducing the vaccine in EPI at US$2 per dose

in US$	*Incremental cost per dose administered*		*Total cost for EPI per year*	
	Average	Marginal	Average	Marginal
Purchase Cost	2.20	2.20	8'731'536	8'731'536
Distribution	0.08	0.08	322'981	322'981
Cold Chain Storage	0.03	0.03	106'688	106'688
Management Cost	0.002	0.000	9'268	-
Vaccine Delivery	0.22	0.20	882'535	795'778
Training (Over 1 Year)	0.03	0.03	117'165	117'165
Social Mobilization	0.11	0.08	450'000	300'000
Total Cost	2.68	2.61	10'620'173	10'374'147
Recurrent Costs	2.61	2.55	10'355'959	10'109'933
Non Recurrent Costs	0.07	0.07	264'214	264'214
TOTAL COST PER FIC	8.03	7.84	-	-

Table 0.9 Total cost of introducing the vaccine in EPI at US$4 per dose

in US$	Incremental cost per dose administered		Total cost for EPI per year	
	Average	Marginal	Average	Marginal
Purchase Cost	4.40	4.40	17'463'072	17'463'072
Distribution	0.08	0.08	322'981	322'981
Cold Chain Storage	0.03	0.03	106'688	106'688
Management Cost	0.002	0.000	9'268	-
Vaccine Delivery	0.22	0.20	882'535	795'778
Training (Over 1 Year)	0.03	0.03	117'165	117'165
Social Mobilization	0.11	0.08	450'000	300'000
Total Cost	4.88	4.81	19'351'709	19'105'683
Recurrent Costs	4.81	4.75	19'087'495	18'841'469
Non Recurrent Costs	0.07	0.07	264'214	264'214
Total Cost Per FIC	14.63	14.44	-	-

Table 0.10 Total cost of introducing the vaccine to the EPI at US$6 per dose

in US$	*Incremental cost per dose administered*		*Total cost for EPI per year*	
	Average	Marginal	Average	Marginal
Purchase Cost	6.60	6.60	26'194'608	26'194'608
Distribution	0.08	0.08	322'981	322'981
Cold Chain Storage	0.03	0.03	106'688	106'688
Management Cost	0.002	0.000	9'268	-
Vaccine Delivery	0.22	0.20	882'535	795'778
Training (Over 1 Year)	0.03	0.03	117'165	117'165
Social Mobilization	0.11	0.08	450'000	300'000
Total Cost	7.08	7.01	28'083'245	27'837'219
Recurrent Costs	7.01	6.95	27'819'031	27'573'005
Non Recurrent Costs	0.07	0.07	264'214	264'214
TOTAL COST PER FIC	21.23	21.04	-	-

Table 0.11 Total cost of introducing the vaccine in EPI at US$8 per dose

in US$	*Incremental cost per dose administered*		*Total cost for EPI per year*	
	Average	Marginal	Average	Marginal
Purchase Cost	8.80	8.80	34'926'144	34'926'144
Distribution	0.08	0.08	322'981	322'981
Cold Chain Storage	0.03	0.03	106'688	106'688
Management Cost	0.002	0.000	9'268	-
Vaccine Delivery	0.22	0.20	882'535	795'778
Training (Over 1 Year)	0.03	0.03	117'165	117'165
Social Mobilization	0.11	0.08	450'000	300'000
Total Cost	9.28	9.21	36'814'781	36'568'755
Recurrent Costs	9.21	9.15	36'550'567	36'304'541
Non Recurrent Costs	0.07	0.07	264'214	264'214
TOTAL COST PER FIC	27.83	27.64	-	-

Table 0.12 Total cost of introducing the vaccine in EPI at US$10 per dose

in US$	*Incremental cost per dose administered*		*Total cost for EPI per year*	
	Average	Marginal	Average	Marginal
Purchase Cost	11.00	11.00	43'657'680	43'657'680
Distribution	0.08	0.08	322'981	322'981
Cold Chain Storage	0.03	0.03	106'688	106'688
Management Cost	0.002	0.000	9'268	-
Vaccine Delivery	0.22	0.20	882'535	795'778
Training (Over 1 Year)	0.03	0.03	117'165	117'165
Social Mobilization	0.11	0.08	450'000	300'000
Total Cost	11.48	11.41	45'546'317	45'300'291
Recurrent Costs	11.41	11.35	45'282'103	45'036'077
Non Recurrent Costs	0.07	0.07	264'214	264'214
TOTAL COST PER FIC	34.43	34.24	-	-

3.6 References

1. Tediosi F, Maire N, Smith T, Ross A, Tanner M, Hutton G, 2005. Predicting the cost-effectiveness of introducing a pre-erythrocytic malaria vaccine into the expanded program of immunization schedule in Tanzania. *submitted*

2. Drummond M, O'Brien BJ, Stoddart GL, Torrance G, 1997. Methods for the economic evaluation of health care programmes. 2nd ed. New York: Oxford University Press. Second edition

3. Gold MR, Gold SR, Weinstein MC, 1996. Cost-effectiveness in health and medicine. Oxford: Oxford University Press

4. Little I, Mirrlees J, 1969. Manual of industrial project analysis in developing countries. 4 (1982) ed. OECD, Paris

5. United Nations Industrial Development Organization, 1972. Guidelines for project evaluation. New York: United Nations

6. Dasgupta P, 1970. An analysis of two approaches to project evaluation in developing countries. *Industrialization and Productivity Bulletin, UNIDO 15*

7. Sugden R, Williams A, 1978. Principles of practical cost-benefit analysis. Oxford University Press

8. Drummond MF, Stoddart GL, Torrance GW, 1987. Methods for the economic evaluation of health care programmes. Oxford University Press. First Edition

9. Levin HM, 1983. Cost-effectiveness - A primer. Sage Publications

10. Drummond M, 1980. Principles of economic appraisal in health care. Oxford University Press

11. World Health Organization, 1988. Estimating costs for cost-effectiveness analysis: Guidelines for managers of diarrhoeal disease control programmes. WHO/CDD/SER/88.3. Geneva: World Health Organization.

12. Luce BR, Elixhauser A, 1990. Estimating costs in the economic evaluation of medical technologies. *Int J Tech Assess Health Care 6*: 57--75

13. Creese A, Parker D, 1994. Cost analysis in primary health care: a training manual for programme managers. Geneva: World Health Organization

14. Drummond MF, Jefferson TO, 1996. Guidelines for authors and peer reviewers of economic sumissions to the *BMJ*. *Brit Med J 313*: 275--283

15. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans D, Murray C, 2003. Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization, Geneva

16. Baladi JF, 1996. A guidance process for the costing process. Canadian Coordinating Office for Health Technology Assessment.

17. Udvarhelyi IS, Colditz GA, Rai A, Epstein AM, 1992. Cost-effectiveness and cost-benefit analyses in the medical literature. Are the methods being used correctly? *Annals of Internal Medicine 116*: 238--244

18. Drummond M, Brandt A, Luce B, Rovira J, 1993. Standardising methodologies for economic evaluation in health care. *Int J Tech Assess Health Care 9*: 26--36

19. Rovira J, 1994. Standardising economic appraisal of health technology in the European Community. *Soc Sci Med 38*: 1675--1678

20. Weinstein M, Siegel J, Gold M, Kamlet M, Russell L, 1996. Recommendations of the panel of cost-effectiveness in medicine. *J Am Med Assoc 276*: 1253--1341

21. WHO, 2004. http://www.who.int/immunization_financing/en.

22. Parent du Chatelet I, Gessner BD, da Silva A, 2001. Comparison of cost-effectiveness of preventive and reactive mass immunization campaigns against meningococcal meningitis in West Africa: a theoretical modeling analysis. *Vaccine 19*: 3420--3431

23. Brenzel L, Claquin P, 1994. Immunization programs and their costs. *Soc Sci Med 39*: 527--536

24. Monath TP, Nasidi A, 1993. Should yellow fever vaccine be included in the expanded program of immunization in Africa? A cost-effectiveness analysis for Nigeria. *Am J Trop Med Hyg 48*: 274--299

25. Feilden R, 1990. Estimating vaccine costs for EPI (Expanded Programme on Immunization) cost-effectiveness analysis. *Int J Health Plann Manage 5*: 221--226

26. Brenzel LE, 1990. The cost of EPI: A review of cost and cost-effectiveness studies (1978-1987). *REACH project publication, Arlington, VA*

27. Shepard DS, Sanoh L, Coffi E, 1986. Cost-effectiveness of the expanded programme on immunization in the Ivory Coast: a preliminary assessment. *Soc Sci Med 22*: 369--377

28. Shepard DS, Robertson RL, Cameron CS3, Saturno P, Pollack M, Manceau J, Martinez P, Meissner P, Perrone J, 1989. Cost-effectiveness of routine and campaign vaccination strategies in Ecuador. *Bull World Health Organ 67*: 649--662

29. Creese AL, 1986. Cost-effectiveness and cost-benefit analyses of immunization programs in developing countries. *Advances in international maternal and child health, Vol 6 (edited by Jelliffe D and Jelliffe E F P), pp 901-927 Oxford University Press, New York*

30. Martin JF, 1984. Consequences of the introduction of the new inactivated poliovirus vaccine into the Expanded Programme on Immunization. *Rev Infect Dis 6 Suppl 2*: 480--482

31. Creese AL, Henderson RH, 1980. Cost-benefit analysis and immunization programmes in developing countries. *Bull World Health Organ 58*: 491--497

32. Griffiths UK, Hutton G, das Dores Pascoal E, 2005. Cost-effectiveness of introducing hepatitis B vaccine into the infant immunization schedule in Mozambique. *Health Policy Plan* 20: 50-59

33. Edmunds WJ, Dejene A, Mekonnen Y, Haile M, Alemnu W, Nokes DJ, 2000. The cost of integrating hepatitis B virus vaccine into national immunization programmes: a case study from Addis Ababa. *Health Policy Plan 15*: 408--416

34. Hall AJ, Robertson RL, Crivelli PE, Lowe Y, Inskip H, Snow SK, Whittle H, 1993. Cost-effectiveness of hepatitis B vaccine in The Gambia. *Trans R Soc Trop Med Hyg 87*: 333--336

35. Goodman C, Coleman PG, Mills A, 2001. The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. *Am J Trop Med Hyg 64*: 45--56

36. Ministry of Health, 2003. GAVI National Immunization Program Financial Sustainability Plan 2003. Ministry of Health, Tanzania.

37. Semali IAJ, 2003. PhD Thesis. Understanding stakeholders' roles in health sector reform process in Tanzania: The case of decentralizing the immunization program.

38. Ministry of Health, 2003. Report of EPI annual evaluation meeting held in Iringa from 3rd-7rd March 2003. Department of Preventive Services, Ministry of Health.

39. Ministry of Health, 2004. Expanded Program on Immunization Five Years National Strategic Plan 2000-2004. Dar es Salaam, Tanzania., Ministry of Health.

40. World Health Organisation, 2002. Guidelines for estimating costs of introducing new vaccines into the national immunization system. WHO/V&B/02.11Geneva, Department of Vaccines and Biologicals, World Health Organisation.

41. GAVI, 2002. Annual Progress Report to the Global Alliance for Vaccines and Immunization and The Vaccine Fund by the Government of the United Republic of Tanzania. *http://www vaccinealliance org/home/index php*

42. United Nations Population Division, 2003. World Population Prospects UN 2003. United Nations Department of Economic and Social Affairs.

Chapter 4: Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the Expanded Program on Immunization in Sub-Saharan Africa

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Abstract

We predict the effects of introduction of a pre-erythrocytic vaccine against *Plasmodium falciparum* into a malaria endemic population in Africa. We use a stochastic simulation model which includes components of transmission, parasitology, and clinical epidemiology of malaria and was validated using the results of field trials of the RTS,S/AS02A vaccine. The results suggest that vaccines with efficacy similar to that of RTS,S/AS02A have a substantial impact on malaria morbidity and mortality during the first decade following their introduction, but have negligible effects on malaria transmission at levels of endemicity typical for sub-Saharan Africa. The main benefits result from prevention of morbidity and mortality in the first years of life. Vaccines with very short half-life or low efficacy may have little overall effect on incidence of severe malaria. A similar approach can be used to make predictions for other strategies for deployment of the vaccine and to other types of malaria vaccines and interventions.

4.1 Introduction

The development of a safe and effective vaccine against *Plasmodium falciparum* is recognized as one of the major unmet medical needs in non-industrialised countries.[1,2] As a result of recent funding initiatives various candidate vaccines targeting different stages of the parasite are in pre-clinical and clinical development.[2] The most advanced vaccine development program is currently that of the pre-erythrocytic vaccine, RTS,S/AS02A, which recently demonstrated an efficacy of 45% in preventing *P. falciparum* infection in children in Mozambique.[3]

Partially protective vaccines have complex effects on the dynamic interactions between the host and an infectious agent.[4] It is generally acknowledged that a malaria vaccine is unlikely to be 100% effective and the effects of imperfectly protective malaria vaccines may be particularly complex. In order to make predictions of the likely public health impact of a range of malaria vaccines we have developed a stochastic simulation model of the epidemiology of *P. falciparum* in endemic areas.[5] We have now used this model to simulate the likely health impact of introducing the RTS,S/AS02A into malaria endemic populations via the expanded program on immunization (EPI). The model considers both the short- and long term effects of a vaccination program on the burden of disease, allowing for the temporal dynamics of effects on immunity and transmission.

4.2 Materials and methods

Epidemiological model

The epidemiological model is a stochastic individual-based simulation of *P. falciparum* malaria in endemic settings that uses a 5-day time step with the pattern of transmission as the input. For every individual in the simulated population each discrete *P. falciparum* infection is characterised by simulated duration, parasite densities,[6] infectivity[7] and anemia risk.[8] At each time point, clinical episodes of malaria or malaria attributable mortality may occur with probabilities depending on the simulated parasite density and recent exposure.[9-11]

For the present analyses we simulate populations of 100,000 individuals, with an approximately stationary age distribution matching that of the demographic surveillance site in Ifakara, south-eastern Tanzania, 1997-1999.[12]

We run the model under a series of assumed transmission patterns (Table 4.1). Each simulation assumes a recurring annual pattern of the vectorial capacity. The simulated population has been subjected to this pattern for a lifetime at the start of the vaccination program to ensure that the level of acquired immunity is correct for all ages. We then consider the transient behavior of the model during a follow-up period of 20 years. We simulate case-management and the effects on malaria transmission using a reference scenario as described in an accompanying paper.[13] This reflects a typical rural setting in Tanzania with mesoendemic malaria transmission.

Table 0.1 Variables that vary between scenarios

Variable	Description	Levels
Coverage	*Proportion of eligible individuals who receive all 3 vaccine doses. (coverage with 1st 2nd and 3rd dose).*	*50% (70%, 85%,85%)* ***89% (95%, 95%, 99%)*** *100% (100%, 100%, 100%)*
Initial efficacy of the vaccine	*Efficacy in fully vaccinated individuals immediately after 3rd dose. Numbers in brackets show efficacy after 1st and 2nd dose.*	*0.3 (0.2, 0.25)* ***0.52 (0.4, 0.46)*** *0.8 (0.6,0.7)* *1.0 (1.0, 1.0)*
Decay of the efficacy of the vaccine.	*Time after vaccination at which the vaccine efficacy is 50% of initial value, assuming exponential decay of protection.*	*6 months* *1 year* *2 years* *5 years* ***10 years*** *no decay*
Variation in vaccine efficacy between hosts[14]	*b is the parameter of the beta distribution used to describe inter-host variation*	*All or nothing (b=0.01),* ***Intermediate(b=10),*** *Homogeneity(b=100000)*
Intensity of transmission	*infectious bites per annum prior to the introduction of the vaccine*	*High Transmission: 82* ***Reference : 21*** *Low Transmission: 5.1*
Seasonality	*Source of data for seasonal distribution of inoculations*	***Namawala, Tanzania,***[24] *No seasonality*

Each level of each variable defines a scenario that was compared with the reference. In each scenario, the variables not being evaluated were fixed at the reference levels (indicated in bold).

Reference Vaccine Scenario

The simulated vaccine is a pre-erythrocytic vaccine that protects vaccinated individual by reducing the force of infection. Relevant characteristics of the simulated vaccine were chosen to match the data from a Phase 2b clinical trial in children aged 1-4 in Mozambique.[3] We have simulated the action of the vaccine in this trial and fitted the efficacy to the trial data.[14] These simulations suggested that pre-existing semi-immunity leads to a slight underestimation of the underlying efficacy of the vaccine in such a trial. Following this, we therefore assume that the vaccine provides an initial reduction in the force of infection of 52% corresponding to the 45% efficacy in extending time to first infection after 3 doses. There are no data available on the efficacy after 1 or 2 doses of RTS,S/ASO2A. We assume a reduction in the force of infection of 40% and 46% after the first and the second dose. The Manhiça trial did not demonstrate any decay of the efficacy against infection. However, decay in protection is possible when longer time periods are considered and is likely to have important implications for vaccine effectiveness. We assume an exponential decay of the primary efficacy of the vaccine and set the half-life to 10 years for the reference vaccine.

We expect that the protection provided by the vaccine is not homogenously distributed among the vaccinated individuals. We assign initial values for the

efficacy of the vaccine which are drawn from a beta-distribution with parameter *b=10* (a justification is given in an accompanying paper[14]).

Simulation approach

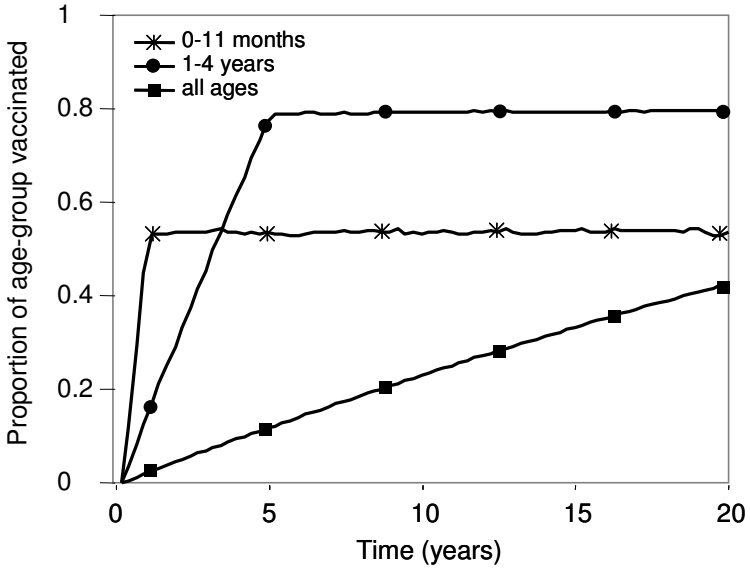
We simulate the introduction of vaccination at the target ages of 1, 2 and 3 months age in a random sample of infants. 95% of infants receiving the first dose, 95% of those receiving the second dose and 99% of those receiving the first two doses complete the course of vaccination. We assume all vaccines to be delivered at the target age, and that no infant received dose 2 without receiving dose 1, or dose 3 without receiving dose 2. This results in a cohort effect, because the proportion of the population who have received the full vaccination course gradually increases throughout the 20 year follow-up (Figure 4.1). Even by the end of this period vaccination coverage in older age groups is still zero, hence we do not consider the equilibrium that would eventually be reached if vaccination continued indefinitely.

The introduction of vaccination leads to transient behaviour that may in principle modify the level of *P. falciparum* transmission. We consider the effects after periods of 5, 10 and 20 years following initiation of the vaccination program. We plot the cumulative numbers of events averted. Where the cumulative number of episodes averted increases approximately linearly over time, (indicating constant effectiveness) we compute the effectiveness of vaccination over the whole 20 year follow-up as:

$$\text{Cumulative Effectiveness} = 1 - \frac{\text{Cumulative number of events in vaccine scenario}}{\text{Cumulative number of events in comparison scenario}}$$

where the comparison scenario is identical to the vaccination scenario in all respects other than the inclusion of vaccination. In addition, we present age-prevalence of parasitemia and anemia as well as age-incidence of different clinical outcomes averaged over 1 year of simulated follow-up starting 4, 9 and 19 years into the follow-up period.

Figure 0.1 Proportion of the age-group which has received 3 doses of vaccination by age and time since start of program



Effects of vaccine characteristics

We expect the predictions about the effectiveness of the vaccine to depend on assumptions about the key properties of the vaccine. In addition, effectiveness depends on the proportion of the population that has been vaccinated. Effectiveness may be an accelerating function of coverage if vaccination has a community effect through reduction of the infectivity of the human hosts. We therefore modeled a range of different assumptions about the proportion of infections that are prevented after an individual has received 1, 2, or 3 doses of the vaccine, the rate of decay of protection against infection and the variation in efficacy between individuals. In order to keep the number of simulated scenarios manageable we start from the reference scenario described above and vary one assumption at a time (Table 4.1).

Effects of transmission intensity and seasonality

In addition to the reference scenario we also generate simulation results corresponding to a range of transmission intensities. There are characteristic shifts in the ages distributions of clinical events in *P. falciparum* at different transmission intensities[9,10] and we wanted to explore how these would modify vaccine effectiveness. Starting from the reference scenario described above, we explore the effect of increasing or decreasing the annual entomological inoculation rate (EIR) prior to the introduction of the vaccine within a range found in areas of stable endemic malaria. In addition, we study the impact of different

seasonal patterns of EIR by simulating the case of a completely non-seasonal environment with the same yearly average EIR as in the reference scenario.

4.3 Results

Reference Vaccination Scenario

In the reference vaccination scenario the introduction of vaccine leads to lower parasite prevalence for all age groups that had received the vaccine, resulting in a cohort effect with the effect gradually moving into older age-groups (Figure 4.2a). Corresponding to the reduction in parasite prevalence, anemia prevalence is also reduced but because the anemia is concentrated in the first few years of life,[8] anemia prevalence becomes stable within the first few years of vaccination (Figure 4.2b).

The incidence of malaria episodes and mortality decrease for children less than 5 years of age within the first few years of vaccination and remain reduced over the 20 year timespan (Figure 4.3). These dynamic effects resulted almost entirely from the cohort effect of introducing vaccination gradually into the population and hardly at all from community effects due to reduction in transmission. The level of transmission was reduced only very slightly in the vaccine scenario compared with the reference (data not shown). Indeed, none of the scenarios we studied resulted in major effects on transmission to the vector within the 20 year time-span. After 10 years of vaccination the incidence of uncomplicated episodes in 5-9 year old children remains lower than in unvaccinated children, while severe episodes and mortality incidence have slightly increased in incidence in this age group (Figure 4.3). This is because the prevention of infections reduces the acquisition of asexual blood stage immunity. By the end of the 20 year follow-up period, all incidence measures are somewhat higher in the 10-19 year age group of the vaccinated population, though the cumulative number of events they have experienced over the whole 20 year period is reduced.

The approximately linear increase in cumulative numbers of deaths averted (Figure 4.4c) indicates that the vaccine reduces mortality by a more or less constant amount throughout the 20 year intervention period. Overall, vaccination also leads to substantial reductions in the incidence of uncomplicated episodes of malaria over the 20 year follow-up (Figure 4.4) but the benefit of the vaccination program in preventing uncomplicated episodes decreases over time, as indicated by a reduction in the gradient of the curve over time (Figure 4.4a).

The decay in the benefit was even more marked when assessed in terms of numbers of severe episodes (Figure 4.4b). After 10 years of vaccination the overall incidence of severe episodes returns to a level similar to that in the

absence of vaccination. This is due to the shift in incidence to older ages (Figure 4.3b).

The average effectiveness of the vaccine over the 20 year follow-up period differed for the different clinical outcomes. The average effectiveness in preventing uncomplicated episodes and death were 0.067, and 0.12 respectively (Figure 4.5). The overall effectiveness in preventing severe episodes, of 0.052, is difficult to interpret because of the heterogeneity in the effect over time.

Figure 0.2 Effect of the reference vaccine on prevalence of parasitemia and anemia over time

a. age-prevalence of parasitemia; b. age-prevalence of anemia. The data are averaged over periods of 1 year starting at 4, 9, and 19 years after the onset of the intervention.

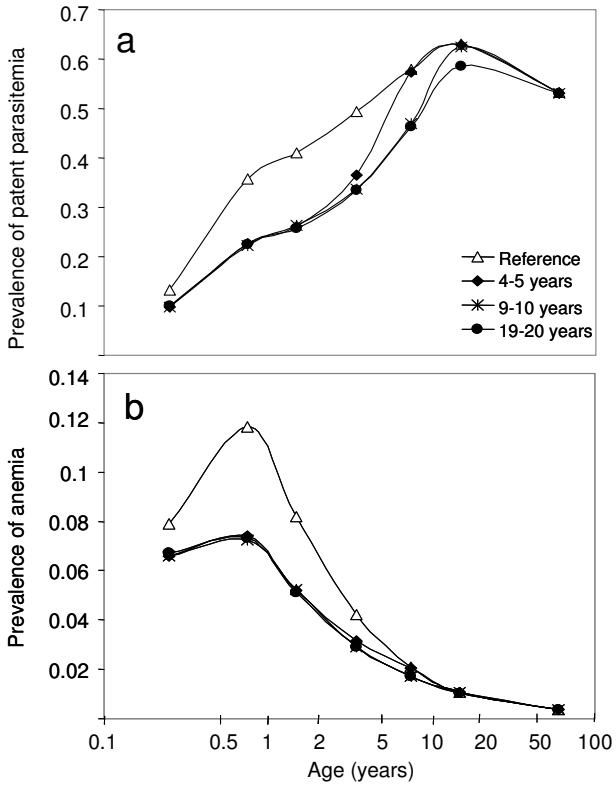


Figure 0.3 Effect of time since the start of the vaccination program on age-incidence patterns

The data are averaged over periods of 1 year starting at 4, 9, and 19 years after the onset of the intervention. a. Uncomplicated episodes b. Severe episodes c. Mortality

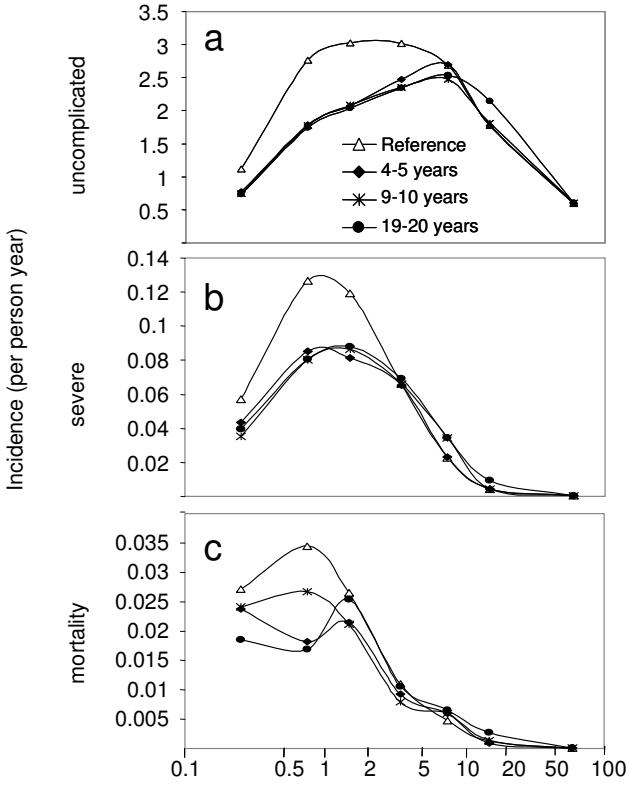


Figure 0.4 Effect of the reference vaccine over time under different assumptions about the initial efficacy of the vaccine (30, 52, 80, 100 percent protection against infection after third dose)

a. Uncomplicated episodes averted; b. Severe episodes averted; c. Deaths averted

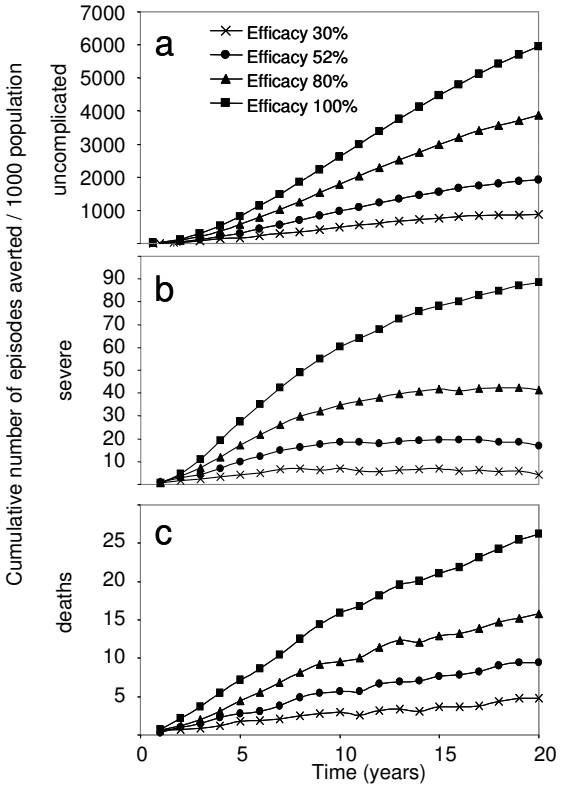
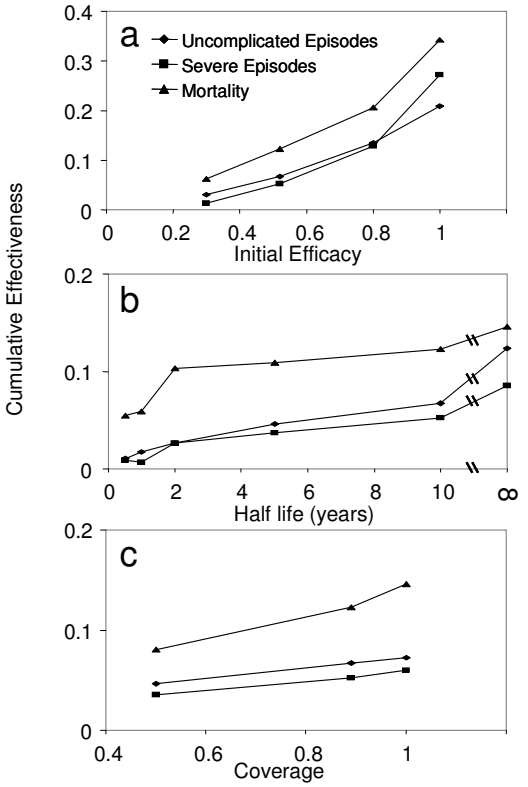


Figure 0.5 Cumulative effectiveness over 20 years against uncomplicated and severe episodes and mortality

a. Effect of different assumptions about the initial efficacy; b. Effect of different assumptions about the decay of the protective effect; c. Effect of different assumptions about the coverage of the vaccination program.



Effect of Vaccine Efficacy

We considered 4 different values for the initial efficacy of the vaccine (Table 4.1). An efficacy of 30% corresponds approximately to the lower limit that Phase IIb clinical trials have so far been powered to detect. Vaccines with lower efficacy than this are unlikely to be considered for further development. An efficacy of 52% corresponds to our best estimate of the initial efficacy of the RTS,S/ASO2A vaccine in a recent trial in Mozambique[14] (this is rather higher than the average efficacy measured during the trial[3]). 80% efficacy corresponds to a rule of thumb often used to evaluate partially efficacious vaccines, while 100% efficacy corresponds to a perfect vaccine, and thus allows us to assess the maximum possible effect achievable by our model of vaccine delivery.

An increase in the vaccine efficacy (defined as the proportion of infections averted) results in a near-proportional increase in effectiveness over the whole 20 year follow-up, whether this is measured in terms of prevention of uncomplicated, severe or fatal episodes (Figure 4.4 and Figure 4.5a). The cumulative number of

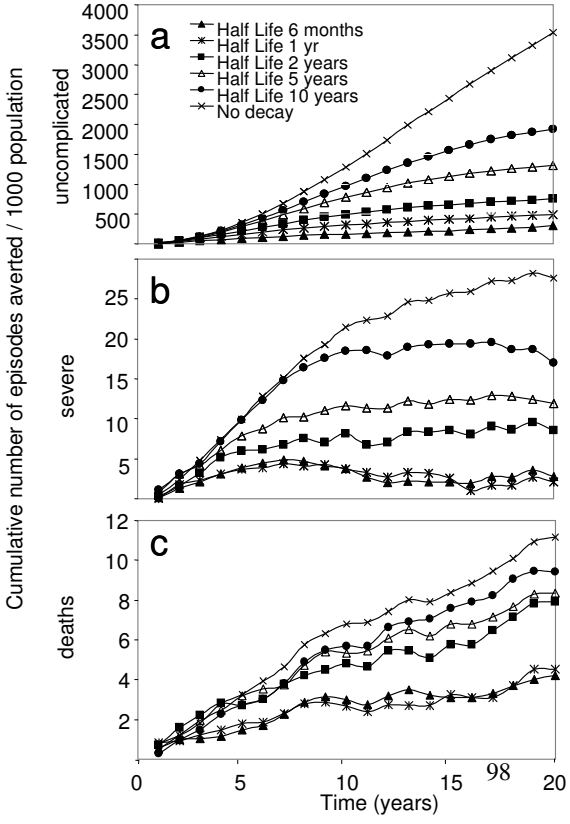
events averted is highest for the most efficacious vaccine with effects on uncomplicated episodes and mortality approximately proportional to the initial efficacy, but only a vaccine with a very high efficacy remains effective in reducing the incidence of severe episodes in the latter part of the 20 year follow up period (Figure 4.4). The effects of changes in efficacy on age-prevalence of parasitemia or anemia or in the age-incidence of clinical events in the low and high-efficacy scenarios are similar to those in the reference scenario.

Effects of waning of the protective effect of the vaccine

Assuming a faster decay of the vaccine effect leads to a reduction in all effectiveness measures, and the converse is observed when the rate of decay is decreased. The effectiveness against uncomplicated episodes is roughly proportional to the half-life (Figure 4.5b; Figure 4.6a). However, effectiveness for the other clinical outcomes does not increase linearly with half-life (Figure 4.5). An increase of the half-life from 6 months to 1 year has little effect on the effectiveness against severe episodes or mortality, but there is a marked increase in effectiveness if the half-life increases to 2 years (Figure 4.6bc). There is only a small further improvement in increasing half-life from 2 to 5 or 10 years.

Figure 0.6Effect of the reference vaccine over time under different assumptions about the decay of the protective effect of the Vaccine (half-life 6 months, 1 yr, 2 yrs, 5 yrs, no decay)

a. Uncomplicated episodes averted; b. Severe episodes averted; c. Deaths averted

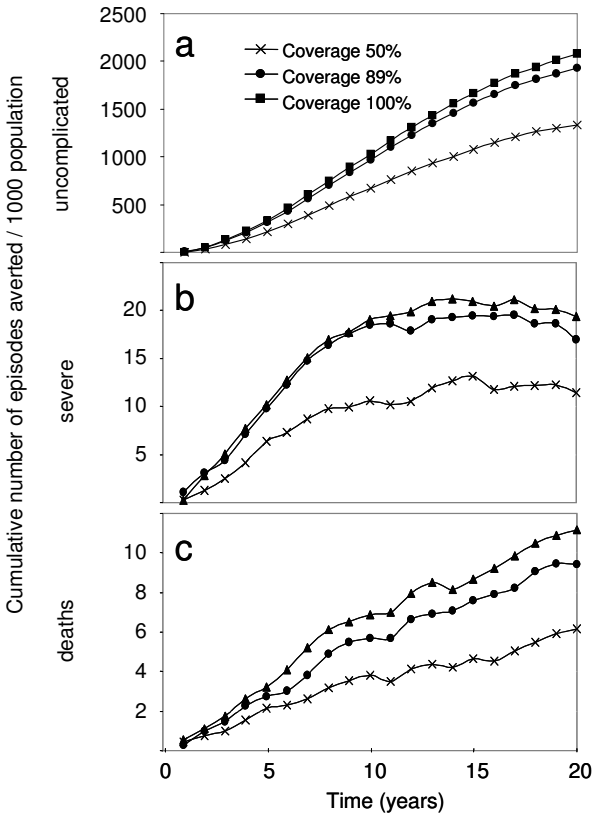


Effect of Vaccination coverage

The effect of varying the values of coverage is similar to the effect of varying the initial efficacy, with a low coverage resulting in similar epidemiological patterns to that of a reduced vaccine efficacy. While increasing coverage to high levels can be of crucial importance with fully protective vaccines when the objective is to eliminate transmission, the impact of 100% coverage is more or less proportional to that of the 89% coverage in our reference scenario (Figure 4.7).

Figure 0.7 Effect of the reference vaccine over time under different assumptions about the proportion of the population covered (50, 89,100 percent receive all 3 doses

a. Uncomplicated episodes averted; b. Severe episodes averted; c. Deaths averted



Effect of variation in efficacy between individuals

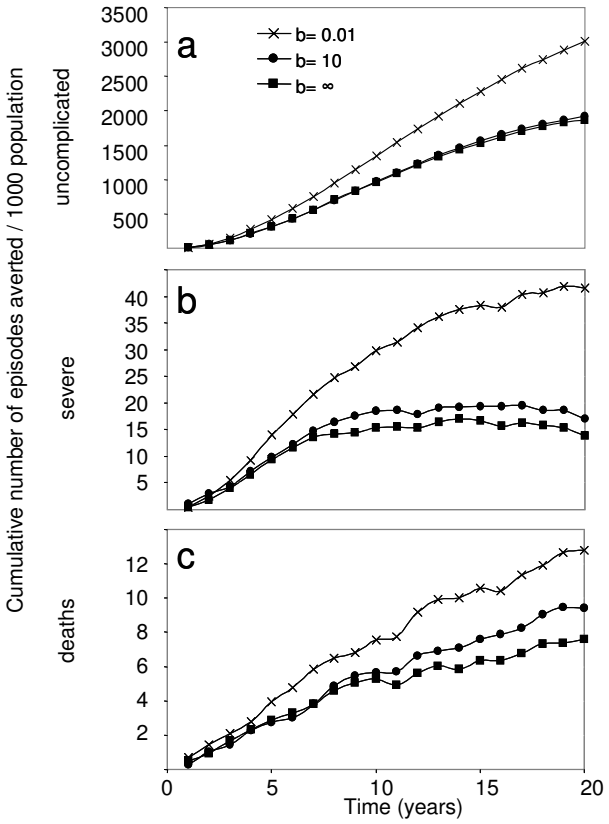
An all-or-nothing response to the vaccine (b=0.01) results in a higher number of illness episodes and deaths averted than are found in a scenario with the same mean efficacy, but less variation between individuals. With such a vaccine the

population is equivalent to a mixture of individuals vaccinated with a 100% effective vaccine, together with unvaccinated individuals. As with the simulation of the 100% effective vaccine, however, the number of severe episodes averted decreases over time. This is due to the decay in the efficacy (simulated with a half-life of ten years). If there is no decay in efficacy we expect the effectiveness of such a vaccine to increase with the coverage throughout the follow-up period.

When there is no heterogeneity in vaccine efficacy (b=100000), (Figure 4.8) the pattern is very similar to that of the reference vaccine (b=10), in which the degree of heterogeneity was chosen to match the data of the RTS,S/AS02A vaccine trial in Mozambique.[14]

Figure 0.8 Effect of the reference vaccine over time under different assumptions about the distribution of the protective effect of the vaccine among vaccinated individuals (b = 0.01, b=10, b =100000)

a. Uncomplicated episodes averted; b. Severe episodes averted; c. Deaths averted



Effect of transmission intensity and seasonality

The absolute number of clinical episodes and deaths averted by a vaccine is affected by the transmission intensity in ways that changed over the course of the simulated vaccination program (Figure 4.9).

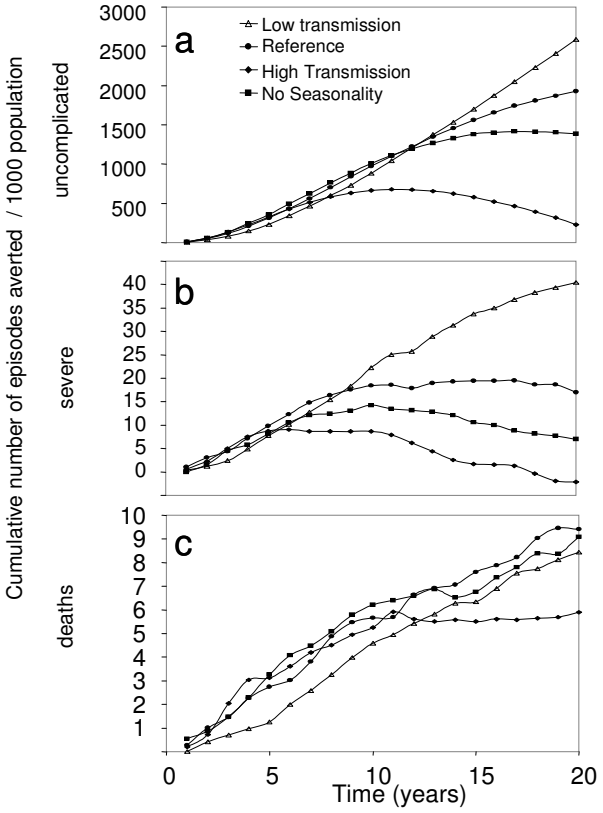
For the first few years of follow-up the number of events averted was lowest at low transmission intensity due to the lower numbers of events in the vaccinated age group. Protection against uncomplicated episodes increased over time, the effect on mortality remained approximately constant, and that on severe morbidity decayed at a much slower rate than in the reference scenario. A net reduction in incidence of severe episodes was consequently still evident after 20 years of follow-up, while the total number of deaths averted over the 20 year period was lower than in the reference scenario.

At high transmission the initial gains were similar to those seen for the reference scenario, but the overall incidence of uncomplicated episodes became higher than

that in the unvaccinated scenario after about 10 years of the vaccination program (Figure 4.9ab). There was no such adverse effect on mortality rates, but the initial gain seen during the first ten years of the program did not continue (Figure 4.9c). While the degree of seasonality hardly affects the cumulative number of deaths averted, the number of uncomplicated episodes averted is lower in the absence of seasonality than in the reference scenario. The cumulative efficacy against uncomplicated episodes is reduced from 0.067 to 0.050 in the absence of seasonality.

Figure 0.9 Effect of the reference vaccine over time in different transmission intensities

a. Uncomplicated episodes averted; b. Severe episodes averted; c. Deaths averted



4.4 Discussion

We use a stochastic simulation model of the transmission dynamics and epidemiology of *P. falciparum* malaria in endemic areas to assess the likely impact of a pre-erythrocytic vaccine introduced via the EPI. This is the first major attempt to combine dynamic modeling of malaria transmission with predictions of parasitological and clinical outcome, using models that have been fitted to field epidemiology data from a range of sites across Africa.

We have based our simulations as much as possible on field data, but many uncertainties and approximations remain, both in our epidemiological models and our model of vaccination. The uncertainty in the field estimate of efficacy of RTS,S/AS02A is substantial; the efficacy of incomplete courses of vaccination is unknown; as is the rate of waning of vaccine efficacy.

We agree with previous dynamic models of the impact of malaria vaccination[15-18] that a 'leaky' anti-infection vaccine will have little effect on transmission in endemic areas. Our estimates of transmission effects are even smaller than those in most previous models because we predict that reduction in human infection will have little effect on infectiousness to vectors (except in the case of complete protection of a sub-set of the population). We nevertheless identify substantial potential public health benefits of vaccination because severe disease is largely concentrated in the first years of life (in our model this arises largely because of age-dependent cofactors[9]) and can be averted by delaying exposure to blood-stage parasites.

We would expect a pre-erythrocytic vaccine to have much more effect on transmission in areas of unstable malaria such as highland areas of East Africa,[19] KwaZulu-Natal[20] or areas of low transmission outside Africa. This raises the issue of whether the best delivery strategy in such areas might then be a mass-vaccination campaign, contributing to local elimination. Mathematical models of the impact of such a vaccination program need not consider the complexities of acquired clinical immunity, and so might reasonably be based on conventional compartment models.[17] Extension of these models to allow appropriately for heterogeneities in transmission[21] would be of critical importance.

In our model, the dynamics result mainly from a cohort effect on coverage and from the dynamics of immunity, rather than from effects on transmission. The effectiveness of vaccination (the proportion averted of all the events in the population) cannot reach equilibrium until after the oldest people are vaccinated, so even 20 year simulations do not approach equilibrium. Effectiveness in the initial years of a program is likely to be much lower than vaccine efficacy, because only a small proportion of the people will be vaccinated.

The 20 year time horizon allows us to see that the effect of a vaccine program on illness incidence will change over time, although we predict a roughly constant reduction in the crude mortality rate throughout the follow-up. After about ten years, there is net reduction in cumulative numbers of clinical episodes only in low transmission scenarios, with a predicted increase in high transmission. This is due to an increase in severe malaria incidence in children over five years old who have accrued less immunity to asexual blood stage parasites during their childhood. This partly results from the models used for predicting uncomplicated episodes[10] and severe malaria,[9] which are fitted to data that suggest the lifetime number of clinical episodes[22] and the incidence of hospital admissions for severe malaria[23] are highest at intermediate levels of transmission.

With a vaccine with high efficacy in a proportion of the population (i.e. with a low value of *b*), effectiveness continues to increase as the vaccinated proportion increases, though in our simulations this effect is gradually lost due to decay in vaccine efficacy. With vaccines with partial efficacy in all individuals, (the model we propose for RTS,S/AS02A[14]) the factors attenuating the efficacy, such as interactions with the epidemiological effects of acquired immunity become more important as the vaccination program proceeds. In very low transmission settings we predict initial increases in effectiveness, since the proportion vaccinated increases before the first vaccinees leave the age-range of high vulnerability. At higher transmission there is little evident increase in effectiveness as the number of fully-vaccinated individuals increases.

No vaccinated child reached more than 20 years of age in our simulations, so very long-term effects of vaccination are not captured. This is important when comparing different decays or initial efficacies, as the relationship between the duration during of protection and the life-expectancy of the vaccinated individual may be important in determining the effectiveness. However we are very uncertain about the risk of severe malaria that such adults would experience. There are few data available from which to estimate severe malaria risk in adolescents or adults with limited previous exposure.[9]

Vaccination reduces the incidence of uncomplicated episodes because it leads to fewer successful infections. The reduced exposure to parasites leads to less acquired asexual-stage immunity, hence the longer-term level of clinical protection is lower than the initial efficacy. In our models, the pyrogenic threshold, which determines the parasite density that leads to acute illness, also depends on the recent exposure to parasites and is therefore lower in vaccinated individuals.[14] Vaccination can also modify the proportion of acute episodes that are severe by leading to a shift in clinical episodes to an older age, when the host is protected from co-morbidity and from other age-dependent factors enhancing susceptibility. With an efficacious vaccine, efficacy against severe malaria may

be greater than that against infection. Conversely, if the vaccine does not offer a sufficiently high level of protection for a long enough time, the lower level of asexual-stage immunity means that an increased proportion of clinical attacks result in severe malaria.

The application of our models can be extended not only to include other means of deployment (including regimens with booster doses of vaccines); to other types of vaccines (asexual blood stage and transmission blocking); and to consider the inclusion of vaccination within integrated control programs. We have seen that a pre-erythrocytic vaccine will be most effective at low transmission intensities, but that on its own it is unlikely to reduce transmission very much except possibly when this is already low. It may be that such a vaccine will be most effective if deployed in conjunction with vector control measures that reduce the vectorial capacity at the same time.

4.5 References

1. World Health Organisation, 1996. Investing in Health Research and Development. TDR/Gen/96.1Geneva, World Health Organisation.

2. Ballou WR, Arevalo-Herrera M, Carucci D, Richie TL, Corradin G, Diggs C, Druilhe P, Giersing BK, Saul A, Heppner DG, Kester KE, Lanar DE, Lyon J, Hill AV, Pan W, Cohen JD, 2004. Update on the clinical development of candidate malaria vaccines. *Am J Trop Med Hyg 71 (2 Suppl)*: 239--247

3. Alonso PL, Sacarlal J, Aponte J, Leach A, Macete E, Milman J, Mandomando I, Spiessens B, Guinovart C, Espasa M, Bassat Q, Aide P, Ofori-Anyinam O, Navia MM, Corachan S, Ceuppens M, Dubois MC, Demoitie MA, Dubovsky F, Menendez C, Tornieporth N, Ballou WR, Thompson R, Cohen J, 2004. Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial. *Lancet 364*: 1411--1420

4. Halloran ME, Watelet L, Struchiner CJ, 1994. Epidemiologic effects of vaccines with complex direct effects in an age-structured population. *Math Biosci 121*: 193--225

5. Smith T, Killeen G, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M, 2006. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: Overview. *Am J Trop Med Hyg. In press.*

6. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, Molineaux L, 2006. A model for natural immunity to asexual blood stages of *Plasmodium falciparum* in endemic areas. *Am J Trop Med Hyg. In press.*

7. Ross A, Killeen G, Smith T, 2006. Relationships of host infectivity to mosquitoes and asexual parasite density in *Plasmodium falciparum. Am J Trop Med Hyg. In press*

8. Carneiro I, Smith T, Lusingu J, Malima R, Utzinger J, Drakeley C, 2006. Modeling the relationship between the population prevalence of *Plasmodium falciparum* malaria and anemia. *Am J Trop Med Hyg. In press*

9. Ross A, Maire N, Molineaux L, Smith T, 2006. An epidemiological model of severe morbidity and mortality caused by *Plasmodium falciparum. Am J Trop Med Hyg. In press*

10. Smith T, Ross A, Maire N, Rogier C, Molineaux L, 2006. An epidemiologic model of the incidence of acute illness in *Plasmodium falciparum* malaria. *Am J Trop Med Hyg. In press*

11. Ross A, Smith T, 2006. The effect of malaria transmission intensity on neonatal mortality in endemic areas. *Am J Trop Med Hyg. In press*

12. INDEPTH Network, 2002. Population, Health and Survival at INDEPTH Sites. Ottawa: IDRC

13. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, Tanner M, 2005. An approach to model the costs and effects of case management of *Plasmodium falciparum* malaria in sub-Saharan Africa. *submitted*

14. Maire N, Aponte J, Ross A, Thompson R, Utzinger J, Smith T, 2005. Modeling a field trial of the RTS,S/ASO2A malaria vaccine. *Am J Trop Med Hyg. In press*

15. Anderson RM, May RM, Gupta S, 1989. Non-linear phenomena in host-parasite interactions. *Parasitology 99 Suppl*: S59--S79

16. Halloran ME, Struchiner CJ, Spielman A, 1989. Modeling malaria vaccines. II: Population effects of stage-specific malaria vaccines dependent on natural boosting. *Math Biosci 94*: 115--149

17. Koella JC, 1991. On the use of mathematical models of malaria transmission. *Acta Trop 49*: 1--25

18. Struchiner CJ, Halloran ME, Spielman A, 1989. Modeling malaria vaccines. I: New uses for old ideas. *Math Biosci 94*: 87--113

19. Abeku TA, Hay SI, Ochola S, Langi P, Beard B, de Vlas SJ, Cox J, 2004. Malaria epidemic early warning and detection in African highlands. *Trends Parasitol 20*: 400--405

20. Kleinschmidt I, Sharp B, Mueller I, Vounatsou P, 2002. Rise in malaria incidence rates in South Africa: a small-area spatial analysis of variation in time trends. *Am J Epidemiol 155*: 257--264

21. Dye C, Hasibeder G, 1986. Population dynamics of mosquito-borne disease: effects of flies which bite some people more frequently than others. *Trans R Soc Trop Med Hyg 80*: 69--77

22. Trape JF, Rogier C, 1996. Combating malaria morbidity and mortality by reducing transmission. *Parasitol Today 12*: 236--240

23. Marsh K, Snow R, 1999. Malaria transmission and morbidity. *Parassitologia 41*: 241--246

24. Smith T, Charlwood JD, Kihonda J, Mwankusye S, Billingsley P, Meuwissen J, Lyimo E, Takken W, Teuscher T, Tanner M, 1993. Absence of seasonal variation in malaria parasitaemia in an area of intense seasonal transmission. *Acta Trop 54*: 55--72

Chapter 5: Predicting the cost-effectiveness of introducing a pre-erythrocytic malaria vaccine into the Expanded Program on Immunization in Tanzania

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Abstract

We model the cost-effectiveness of the introduction of a pre-erythrocytic malaria vaccine into the Expanded Program on Immunization. We use a dynamic stochastic simulation model of the epidemiology of *Plasmodium falciparum* in endemic areas and of case-management in Tanzania. We consider a range of vaccine characteristics and a range of transmission settings. At low vaccine prices the cost-effectiveness of such vaccines may be similar to that of other established preventative and curative interventions against malaria. The cost-effectiveness ratio increases rapidly and approximately linearly with vaccine cost-per-dose. The approach can be adopted for comparative analyses of the cost effectiveness of different vaccines and other intervention strategies.

5.1 Introduction

The goal of economic evaluation of health care interventions in general, and malaria control measures in particular, is to provide policy-makers with guidance about how scarce resources can be allocated so that the social and economic benefits are maximized.[1,2] Economic evaluation not only shows how efficient it is to spend resources on existing interventions available, but also predicts how efficient new interventions could be if they were to be developed, or if existing interventions had different characteristics. Thus economic evaluation is an essential part of the appraisal of candidate malaria vaccines. For example, policy makers may wish to know how efficacious a vaccine would need to be in order to be cost-effective.

Cost-effectiveness analysis (CEA) usually is the method of choice in evaluating alternative health interventions, because health decision makers are primarily interested to know what health improvements can be bought with a given budget, and not the overall economic impact *per se.*[1,2]

The present paper models the cost-effectiveness of a pre-erythrocytic malaria vaccine, using a dynamic stochastic simulation model of the epidemiology of *Plasmodium falciparum* in endemic areas and of case-mangement in Tanzania.[3,4] Our objective is to assess the potential cost-effectiveness of introducing this malaria vaccine into the Expanded Program on Immunization (EPI) under a range of scenarios, conditions, and assumptions.

We present the vaccine cost-effectiveness for a single country, Tanzania. This first stage enables us to specify model inputs without having to consider simultaneously many heterogeneous settings, as would be the case for sub-Saharan Africa. Even a single country does not present a single uniform context for ecological, epidemiological, socio-economic and health system inputs, but there is less heterogeneity than at the multi-country level.

5.2 Materials and methods

Perspective and boundary

The study is a cost-effectiveness analysis adopting a societal perspective for both costs and effects, and thus considers all relevant resource inputs to the intervention, and resource consequences and health impacts resulting from the intervention.

The costs of vaccine delivery[4] include all resource inputs irrespective of whether these costs are borne by government, donors, the patient, the wider community, or a mixture of these. Case management costs[3] likewise include all resource inputs irrespective of whether these are borne by government, the patient, or both. Vaccine delivery costs and case management costs include both the direct costs of service provision and costs directly associated with the service, which essentially means the costs for the patient(s) accessing the services, covering additional transport and sustenance costs.

A societal perspective in cost-effectiveness analysis also requires that direct economic impacts of the intervention should be taken into account. In the case of a vaccine which reduces morbidity episodes as well as mortality, there is a clear impact on productive time either leading to higher income (in the case of market work) or higher unsold production (in the case of non-market work). This can either be through a gain in production of the averted malaria case, or where the patient is a child, the production gained of the carer who would have cared for the averted malaria case. Therefore, the results include these hypothesized economic impacts.

Given the dynamic nature of the epidemiological model, and the lower transmission rates to other non-vaccinated individuals associated with an effective vaccine, the health effects of the intervention can also include changes in morbidity and mortality of the non-vaccinated population as a result of reduced transmission. However, our epidemiological analysis implies that these impacts will be minimal in the epidemiological settings that we have analyzed.[5]

Model overview

To predict the cost-effectiveness of the malaria vaccine we use a stochastic simulation model of the epidemiology of *P. falciparum* in endemic areas of Africa.[6] This includes a sub-model for the case management of malaria in Tanzania.[3] We link these elements with costing of vaccine delivery in the Tanzania setting.[4]

The epidemiological model is a stochastic individual-based simulation of malaria infection in endemic areas that uses a 5-day time step. It takes as its input the pattern of the entomological inoculation rate (EIR) in the absence of interventions, with separate values of the EIR specified for each of the 73 5-day periods during the year. We simulate the reference case management scenario in Tanzania[3] to provide a baseline with which to compare simulations where a vaccine is introduced.

The simulated population is maintained as a steady state, and includes individuals of all ages, with immune status depending on their simulated exposure. The denominators for calculation of overall health impacts include individuals who were too old to be vaccinated, and 20 year simulation is thus influenced by cohort effects due to gradual increase in the proportion of the population vaccinated, and by dynamic effects of reduction in exposure on acquisition of natural immunity to asexual parasites.

Alternatives being compared

We compare health outcomes, direct costs and productivity gains of a combined strategy of a new malaria vaccine delivered through EPI in combination with the reference case management scenario for Tanzania with only the reference case management scenario.[3]

The EPI was chosen as the channel for vaccine delivery because in most African countries EPI is well established and achieves reasonably high levels of coverage amongst the target population group. Therefore, it is the only reliable mechanism to deliver a vaccine to a high proportion of infants aged below 1 year.[7-9]

The vaccine modelled is a pre-erythrocytic stage vaccine requiring three doses to fully immunize a child. These doses are administered when infants are 1, 2, and 3 months old, at the same time as the Hepatitis B vaccine. Many of the inputs for the CEA are based on data from the case management model[3] and epidemiological scenarios.[10]

The cost-effectiveness model simulates the health system typical for a rural area of Tanzania.[3] A set of different scenarios were constructed to reflect different malaria transmission intensities representing the stable, annually recurring pattern of malaria transmission. In all simulations the seasonal pattern of transmission was assumed to be that recorded in the village of Namawala, Tanzania, during 1989-1991 where exceptionally precise estimates of dry season transmission were made.[11] The annual EIR for this site was 329 infectious bites per annum. For the reference scenario we use a seasonal pattern of transmission for a mesoendemic site, obtained by dividing the EIR from Namawala for each 5-day period by 16.

(direct measurement of dry-season transmission in meso-endemic areas is impracticable because of low mosquito densities). To simulate a high transmission area we use an EIR of 4 times that of the reference scenario. This is probably more typical of high transmission sites in Africa than the extremely high transmission in Namawala. This gives an overall annual EIR of 21 infectious bites per annum, which is typical for a mesoendemic area in sub-Saharan Africa.[12] The simulations were first run for a warm-up period of 90 years of exposure to define the baseline immune status of the simulated populations, which is highly age-dependent.

For the present analyses the simulations are run in populations of 100,000 individuals, with an approximately stationary age distribution matching that of the demographic surveillance site in Ifakara.[13]

Measuring health gains

To estimate the number of disability adjusted life years (DALYs), years of life lived with disability are calculated on the basis of the duration of disability, and respective disability weights.[3] [14] Weights for different malaria attributable disease conditions have been obtained from the Global Burden of Disease (GBD) study,[15] and age-weighting is applied as in the GBD method. However, in order to assess how sensitive results are to the life table used, DALYs are also computed assuming a zero age weighting. The disability associated with anemia is assigned to the same time period as the malaria infections causing it.

Years of life lost (YLLs) and DALYs are calculated assuming age-specific life expectancies based on the life-table from Butajira, Ethiopia, with an average life expectancy of 46.6 years at birth.[16] This life-table represents that of an East African setting with low malaria transmission and is very similar to that for Hai District, a high altitude and low malaria prevalence site in Tanzania.[13] We thus compute YLLs for each simulated death under the assumption that this life table is the one that would apply in the absence of malaria.

Assumptions on vaccine efficacy

In the reference scenario the efficacy of this hypothetical pre-erythrocytic malaria vaccine is assumed to be 52% reduction in infections in naïve individuals,[10] decaying exponentially with a half-life of 10 years. Since it is likely that the degree of protection provided varies between individuals, in the reference scenario, a value for the initial efficacy is drawn from a beta-distribution with parameter b=10 and assigned to each vaccinated individual.[5]

Coverage

In the reference scenario it is assumed that the coverage rate is the same as that reported in Tanzania for 3 doses of DTP-HBV in the year 2003, which stood at 89%. Given that the coverage for the 1st dose of DTP-HBV was 95%, the drop-out rate from the first to the third dose is 6%.[4]

Case management

The case management model, including both formal and informal treatment, is described elsewhere.[3] It has implications for health outcomes, both in terms of the potential to reduce rates of severe disease, sequelae and death, but also in the impact on transmission intensity and therefore the potential for new infections in the entire population. The rate of treatment seeking among uncomplicated malaria episodes was assumed to be 5%, which although apparently low, is justified due to the very sensitive definition of clinical episodes used. The clinical episodes simulated thus include the very mild fevers that would be unlikely to elicit attendance at a health facility. The model assumes in the reference case a cure rate of 93% for the first-line drug sulfadoxine-pyramethamine (SP) for uncomplicated malaria.[5]

Measuring economic costs and consequences

Costs presented

We considered both marginal and average costs. The marginal cost reflects most closely the additional financial costs that would be incurred when introducing a new intervention. The average cost includes all those costs involved in delivering a health intervention, including the use of spare capacity or slack in the system, those health care resources diverted from other uses, and existing health sector resources that are shared with other health programmes. All cost data are expressed in US$ 2004.

Vaccine delivery costs

The costs of introducing a malaria vaccine into the EPI in Tanzania include those related to an assumed range of vaccine purchase costs, and data collected from Tanzania on likely distribution and cold chain storage costs, management costs, vaccine delivery costs at health facility level, training costs, and social mobilization costs. A detailed description of the methodology used to estimate vaccine delivery costs can be found in an accompanying paper.[4]

The CEA is run under various vaccine price hypotheses ranging from US$ 1.0 to US$ 20 per dose. The vaccine delivery cost estimates according to the different price hypotheses are shown in Table 5.1.

Table 0.1 Incremental delivery cost per fully immunized child (FIC) for the vaccine

Vaccine price (US$ per dose)	Vaccine delivery cost per FIC in US$	
	Average cost	*Marginal cost*
1	4.43	4.24
2	7.43	7.24
4	13.43	13.24
6	19.43	19.24
8	25.43	25.24
10	31.43	31.24
20	*61.43*	*61.24*

Case management costs

The costs of treating those seeking health care for malaria episodes are calculated under the two scenarios being modeled: case management alone and vaccine with case management, allowing us to calculate expected cost savings associated with the introduction of an efficacious malaria vaccine.

The direct costs of care seeking for an uncomplicated malaria episode at official facilities include the cost of an outpatient visit (US$ 1.02 dispensary; US$ 1.27 health centre), a diagnostic test in a proportion of outpatient cases (US$ 0.30), the cost of a course of SP treatment (varying from US$ 0.012 to US$ 0.071, depending on age and weight), the cost of a course of Amodiaquine treatment (varying from US$ 0.018 to US$ 0.114, depending on age and weight), and other costs incurred by patients when visiting an official health facility (US$ 0.30).

The direct costs of a severe malaria patient include inpatient hotel costs per day (US$ 7.8), drug treatment cost during hospitalization (varying from US$ 0.56 to US$ 3.74, depending on age and weight), average length of stay (4.5 days with full recovery), and the costs that patients incur when visiting an official inpatient facility (US$ 1.29 for the average length of stay). The case management cost inputs are presented in detail elsewhere.[3]

Measuring productivity gains

The productivity costs of malaria relate to the productive time lost due to illness, whether it is the patient or the patient carer (especially if a child or elderly patient). In this analysis productivity costs included are those related to time spent by adults seeking official care for their children, time spent by adults caring for children at home, and the time forgone by sick adults due to malaria episodes. Given that inclusion of productivity gains in cost-effectiveness analysis remains controversial, the reference case results do not include these hypothetical productivity gains.

To measure the value of productive time lost, we use the wage rate method which involves multiplying the time lost per episode (for adults only) by the average daily wage in Tanzania. These estimates are adjusted downwards by an estimate of the unemployment rate in Tanzania, thus taking into account that not all those sick or those caring for the sick would have been working.

The time lost per malaria episode is expected to be highly variable. For example, a recent review of the literature available found that for a sick adult the time off work ranges from 1 to 5 days, depending most importantly on severity of disease.[17] For this study, uncomplicated adult malaria cases are assumed to lose 2 working days, while a care taker of a sick child loses 1 working day. Adults with a severe malaria episode are assumed to lose 4.5 days if not hospitalized, or if hospitalized, 1 day more than their length of stay in hospital. A care taker of a child with severe malaria is assumed not to be able to work during the hospitalization period.

For uncomplicated episodes productivity costs are computed under two scenarios. In the first scenario, a productivity cost is attached to only those uncomplicated episodes that get treated, presumed to correspond in general to the more severe episodes. In the second scenario, a productivity cost is attached to all malaria episodes. These two scenarios represent the likely upper and lower bounds on the true productivity costs avertable through the introduction of an efficacious vaccine.

The formulae for calculating productivity costs are presented below, and the data inputs are provided in Table 5.2.

$$I_{cu} = T_{cu}\, w(1-U) \qquad (1)$$

$$I_{cs} = T_{cs}\, w(1-U) \qquad (2)$$

$$I_{au} = T_{au}\, w(1-U) \qquad (3)$$

$$I_{as} = T_{as}\, w(1-U) \qquad (3)$$

where I_{cu} and I_{cs} are the productivity costs of the care taker for uncomplicated and severe malaria, respectively; I_{ac} and I_{as} are the productivity costs of sick adults with uncomplicated and severe malaria, respectively; T_{cu} and T_{cs} are the time lost in days per episode by care taker of sick child for uncomplicated and severe malaria, respectively; T_{au} and T_{as} are the time lost in days for sick adults for uncomplicated and severe malaria, respectively; w is the minimum gross daily wage in Tanzania (US$ 3); and U is the assumed unemployment rate in Tanzania (40%).

Table 0.2 Data inputs for calculation of productivity costs

Item	*Value (US$ 2004)*
Care taker UM	*1.8*
Care taker SM- if patient dies	*3.6*
Care taker SM- if patient fully recovers	*8.1*
Care taker SM-if patient recovers with sequelae	*18.0*
Sick adult UM	*3.6*
Sick adult SM- if patient dies	*5.4*
Sick adult SM- if patient fully recovers	*9.9*
Sick adult SM- if patient recovers with sequelae	*18*

UM - uncomplicated malaria; SM - severe malaria.

Net cost calculations

The net costs associated with current case management and adding the vaccine to case management is computed over time as follows:

$$NC = \sum_{t=1}^{n} \left[\frac{DC(cm_v + v)_t - DC(cm_{nv})_t}{(1+r)^t} \right] \qquad (5)$$

where NC are the net costs including only direct costs; DC (cm_v+v) are the direct costs in the case of the vaccine plus case management; DC (cm_{nv}) are the direct costs of current case management under a "no vaccine" scenario; n is the time period of intervention (20 years); and r is the annual discount rate for future costs and health effects.

Scenario presentation

Reference scenario

In the reference case, results are presented to show cost-effectiveness at four different 5-year time periods during the 20-year follow-up period (1-5 years, 6-10 years, 11-15 years, and 16-20 years) to reflect the possible fact that cost-effectiveness changes depending on time after vaccine introduction. The cost-effectiveness ratios are presented under seven vaccine price assumptions (in US$): 1, 2, 4, 6, 8, 10, and 20. Incremental cost-effectiveness ratios are presented using two different definitions of cost: marginal cost to reflect the likely short-term financial impact of the intervention, and average cost to reflect the long-term and full opportunity cost associated with the intervention. In the reference case, only direct costs are included.

Incremental cost-effectiveness ratios are calculated under four health outcomes relevant for decision making: cost per episode averted, cost per DALY averted, cost per YLL, and cost per death averted. Future costs and benefits are presented both undiscounted and at a discount rate of 3% to reflect time preference.[18]

Sensitivity analysis

In addition to the reference case data assumptions and scenarios, the sensitivity analysis runs these same simulations under different assumptions. The rationales for these scenarios and the epidemiological patterns associated with them are described in the accompanying manuscript.[5]

Different transmission intensity patterns: (a) low stable transmission (Namawala/64 equivalent to 5.2 infectious bites per annum); (b) high transmission (Namawala/4 equivalent to 83 infectious bites per annum). Reference case: EIR 21 infectious bites per annum, corresponding to Namawala/16.

Different levels of vaccine efficacy: (a) 30%; (b) 80%; (c) 100%. Reference case: 52% entered in the model.

Different decay rates for the efficacy: Half-life of 6 months, 1 year, 2 years, 5 years, 10,000 years. Reference case: 10 years.

Different distribution of vaccine effect in the population: where b equals 0.01 and 100,000. Reference case: 10.

Different vaccine coverage rates: (a) a low coverage rate, with 70% of infants receiving their first dose, and 50% their 3rd dose; (b) complete coverage, where 100% of infants receiving three doses. Reference case: 89% 3rd dose; 95% 1st dose.

Inclusion of productivity cost savings: (a) low productivity costs, where those with uncomplicated episodes who do not seek care are assumed not to lose productive time; (b) high productivity costs, where all those predicted by the model to have a malaria episode are assumed to lose productive time.

5.3 Results

Reference case presentation

Health effects

Over 20 years the total number of uncomplicated episodes averted due to the introduction of the vaccine, in the simulated reference population of 100,000 people, is close to 192,485 corresponding to a rate of 0.1 per capita per year, while the total number of severe episodes averted is 1,697, or 0.0008 per capita per year.[5] These health effects represent only a small fraction of the total burden

of disease, because the vaccinated children represent only a small proportion of the total population in the early years of the simulation. The reference scenario also assumes waning of vaccine-induced immunity, so that the protected proportion of the population is never very high and increases only gradually. Furthermore, vaccination with a pre-erythrocytic vaccine effectively postpones many illness episodes, since it reduces acquisition of asexual stage immunity.

The total number of deaths prevented over 20 years is 942. The total number of undiscounted DALYs averted over 20 years is 58,579, corresponding to a rate of 0.029 per capita per year. When DALYs are discounted at 3%, the total number of DALY averted is 26,892, or 0.013 per capita per year. The total number of undiscounted DALYs with no age weighting applied is 48,299 DALYs averted, or 0.024 per capita per year. As most of these DALYs are due to the mortality effects, the total number of YLL is very close to that of DALYs. Figure 5.1 presents the distribution of DALYs averted over the 20 year model period, indicating that the health effects of introducing the vaccine vary over time.

Figure 0.1 Total number of DALYs averted after introducing the vaccine – reference case scenario

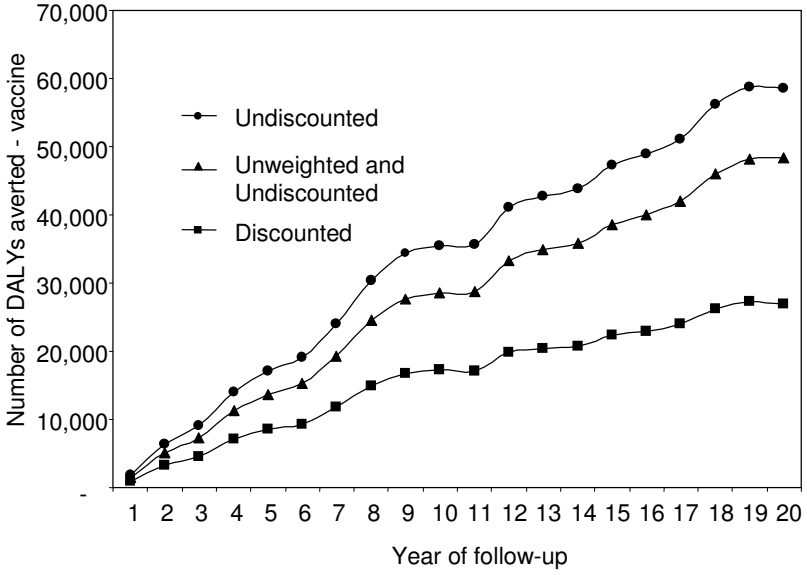


Table 5.3 shows that the number of uncomplicated episodes averted is higher in the second and third 5-year time periods and lower in the first and fourth 5-year time periods, since the start of vaccination. Most of the severe episodes averted occur in the first 10 years of the intervention, with a sharp decline in the third 5-year period, even registering a higher number of severe episodes under vaccination scenario in the fourth 5-year period. Also, a higher proportion of deaths prevented are concentrated in the first 10 years after vaccine introduction. When health outcomes are discounted, this effect is stronger.

Table 0.3 Comparison of discounted and undiscounted health outcomes over the four 5-year time period after the vaccine introduction

Time Period (years)	*1-5*	*6-10*	*11-15*	*16-20*
Health outcomes averted				
Uncomplicated episodes averted	*31289*	*65810*	*59187*	*36199*
Severe episodes averted	*979*	*867*	*96*	*-245*
Deaths averted	*275*	*292*	*193*	*182*
Deaths averted (discounted)	*256*	*236*	*134*	*110*
YLL averted	*16,731*	*18,454*	*12,035*	*11,655*
DALYs averted (undiscounted)	*17,083*	*18,426*	*11,699*	*11,370*
DALYs averted (discounted)	*8507*	*8741*	*5036*	*4608*
DALYs averted (unweighted, undiscounted	*13,657*	*14,953*	*9,933*	*9,755*

YLL =Years of life lost
DALY = Disability Adjusted Life Years

Net costs

The net cost of vaccine introduction for the 20 year period and at a vaccine price of US$1 per dose, is US$447,391, or US$0.22 per capita per year (direct, undiscounted average costs). In the marginal cost analysis, these costs are 3% less at US$433,890. The reference case results are shown in Table 5.4, for discounted and undiscounted costs, and at different vaccine price assumptions.

Figure 5.2 shows that the contribution of different cost components remains stable over the 20-year time period after introduction of the vaccine, comprising inpatient costs, outpatient costs, drug costs and patient costs. Before introduction of the vaccine around 30% of direct costs are due to outpatient visits, around 10% to drugs, 40% to hospital care, and 20% patient costs. After the introduction of the vaccine, over 50% of total direct costs – at a vaccine price of US$ 1 per dose – would be due to the vaccine delivery costs. This proportion increases significantly as the vaccine price increases.

The total number of first, second, and third line drug treatments over time is lower after the introduction of the vaccine (Figure 5.3). The total number of first line drug treatments averted by the vaccine reaches a maximum in the second 5-year interval, then decreases. The number of second and third line treatments averted is high in the first 5-year period after which it decreases to close to zero after 15 years. In the last 5-year period the number of first, second and third line drug treatment is higher when the vaccine is introduced. This is due to the fact that in the last 5-year period the vaccine does not prevent any severe episodes. There is

also a shift in uncomplicated episodes to older ages, where higher drug costs are incurred due to the requirement for a greater dose.

Table 0.4 Net costs in thousand US$, reference case (year 2004)

Vaccine price per dose	Discounting	Time periods							
		Years 1-5		*Years 6-10*		*Years 11-15*		*Years 16-20*	
		AC	*MC*	*AC*	*MC*	*AC*	*MC*	*AC*	*MC*
1	*Undiscounted*	*104*	*104*	*211*	*210*	*327*	*320*	*447*	*434*
	Discounted	*97*	*48*	*183*	*182*	*263*	*259*	*336*	*327*
2	*Undiscounted*	*186*	*182*	*Neg**	*366*	*575*	*734*	*779*	*749*
	Discounted	*173*	*121*	*Neg**	*318*	*464*	*593*	*586*	*565*
4	*Undiscounted*	*350*	*337*	*706*	*680*	*1072*	*1028*	*1441*	*1378*
	Discounted	*326*	*265*	*612*	*590*	*866*	*832*	*1088*	*1041*
6	*Undiscounted*	*513*	*492*	*1035*	*993*	*1568*	*1500*	*2104*	*2008*
	Discounted	*478*	*410*	*899*	*862*	*1268*	*1214*	*1589*	*1518*
8	*Undiscounted*	*677*	*648*	*1365*	*1307*	*2065*	*1971*	*2767*	*2637*
	Discounted	*630*	*555*	*1185*	*1134*	*1670*	*1595*	*2091*	*1994*
10	*Undiscounted*	*840*	*803*	*1695*	*1620*	*2561*	*2443*	*3429*	*3267*
	Discounted	*783*	*700*	*1471*	*1406*	*2072*	*1977*	*2592*	*2471*
20	*Undiscounted*	*1658*	*1580*	*3345*	*3187*	*5044*	*4802*	*6742*	*6414*
	Discounted	*1545*	*1423*	*2903*	*2766*	*4083*	*3887*	*5100*	*4853*

AC – average cost; MC – marginal cost; * indicates a negative value; each figure is the predicted cost for a total population of 100,000 people over the 5 year period.

Figure 0.2 Direct costs (at US$ 1.0 vaccine price per dose)

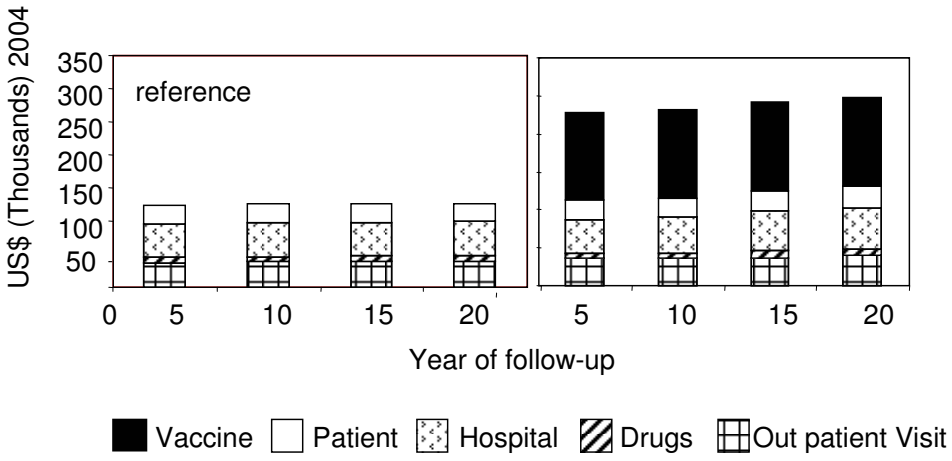
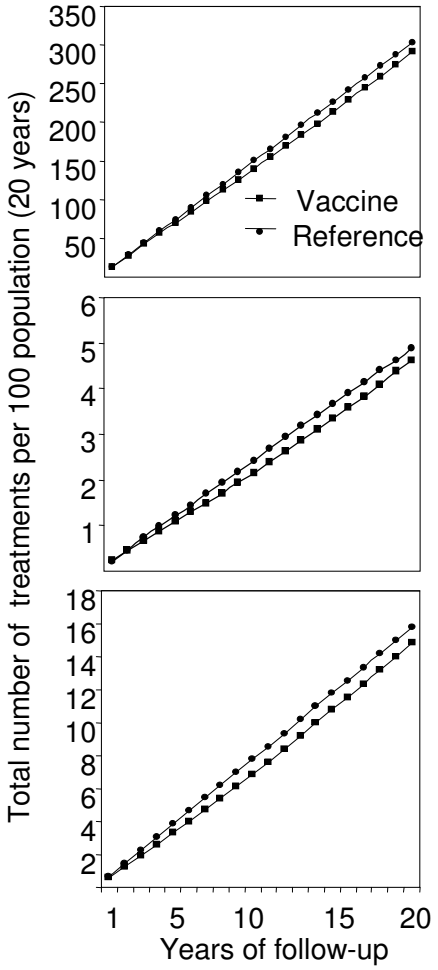


Figure 0.3 Total number of drug treatments under different interventions – reference case



Cost-effectiveness

Cost-effectiveness ratios using undiscounted average cost are presented for the vaccine in Table 5.5, over the entire 20 year intervention period, and by vaccine price. The cost per death averted by introducing the vaccine is US$475, under a vaccine price assumption of US$1 per dose, rising to US$7,158 per death averted at a vaccine dose price of US$20. The cost-effectiveness ratios using the marginal cost are generally between 97% and 99% of the CERs at average cost. Furthermore, discounting costs and health effects makes only a marginal difference to the CER, as shown in Table 5.5.

The undiscounted cost per DALY averted by introducing the vaccine is US$8, under a vaccine price assumption of US$1 per dose, rising to US$115 per death

averted at a vaccine dose price of US$20. The effect of discounting increases the cost per DALY averted by around 50% to US$12 per DALY averted at a vaccine price of US$1 per dose. The effect of taking out the age weighting in the DALY calculation reduces the cost per DALY averted back towards undiscounted levels. Figure 5.4 shows the relationship between cost-effectiveness ratios (for deaths averted and DALYs averted) and vaccine price.

However, the presentation of cost-effectiveness ratios over the entire 20 year intervention period hides some important variations across 5-year time intervals. Furthermore, variations in cost-effectiveness between the four different periods do not show a similar pattern across health outcome measures. Table 5.6 presents cost-effectiveness ratios for selected health outcomes over the four time intervals, and at different vaccine price assumptions.

The cost-effectiveness ratios for cost per death averted are similar in the first two 5-year intervals, but considerably higher in the second two 5-year intervals. At a vaccine price of US$1 per dose, the cost per death averted ranges between US$364 and US$601 over the four time intervals (Figure 5.5). The cost per death increases almost linearly with the vaccine price and at US$20 per dose it ranges between US$6,028 and US$9,332 per death averted at different time periods.

The undiscounted cost per DALY averted follows the same pattern over time as the cost per death averted, with a substantial difference between the first two 5-year periods and the second two 5-year periods (Figure 5.5). At vaccine price of US$1 the cost per DALY averted varied between US$6 and US$11 over time, but it increases with the vaccine price up to a range of US$92 to US$149 at US$ 20 per dose.

The discounted cost per DALY averted is higher, ranging between US$11 and US$16 at US$1 per dose (Figure 5.5). When DALYs are computed undiscounted and assuming zero age weighting, the average direct cost per DALY averted over the four time intervals ranges between US$7 and US$12 at this vaccine price. The cost per DALY averted by the vaccination program is thus lower in the first two 5-year time periods than in the latter. The cost-effectiveness ratio is much higher if both costs and DALYs are discounted at 3% while excluding the age weighting from the DALY calculation leads to a cost effectiveness ratio that is somewhere in between.

Cost-effectiveness ratios for cost per episode averted demonstrate yet another pattern. As most uncomplicated episodes are prevented after a few years from vaccine introduction and before the end of the third 5-year interval, the cost per uncomplicated episode averted is higher in the first and last five years (US$3 at a vaccine price of US$1 per dose) and lower in the second and third 5-year periods (US$2 at a vaccine price of US$1 per dose). This finding is even stronger for the

severe episodes, since most of them are averted in the first ten years, and in the last five years the number of severe episodes is higher in the vaccination scenario than under no vaccination. The cost per severe episode averted is US$106 in the first 5-year period, US$123 in the second 5-year period, and US$1209 in the third. In the fourth 5-year period, the health effect is negative thus giving a negative cost-effectiveness ratio.

Table 0.5 Cost-effectiveness (average cost) of the vaccine over 20 year intervention period, by vaccine price ¨

Outcome	Vaccine price per dose, in US$ (year 2004)						
	1	*2*	*4*	*6*	*8*	*10*	*20*
Cost per death averted							
Undiscounted	475	827	1'530	2'234	2'937	3'640	7'158
Discounted	456	796	1'477	2'158	2'840	3'521	6'926
Cost per DALY averted							
Undiscounted	8	13	25	36	47	59	115
Discounted	12	22	40	59	78	96	190
Undiscounted, un-weighted	9	16	30	44	57	71	140

Figure 0.4 Average (direct) cost per death and DALY prevented introducing the vaccine – reference scenario – 20 years – by vaccine price

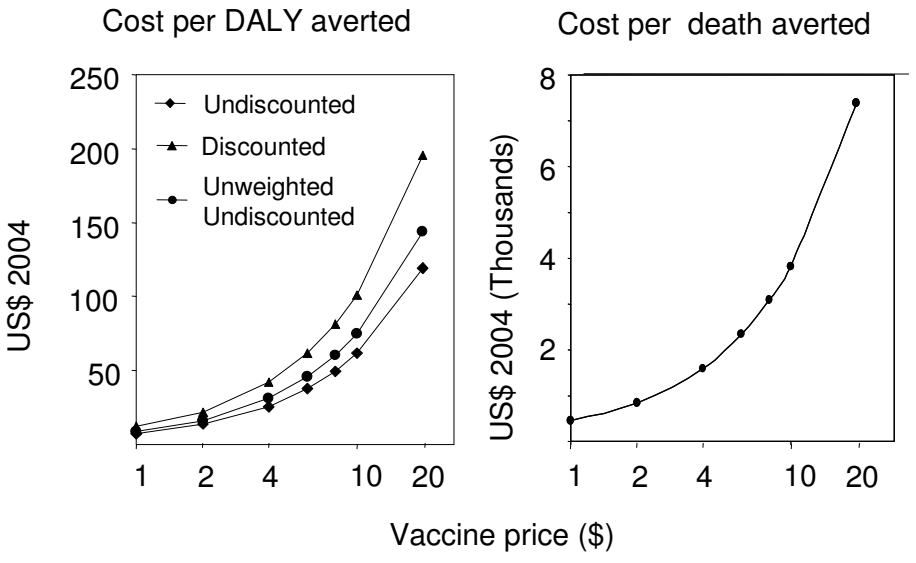
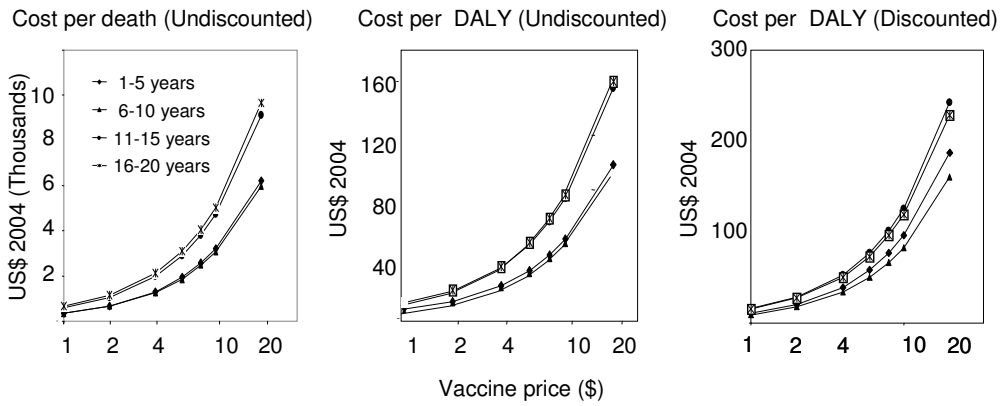


Table 0.6 Cost-effectiveness ratios for selected health outcomes, disaggregated by 5-year time intervals and by vaccine price

Vaccine price per dose (US$)	Time interval	Cost-effectiveness ratios (direct cost) for different health outcomes											
		Uncomplicated. episodes averted		*Severe episodes averted*		*Deaths prevented*		*DALYs averted (undiscounted)*		*DALYs averted (discounted)*		*DALYs averted (undiscounted, unweighted)*	
		AC	*MC*	*AC*	*MC*	*AC*	*MC*	*AC*	*MC*	*AC*	*MC*	*AC*	*MC*
1	*1-5*	3	3	106	106	379	378	6	6	11	11	8	8
	6-10	2	2	123	122	364	362	6	6	10	10	7	7
	11-15	2	2	1'209	1'152	601	573	10	9	16	15	12	11
	16-20	3	3	Neg*	Neg*	663	625	11	10	16	15	12	12
2	*1-5*	6	6	190	186	676	661	11	11	20	20	14	13
	6-10	3	3	219	213	649	632	10	10	17	17	13	12
	11-15	3	3	2'077	1'977	1'033	983	17	16	27	26	20	19
	16-20	6	5	Neg*	-Neg*	1'119	1'058	18	17	26	25	21	20
4	*1-5*	11	11	357	344	1'271	1'226	20	20	38	37	26	25
	6-10	5	5	411	395	1'219	1'174	19	19	33	32	24	23
	11-15	6	6	3'813	3'626	1'897	1'803	31	30	50	48	37	35
	16-20	10	10	Neg*	Neg*	2'032	1'925	33	31	48	46	38	36
6	*1-5*	16	16	524	503	1'866	1'790	30	29	56	54	38	36
	6-10	8	8	603	578	1'789	1'715	28	27	48	46	35	33
	11-15	9	9	5'549	5'275	2'760	2'624	46	43	73	70	54	51
	16-20	15	14	Neg*	Neg*	2'944	2'792	47	45	70	66	55	52
8	*1-5*	22	21	691	662	2'460	2'355	40	38	74	71	50	47
	6-10	10	10	794	760	2'359	2'256	37	36	63	61	46	44
	11-15	12	11	7'285	6'924	3'623	3'444	60	57	96	92	70	67
	16-20	19	18	Neg*	Neg*	3'857	3'659	62	59	91	87	72	68
10	*1-5*	27	26	858	820	3'055	2'920	49	47	92	88	62	59
	6-10	13	12	986	942	2'928	2'798	46	44	79	75	57	55
	11-15	15	14	9'020	8'573	4'487	4'264	74	70	119	113	87	83
	16-20	24	23	Neg*	Neg*	4'769	4'526	76	72	113	107	89	84
20	*1-5*	53	50	1'693	1'614	6'028	5'745	97	92	182	173	121	116
	6-10	26	24	1'946	1'854	5'777	5'504	92	87	155	148	113	107
	11-15	29	27	17'700	16'818	8'804	8'366	145	138	234	223	171	163
	16-20	47	45	Neg*	Neg*	9'332	8'860	149	142	221	210	174	165

AC – average cost; MC – marginal cost; Neg* - indicates a negative cost-effectiveness ratio

Figure 0.5 Average (direct) cost per death prevented and DALY averted introducing the vaccine – reference scenario – by time period and vaccine price



Sensitivity analysis

Effect of Transmission Intensity

The total number of deaths and DALYs averted in the first ten years of the simulation is lower in a low transmission setting (5.2 infectious bites per annum) than in the reference scenario, while in a high transmission setting (83 infectious bites per annum) is close to the number reported in the reference scenario (Figure 5.6). However, in a high transmission setting almost all of the deaths prevented (around 90%) and DALYs averted (around 93%) occur in the first ten years.

The cost per death averted and per DALY averted in a high transmission setting is thus equal to that in the reference scenario in the first 5 year period, but it is almost twice the cost per death averted in the second 5-year period, and then the CER increases dramatically in the following years (Table 5.7). In a low transmission setting, the cost per death prevented and per DALY (both undiscounted and discounted) averted are twice as high as those in the reference scenario in the first five years, and lower in the following years (Table 5.7).

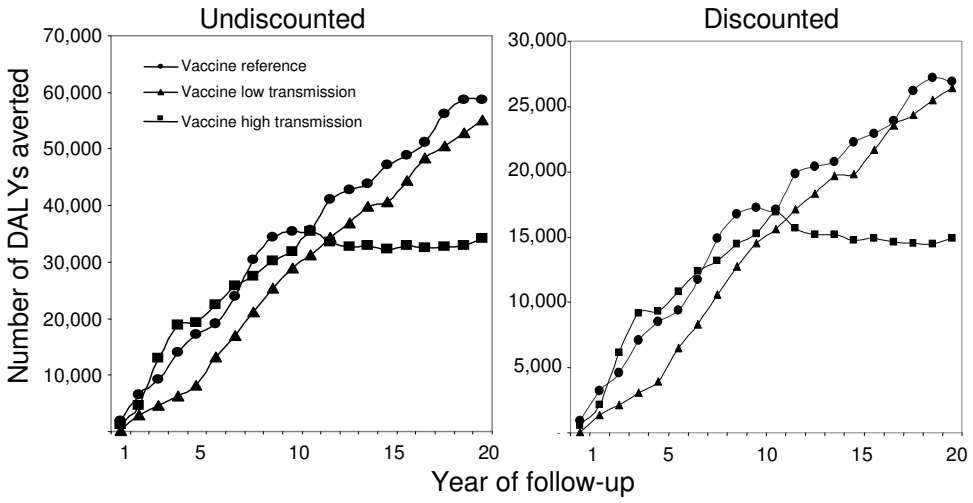
Table 0.7Cost-effectiveness ratios under different scenarios in the sensitivity analysis (US$, year 2004, using average costs, vaccine price US$1 per dose)

	Price=1	Cost per DALY averted				Cost per Death prevented			
	Scenario/time period	*1_5*	*6_10*	*11_15*	*16_20*	*1_5*	*6_10*	*11_15*	*16_20*
Reference case	*undiscounted*	6.1	5.8	9.9	10.6	378.9	364.5	601.4	663.1
	discounted	11.4	9.8	16.0	15.7	379.6	362.4	599.7	657.4
	*undiscounted**	7.6	7.1	11.7	12.4				
Low transmission	*undiscounted*	13.0	4.7	8.8	7.4	845.4	293.7	579.9	512.1
	discounted	25.3	7.4	13.3	9.8	421.8	122.7	104.4	74.7
	*undiscounted**	16.2	5.9	10.6	9.0				
High transmission	*undiscounted*	5.5	9.5	309.7	68.1	339.4	559.4	4'965.7	3'281.7
	discounted	10.6	16.2	Neg*	725.7	234.7	171.3	146.9	97.7
	*undiscounted**	6.8	11.4	128.3	59.4				
Half- life 6 mths	*undiscounted*	12.6	13.5	Neg*	17.8	744.8	795.9	9'798.5	1'067.5
	discounted	23.5	23.0	Neg*	21.3	729.1	779.5	8'568.5	1'079.5
	*undiscounted**	15.8	16.5	827.8	22.3				
Half life 1 year	*undiscounted*	9.9	22.4	37.9	13.9	618.6	1'332.0	2'080.8	909.2
	discounted	18.5	41.5	62.5	19.4	607.5	1'299.3	2'212.6	938.3
	*undiscounted**	12.3	26.4	42.8	16.7				
Half life 2 years	*undiscounted*	6.4	9.2	19.3	9.3	401.4	552.9	1'201.0	554.8
	discounted	12.0	15.6	31.7	12.4	391.9	548.0	1'212.3	555.7
	*undiscounted**	8.1	11.2	22.8	11.2				
Half life 5 years	*undiscounted*	5.5	8.2	13.1	11.8	336.7	517.3	804.0	761.3
	discounted	10.3	14.0	21.3	16.8	336.1	514.1	801.5	766.2
	*undiscounted**	6.9	10.0	15.3	13.9				
Half- life 10000 years	*undiscounted*	5.2	4.5	11.2	6.2	323.0	287.3	673.8	406.0
	discounted	9.9	7.5	18.1	8.6	321.6	285.7	671.4	403.8
	*undiscounted**	6.5	5.6	5.6	5.6				
Efficacy 30%	*undiscounted*	9.7	14.1	26.8	15.7	625.9	917.9	1'706.5	1'080.6
	discounted	18.2	23.7	45.1	23.6	622.1	921.1	1'768.3	1'092.1
	*undiscounted**	12.1	17.5	30.9	18.7				
Efficacy 80%	*undiscounted*	3.5	3.0	5.0	6.2	219.9	187.3	318.9	407.2
	discounted	6.7	5.0	7.9	9.5	222.4	184.8	315.2	408.5
	*undiscounted**	4.3	3.7	3.7	3.7				
Efficacy 100%	*undiscounted*	1.9	1.4	2.8	3.2	120.2	89.8	175.4	205.4
	discounted	3.7	2.3	4.3	4.5	121.5	89.3	173.8	204.7
	*undiscounted**	2.4	1.8	3.3	3.7				
Coverage 50%	*undiscounted*	5.1	6.8	15.6	8.2	325.0	437.8	916.2	529.1
	discounted	9.7	11.7	27.3	11.8	326.6	441.3	934.5	535.8
	*undiscounted**	6.4	8.3	17.3	9.8				
Coverage 100%	*undiscounted*	5.7	5.0	11.6	8.0	355.0	316.3	698.8	517.0
	discounted	10.7	8.3	18.4	11.2	354.6	310.7	689.7	512.8
	*undiscounted**	7.1	6.2	13.7	9.6				
b 0.01	*undiscounted*	4.0	4.3	5.7	7.6	253.1	272.1	354.6	503.3
	discounted	7.5	7.2	8.6	10.9	254.4	269.6	350.2	506.1
	*undiscounted**	*4.6*	*4.8*	*6.6*	*8.6*				
b 100000	*undiscounted*	*5.4*	*6.8*	*17.9*	*15.3*	*348.1*	*430.5*	*1056.4*	*980.9*
	discounted	*10.2*	*11.7*	*31.3*	*27.5*	*324.9*	*345.5*	*733.5*	*587.5*
	*undiscounted**	*6.7*	*8.4*	*8.4*	*8.4*				

Neg* indicates a negative cost-effectiveness ratio

b is the parameter of the beta distribution used to model variation between individuals in the efficacy of the vaccine

Figure 0.6 Number of DALYs averted due to vaccine introduction in different transmission settings

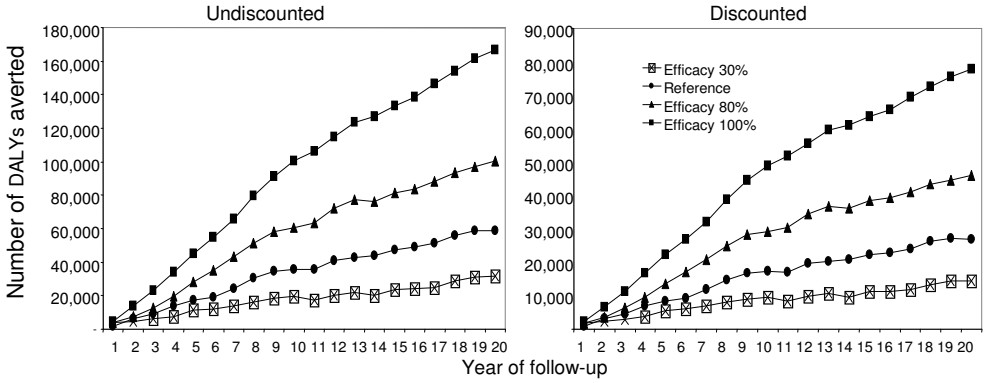


Effects of different vaccine efficacy

The cost-effectiveness simulations in the reference scenario assume that vaccination reduces the force of infection by 52%. Figure 5.7 shows the number of deaths averted over the 20 year period at different levels of vaccine efficacy. The impact on DALYs averted shows a similar pattern.

Table 5.7 shows the cost-effectiveness results under different efficacy assumptions. If the efficacy of the vaccine is 30% instead of 52%, the direct costs per death prevented and per DALY averted would be considerably higher, with the highest difference being in the second and third 5-year periods where it is over 200%. Increasing the efficacy to 80% would reduce the cost-effectiveness ratios by around 50% to between US$3 and US$6 per DALY averted, and US$200 to US$400 per death averted. The cost-effectiveness of a completely efficacious vaccine would result in a considerable further improvement in the cost-effectiveness ratio, to US$1.4 to US$3.2 per DALY averted.

Figure 0.7 Total number of DALYs averted at different levels of vaccine efficacy

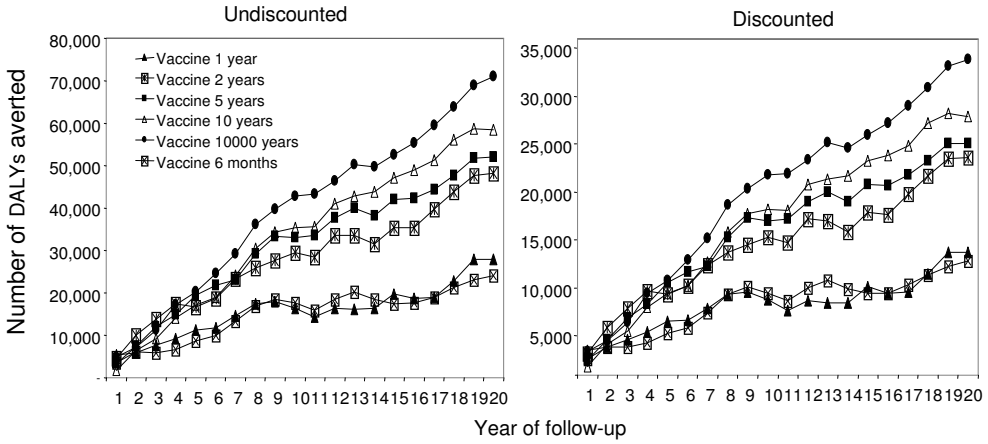


Effects of decay of efficacy

The reference scenario assumes a half-life of protection against infection of ten years. The cost-effectiveness simulations are run assuming different duration of vaccine protection from 6 months up to 10000 years, approximating a non-decaying efficacy. The impact on DALYs averted is shown in Figure 5.8.

As expected, the longer the duration of efficacy the lower are the cost-effectiveness ratios (Table 5.7). However, the improvements in cost effectiveness ratios are not linear. Improving the half-life from six months to 5 years leads to substantial improvements in the cost-effectiveness ratio, but the differences in cost-effectiveness between five and ten years efficacy duration are slightly smaller.

Figure 0.8 Total DALYs averted at different levels of vaccine efficacy decay (half-life)

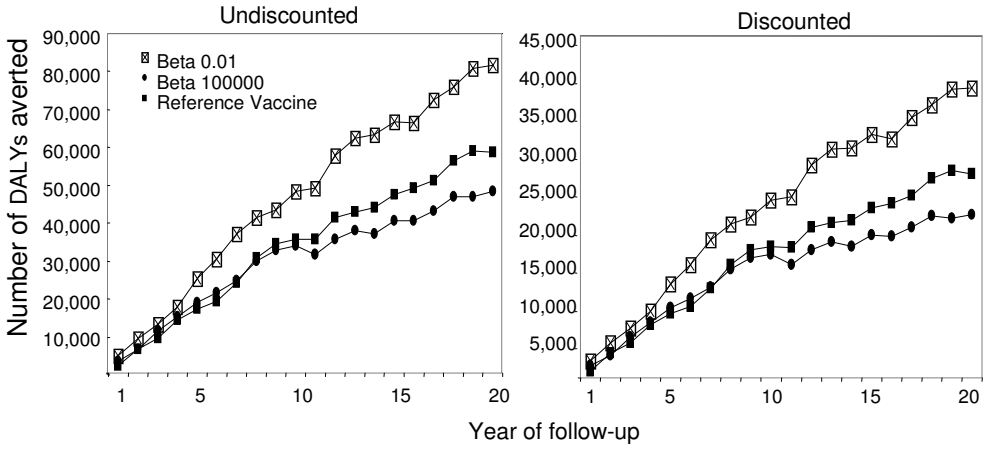


Effects of variation in vaccine efficacy between individuals

The distribution of vaccine efficacy among the vaccinated infants has a moderate impact on the number of deaths and DALYs that can be averted introducing the vaccine. The two alternative scenarios modelled, assuming either an all-or-nothing response or complete heterogeneity, show that the more the efficacy is concentrated in a few vaccinated subjects, the more deaths and DALY can be prevented.

This finding is also reflected in the cost-effectiveness ratios that are more favourable than the reference case if b=0.01 (i.e. efficacy concentrated among fewer individuals), and less favourable if the effect was completely dispersed (Figure 5.9).

Figure 0.9 Total DALYs averted under different assumptions about heterogeneity in initial efficacy

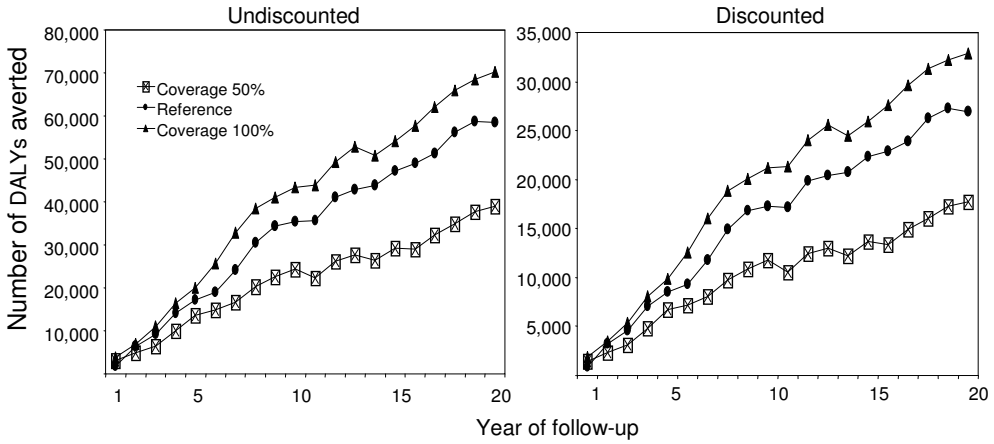


Effects of the coverage rate

The reference scenario assumes a fairly high vaccine coverage rate (89%) as reported in Tanzania for DTP-HB vaccine in year 2003.[4] We also simulate a coverage rate of 50% which is likely to be closer to that in many malaria endemic countries, and coverage of 100% which allows us to analyze which effects are due to incomplete coverage. The cost-effectiveness simulations are thus run assuming a low coverage rate (50%) and complete coverage (100%). A lower coverage rate leads to significant reduction in the total number of deaths and of DALYs averted over the 20 year simulation (Figure 5.10).

The cost per death prevented and per DALY averted assuming a coverage rate of 50% is between 20% and 50% higher than in the reference scenario in the central ten years of simulation, while it is slightly lower in the first and last five years (Table 5.7). A complete coverage would increase slightly the number of deaths prevented and more significantly the number of DALY averted compared to the reference scenario, while the cost per deaths and DALY averted would be slightly lower.

Figure 0.10 DALYs averted under different assumptions about vaccine coverage



Inclusion of productivity costs

The economic implications of reducing the burden of malaria go beyond the direct costs due to health care treatment. In the sensitivity analysis we model the cost-effectiveness results including the productivity costs of productive time lost due to the disease. Results are presented for two assumptions of the proportion of malaria episodes where there is a productivity cost associated with the disease: the high productivity cost case where productivity costs are incurred by all episodes predicted by the epidemiological model, and the low productivity cost case where there are no productivity costs associated with uncomplicated episodes unless the patient seeks treatment.

Over the entire 20 year follow-up period, introducing the vaccine would lead to savings in productivity costs of around US$263,634 in the high productivity cost scenario and $28,443 in the low productivity cost scenario. However, as do the effects of the vaccine vary over time, so do the savings in productivity costs vary over time (Table 5.8). Under the high productivity cost scenario, the savings in

productivity costs reduce the total net cost of introducing the vaccine by between 49% and 90% in different time periods, at a vaccine price of US$1 per dose. The savings are significantly reduced to an impact on total net cost of 3% to 4% when the vaccine price increases to US$20 per dose.

Under the low productivity cost scenario, the reductions in the net cost of introducing the vaccine are significantly lower than under the high productivity cost scenario. Total net cost reductions would occur only in the first 3 5-year periods, giving reductions of 5% to 7% and 5% at US$1 per dose and under 1% at US$20 per dose. In the fourth 5-year period productivity costs would be actually higher with the vaccine. This leads to an increase in the net cost of introducing the vaccine in the last ten year of follow-up.

As a consequence, the cost per DALY averted (discounted) is lower when productivity costs are included, as presented in Table 5.9. Under the high productivity cost scenario, the total cost per DALY averted would be between US$1.7 and US$8.1 at a vaccine price of US$1 per dose. These figures represent a reduction in cost per DALY averted of between 63% and 89% when compared to the CER containing only direct costs. However, as the vaccine price increases the cost per DALY becomes closer to the reference case analysis CER. For example, at US$20 per dose the cost per DALY averted would be between US$148 and US$227 in different time periods, which is similar to that including only direct costs.

Table 0.8 Hypothetical value of production time gained due to less time spent ill, after vaccine introduction (US$, year 2004)

Time period	High productivity cost scenario		Low productivity cost scenario	
(years)	*Undis-counted*	*Dis-counted*	*Undis-counted*	*Dis-counted*
1-5	*63,478*	*57,173*	*15,260*	*14,074*
6-10	*124,743*	*98,807*	*18,603*	*15,114*
11-15	*105,779*	*72,440*	*6,238*	*4,407*
16-20	*59,366*	*35,214*	*-8,771*	*-5,153*

Table 0.9 Cost per DALY averted including direct and productivity costs (US$, year 2004)

Vaccine price per dose	Time period (years)	Cost per discounted DALY averted	
		High productivity cost scenario	*Low productivity cost scenario*
1	*1-5*	3.98	9.76
	6-10	Neg*	8.07
	11-15	1.66	15.12
	16-20	8.12	16.80
2	*1-5*	13.50	18.72
	6-10	6.15	15.73
	11-15	13.88	26.61
	16-20	19.60	27.59
4	*1-5*	32.55	36.63
	6-10	22.44	31.05
	11-15	38.31	49.59
	16-20	42.56	49.18
6	*1-5*	51.60	54.54
	6-10	38.73	46.37
	11-15	62.75	72.56
	16-20	65.51	70.77
8	*1-5*	70.65	72.46
	6-10	55.02	61.69
	11-15	87.18	95.54
	16-20	88.47	92.36
10	*1-5*	89.70	90.37
	6-10	71.32	77.01
	11-15	111.61	118.52
	16-20	111.43	113.95
20	*1-5*	180.41	179.93
	6-10	148.91	153.62
	11-15	227.97	233.40
	16-20	220.77	221.91

Neg - indicates that there is a cost saving and a health benefit*

5.4 Discussion

We have used a stochastic simulation of *P. falciparum* epidemiology combined with a case management model for a Tanzanian setting[3] to explore the potential cost-effectiveness of a pre-erythrocytic malaria vaccine. To our knowledge, this is the first time that dynamic models of malaria transmission and disease have been used to evaluate the cost-effectiveness of malaria vaccines. We have used vaccines with different characteristics introduced via the EPI in Tanzania to illustrate the approach. The models can readily be extended to other types of vaccine, and to different epidemiological and socio-economic settings.

Over the vaccine price range of US$ 1.0 to US$ 20 per dose, the CER is almost proportional to the price per dose, ranging (in the reference analyses) between US$ 12 and US$ 190 per (discounted) DALY averted. In the sub-Saharan African context, CERs towards the lower end of this range would be very attractive for health ministries.[18,19] Up to a vaccine price per dose of almost US$ 10, the cost per discounted DALY averted remains under US$ 100. When productivity costs due to morbidity are included, our CERs are even lower than those estimated including only direct costs. However, this difference diminishes with the increase of vaccine price. There is little difference between marginal and average costs, which means that substantial savings cannot be achieved by taking up spare capacity in the health system: the cost of the vaccine is the major determinant of costs.

These results should be interpreted in the context of CEA of other malaria control strategies. At vaccine price towards the lower end of the range used, our cost-effectiveness estimates of vaccination compare favorably with those of several other malaria control interventions estimated for the Global Forum for Health Research (GFHR)[20], but these comparisons are problematical because of differences in the methodology. Although the GFHR study used DALY calculations based on an African life-table with similar life expectancies to those that we use, our models differ by including dynamic effects that result in age- and time- shifts in the burden of disease.

The indirect economic impact of malaria is clearly important and we aimed to capture these effects by including productivity costs in some analyses. However there are many pitfalls in measuring potential or actual economic impact in the context of rural Africa where most of the population are subsistence farmers, child-care is often performed by older siblings, work is seasonal and work inputs may be shifted over time and between household members. We had no empirical studies available for our estimates of time use or on the impact of malaria episodes on productive capacity. Concerns about equity effects, inadequate data,

or methods for estimating economic benefits mean that indirect costs are often excluded from CEA.[2,17] Indirect costs were not included in the GFHR study[20], or in any other cost-effectiveness studies to date of malaria interventions, and nor were they included in the analyses underpinning WHO guidelines for CER thresholds for considering health interventions as attractive or very attractive (18). Our analyses that include productivity costs are thus even less comparable with those of other studies.

A major impact of malaria on productivity is likely to be via the effects on premature mortality, but it is inappropriate to include in a CEA the "costs of mortality", as available from estimates of life-time earnings forgone or willingness to pay studies, since this would result in double counting of the benefits of averting deaths.[1,2,21] Among the microeconomic studies on the economic consequences of malaria published so far, only one[22] has included productivity costs due to premature mortality. That study estimated the economic burden of malaria and not the cost-effectiveness of interventions.

A malaria vaccine may also have positive impacts on social and economic development that are not captured by the productivity cost savings. Endemic malaria is associated with substantially lower indices of economic development at the national level,[23,24] and reducing the burden of malaria might have macroeconomic benefits that are not captured in microeconomic analyses. However the epidemiological analyses[5] clearly indicate that on their own, vaccine programs with profiles like those we investigated will avert a proportion of illness events that is much lower than the primary vaccine efficacy, and will have little or no effect on malaria endemicity. In this context it would be surprising if they had substantial effects on economic development.

Indeed, we obtain only modest estimates of the wider economic benefits of a vaccination program if we apply the recently suggested approach[25] of estimating these benefits by multiplying the number of DALYs averted by the average GDP per capital. Using our prediction that a pre-erythrocytic malaria vaccine would avert between 0.013 and 0.029 DALYs per capita per year and the GDP per capita of Tanzania (US$ 322 in 2005), the annual per capita economic benefits would be between US$ 4.2 and US$ 9.3 (according to whether DALYs are discounted or not and aged weighted or not).

These conclusions reflect the reference case, but the CER is highly sensitive to assumptions about the epidemiological setting and vaccine characteristics including the transmission intensity, the efficacy and duration of protection (Table 5.7). The CER varied with the time since the start of the vaccination programme, because the epidemiological model does not reach equilibrium within the time-scale of the simulation.[5] In general the cost per DALY averted is lower in the first

phase of the vaccination program than later, with the highest cost per DALY in the third 5-year time period after the start of the program. Extending the duration of protection increases the cost-effectiveness ratios in the third and fourth 5-year time periods. A vaccine boost at some specified time point may have a similar effect, although this would involve additional costs which would be included in calculation of the CER. We have not addressed the emerging problem of drug resistance, which could be included in the case management model and would presumably increase the cost per DALY averted.

Our simulations considered only a limited set of sources of heterogeneity. In particular we assumed that each person in the simulation was exposed to the same entomological challenge, and that the chances of being vaccinated were independent of individual susceptibility to disease. We also assumed homogeneous probabilities of accessing health care. Over a period of 20 years the introduction of a new malaria vaccine would definitely have an impact on the health system and on the case management of malaria. It would be possible to simulate more realistic patterns of heterogeneity but the field data on which to base such models are very limited.

Some counter-intuitive behavior in cost-effectiveness ratios corresponds to health effects in the model. When episodes are delayed rather than averted, they occur in older individuals who may require larger drug dosages. Thus the health benefit of delaying illness may be partially offset by increased costs. The epidemiological model also corresponds with field data that suggests a maximum incidence of clinical episodes (though not mortality) at intermediate transmission intensities,[26-29] so it is quite possible for reductions in malaria transmission to lead to increased case-loads.

The proportion of clinical episodes averted varies by transmission intensity[5] and so do the numbers of DALYs averted. The numbers of clinical episodes continues to decline after ten years of the vaccine introduction only in low transmission scenarios. This is explained by the fact that in high transmission settings there is an increase in severe malaria incidence in children over five years old, due to reduced accrual of immunity to asexual blood stage parasites during early childhood. In addition, the pyrogenic threshold, which determines the parasite density that leads to acute illness, depends on the recent exposure to parasite and can be lower in vaccinated individuals.[10] In the model, the lower level of acquired immunity in vaccinated individuals and the resulting inability to effectively control parasite densities also leads to higher proportion of the acute episodes being severe.

An extension to the current work will be to carry out a full probabilistic sensitivity analysis; this will enable us to present acceptability curves in addition to the

presentation of cost-effectiveness ratios in this paper. However the present analyses already indicate that a pre-erythrocytic malaria vaccine, even one with moderate efficacy and minimal effectiveness in reducing transmission to the vector, could be a cost-effective intervention in reducing the intolerable burden of malaria in sub-Saharan Africa.

5.5 References

1. Drummond MB, O'Brien B, Stoddart GL, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford University Press; 1997

2. Gold MR, Gold SR, Weinstein MC. Cost-effectiveness in health and medicine. Oxford: Oxford University Press; 1996

3. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, Tanner M, 2006. An approach to model the costs and effects of case management of *Plasmodium falciparum* malaria in sub-Saharan Africa. *submitted*

4. Tediosi F, Hutton G, 2005. The costs of introducing a malaria vaccine through the expanded program on immunization in Tanzania. *Am J Trop Med Hyg, in press.*

5. Maire N, Tediosi F, Ross A, Smith T, 2006. Predicting the epidemiological impact of introducing a pre-erythrocytoc malaria vaccine into the expanded program on immunization schedule in sub-Saharan Africa. *Am J Trop Med Hyg, in press*

6. Smith T, Killeen G, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M, 2006. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: Overview. *Am J Trop Med Hyg, in press.*

7. Hall AJ, Robertson RL, Crivelli PE, Lowe Y, Inskip H, Snow SK, Whittle H, 1993. Cost-effectiveness of hepatitis B vaccine in The Gambia. *Trans R Soc Trop Med Hyg 87*: 333--6

8. Edmunds WJ, Dejene A, Mekonnen Y, Haile M, Alemnu W, Nokes DJ, 2000. The cost of integrating hepatitis B virus vaccine into national immunization programmes: a case study from Addis Ababa. *Health Policy Plan 15*: 408--16

9. Griffiths U, Hutton G, das Dores Pascoal E, 2005. Cost-effectiveness of introducing hepatitis B vaccine into the infant immunization schedule in Mozambique. *Health Policy Plan* 20: 50-59

10. Maire N, Aponte J, Ross A, Thompson R, Utzinger J, Smith T, 2006. Modeling a field trial of the RTS,S/ASO2A malaria vaccine. *Am J Trop Med Hyg, in press*

11. Smith T, Charlwood JD, Kihonda J, Mwankusye S, Billingsley P, Meuwissen J, Lyimo E, Takken W, Teuscher T, Tanner M, 1993. Absence of seasonal variation in malaria parasitaemia in an area of intense seasonal transmission. *Acta Trop 54*: 55--72

12. Hay SI, Rogers DJ, Toomer JF, Snow R, 2000. Annual *Plasmodium falciparum* entomological inoculation rates (EIR) across Africa: literature survey, Internet access and review. *Trans R Soc Trop Med Hyg 94*: 113--127

13. INDEPTH Network. Population, Health and Survival at INDEPTH Sites. Ottawa: IDRC; 2002

14. Murray CJL, Lopez AD. Estimating causes of death: new methods and global and regional applications for 1990. In: Murray CJL, Lopez AD, eds. The global burden of disease. Geneva: World Health Organisation; 1996.

15. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Harvard: Harvard University Press; 1996

16. INDEPTH Network. Model life tables for sub-Saharan Africa. Aldershot, England: Ashgate; 2004

17. Chima RI, Goodman CA, Mills A, 2003. The economic impact of malaria in Africa: a critical review of the evidence. *Health Policy 63*: 17--36

18. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans D, Murray C. Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization, Geneva; 2003

19. Goodman CA, Coleman PG, Mills A, 1999. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet 354*: 378--385

20. Goodman C, Coleman P, Mills A. Economic analysis of malaria control in sub-Saharan Africa. Geneva: Global Forum for Health Research; 2000

21. Weinstein M, Siegel J, Gold M, Kamlet M, Russell L, 1996. Recommendations of the panel of cost-effectiveness in medicine. *JA MA 276*: 1253--1341

22. Shepard DS, Ettling MB, Brinkmann U, Sauerborn R, 1991. The economic cost of malaria in Africa. *Trop Med Parasitol 42*: 199--203

23. Sachs J, Malaney P, 2002. The economic and social burden of malaria. *Nature 415*: 680--685

24. Malaney P, Spielman A, Sachs J, 2004. The malaria gap. *Am J Trop Med Hyg 71(2 Suppl)*: 141--146

25. Sachs JD, 2001. Macroeconomics and health: investing in health for economic development. Geneva, Commission on Macroeconomics and Health, WHO.

26. Marsh K, Snow R, 1999. Malaria transmission and morbidity. *Parassitologia 41*: 241--246

27. Ross A, Maire N, Molineaux L, Smith T, 2006. An epidemiological model of severe morbidity and mortality caused by *Plasmodium falciparum. Am J Trop Med Hyg, in press.*

28. Smith T, Ross A, Maire N, Rogier C, Trape JF, Molineaux L, 2006. An epidemiological model of the incidence of acute illness in *Plasmodium falciparum* malaria. A*m J Trop Med Hyg, in press*

29. Trape JF, Rogier C, 1996. Combating malaria morbidity and mortality by reducing transmission. *Parasitol Today 12*: 236--240

Chapter 6: Simulation of the cost-effectiveness of malaria vaccines

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Abstract

Background

A wide range of possible malaria vaccines is being considered and there is a need to identify which vaccines should be prioritized for clinical development. An important element of the information needed for this prioritization is a prediction of the cost-effectiveness of potential vaccines in the transmission settings in which they are likely to be deployed. This analysis needs to consider a range of delivery modalities to ensure that clinical development plans can be aligned with the most appropriate deployment strategies.

Methods

The simulations are based on a previously published individual-based stochastic model for the natural history and epidemiology of Plasmodium falciparum malaria. Three different vaccine types: pre-erythrocytic vaccines (PEV), blood stage vaccines (BSV), mosquito-stage transmission-blocking vaccines (MSTBV), and combinations of these, are considered each delivered via a range of delivery modalities (Expanded Programme of Immunization - EPI-, EPI with booster, and mass vaccination combined with EPI). The cost-effectiveness ratios presented are calculated for four health outcomes, for assumed vaccine prices of US$ 2 or US$ 10 per dose, projected over a 10-year period.

Results

The simulations suggest that PEV will be more cost-effective in low transmission settings, while BSV at higher transmission settings. Combinations of BSV and PEV are more efficient than PEV, especially in moderate to high transmission settings, while compared to BSV they are more cost-effective in moderate to low transmission settings. Combinations of MSTBV and PEV or PEV and BSV improve the effectiveness and the cost-effectiveness compared to PEV and BSV alone only when applied with EPI and mass vaccinations. Adding booster doses to the EPI is unlikely to be a cost-effective alternative to delivering vaccines via the EPI for any vaccine, while mass vaccination improves effectiveness, especially in low transmission settings, and is often a more efficient alternative to the EPI. However, the costs of increasing the coverage of mass vaccination over 50% often exceed the benefits.

Conclusions

The simulations indicate malaria vaccines might be efficient malaria control interventions, and that both transmission setting and vaccine delivery modality are important to their cost-effectiveness. Alternative vaccine delivery modalities to the EPI may be more efficient than the EPI. Mass vaccination is predicted to provide substantial health benefits at low additional costs, although achieving high coverage rates can lead to substantial incremental costs.

6.1 Background

Plasmodium falciparum malaria represents one of the world's major causes of morbidity and mortality[1] [2] and there is a pressing need for new effective interventions, which, combined with the existing strategies, could effectively reduce the burden of malaria in endemic areas[3].

Among these potential new interventions are vaccines and, although there is currently no licensed malaria vaccine, a number of candidates are under development. The complexity of the malaria life cycle means that a number of different stages of the parasite can be targeted. The candidate that is most advanced in clinical development[4] [5] targets pre-erythrocytic stages of the parasite.

Appraisals of candidate malaria vaccines should not include only efficacy and effectiveness evaluations but also cost effectiveness analyses (CEA) aimed at guiding vaccine developers, funding agencies[6], and policy makers to allocate resources so that social and economic benefits are maximized[7] [8]. CEA can help in evaluating alternative health interventions because health decision makers are primarily interested in knowing what health improvements can be bought with a given budget, and not the overall economic impact *per se*[9] [10]. Previously, the likely epidemiological effects[11] and cost-effectiveness[12] of pre-erythrocytic vaccines when delivered in areas of stable endemic malaria via the Expanded Programme on Immunization (EPI) were estimated based on a dynamic model of malaria epidemiology[13]. These simulations showed that at moderate vaccine prices the cost-effectiveness of such vaccines may be similar to that of other preventive and curative interventions against malaria. However, more evidence is needed on the likely cost-effectiveness of different malaria vaccines under development, and on the implications for it of adopting alternative means of deployment. The cost-effectiveness of a malaria vaccine will depend not only on the vaccine profile and the transmission setting, but also on the vaccination coverage that can be achieved, on the vaccine delivery costs, and of the operational feasibility of the delivery modalities adopted to deploy it.

A companion article to the present one[14], reports on the simulations of the likely epidemiological effects of three different malaria vaccine types: pre-erythrocytic vaccines (PEV), blood stage vaccines (BSV), mosquito-stage transmission-blocking vaccines (MSTBV), and combinations of these. A range of different delivery modalities (EPI, EPI with booster, and mass vaccination combined with EPI) were considered. In this article, both the health system and vaccine delivery costs are attached to the events recorded in these simulations to calculate cost-effectiveness ratios for each deployment strategy and each vaccine, and for each of four health outcomes over a 10-year time-horizon.

6.2 Methods

Perspective and boundary

The simulations refer to CEA under the perspective of the society as a whole, although only direct costs are included. They thus consider all relevant direct resource inputs and costs to the interventions, and resource consequences, costs, and health impacts resulting from the interventions. The indirect economic impact of malaria such as potential earning forgone of patients and unpaid carers is not included, as its inclusion is controversial in CEA[15 16]. The CEA follows standard cost-effectiveness methodology[8 17-21].

Interventions being compared

The simulations of vaccines are based on a previously described model for the natural history and epidemiology of *P. falciparum* malaria[13]. This model uses an underlying model based on descriptions of the course of parasite densities in malaria therapy patients[22]. The parameterization of the model for the present simulations is described in the companion article[14] and reviewed in more detail elsewhere[23]. Briefly, each simulated vaccine is characterized by an average initial efficacy (the efficacy reached after completion of a schedule of three doses), and by a half-life of this efficacy, which is assumed to decay exponentially with time. The vaccinated population is assumed to be heterogeneous in the response to vaccination, and to allow for this we assign initial values for efficacy drawn from a beta-distribution[11] (simulated vaccines are delivered at specified ages, and a range of coverage values is considered for vaccination to allow for individuals who do not complete the full schedule).

The effects of the three different vaccine types and four combinations were modeled as follows (see also [14]):

(i) Pre-erythrocytic vaccines (PEV)

Pre-erythrocytic vaccines are assumed to lead to a reduction in the proportion of inoculations from the bites of infected mosquitoes that lead to blood stage infection and the vaccine efficacy is assumed to be equal to the proportion by which this force of infection is reduced.

(ii) Blood stage vaccines (BSV)

A blood stage vaccine is assumed to reduce parasite densities at each time step by a proportion equal to the vaccine efficacy.

(iii) Mosquito stage transmission blocking vaccines (TBV)

Vaccine efficacy is equivalent to the proportional reduction of the probability that a mosquito becomes infected from any one feed on an infectious vaccinated human.

(iv) Combination vaccines

Combination vaccines of PEV with TBV, BSV with TBV, BSV with PEV and also a three-way combination of PEV with both BSV and MSTBV are considered. For each combination, PEV and BSV are assumed to be matched in both the initial efficacy and in their rate of decay. Only combinations of PEV, BSV and of PEV-BSV with high efficacy MSTBV are considered since it is unlikely that a MSTBV with low efficacy would be developed.

Vaccine delivery modalities

The delivery of the three vaccine types and their combinations through the following three strategies are simulated:

(i) EPI

Delivery of the vaccines through the EPI according to the usual diphtheria tetanus pertussis (DTP3) vaccine schedule: age 1, 2 and 3 months.

(ii) EPI with booster

In addition to the above EPI schedule, this modality includes booster doses at 1, 2, 3 and 4 years after the last EPI schedule. The effect of a booster dose is to restore the protective efficacy to the level achieved after the third dose in the same individual.

(iii) Mass vaccination combined with EPI

Delivery via EPI to infants is supplemented with a mass vaccination campaign at the beginning of the intervention period and additional campaigns after five years.

Vaccine coverage

For vaccines delivered via EPI, the assumed coverage of full vaccination (three doses) corresponds to that reported in Tanzania for three doses of diphtheria tetanus pertussis–hepatitis B virus vaccine in the year 2003, which stood at 89%. The assumed dropout rate from the first to the third dose is 6% since coverage for the first dose of DTP-HBV vaccine was 95%. When booster doses are included, it is assumed that 99% of those that receive the third EPI dose will be given a booster dose 1, 2, 3 and 4 years after the last EPI dose. For mass vaccination the coverage levels of 30, 50 and 70% are simulated.

Case management model

As detailed in the companion article[14], the simulations of the effects of vaccine interventions use a case management model including both formal and informal

treatment, similar to a previous study of the authors[24]. An artemisinin-based combination therapy (ACT), artemether-lumefantrine, is used as first line treatment for uncomplicated malaria, as per recent policy changes, and the drug action model was modified accordingly, both in terms of the potential to reduce rates of severe disease, sequelae and death, and the impact on transmission intensity. The model assumes that 90% of patients comply with the ACT treatment schedule and have a cure rate of 85%, while in non-compliers there is no effect.

Measurement of health impact

The effect of vaccines is evaluated by simulating the malaria dynamics in a population of 100,000 people over a 10-year time horizon. For each of the seven vaccine options, and each delivery modality, the simulations start from a reference set of assumptions (Table 1 of the companion article[14]). Each of the 21 vaccine schemes is compared with the reference situation at six different transmission intensities to obtain cost effectiveness results for each of the 126 vaccine scenarios in preventing the following outcomes: uncomplicated episodes, severe episodes, deaths and DALYs.

Each simulation is repeated three times using different seeds to initialize the random number generator, and each of these simulations is compared with an independent simulation of a reference scenario: a control population with no vaccine, but with the same human demography, baseline transmission, and health system.

To estimate the number of disability adjusted life years (DALYs), years of life lived with disability are calculated on the basis of the duration of disability, and respective disability weights. Weights for different malaria attributable disease conditions have been obtained from the Global Burden of Disease (GBD) study[25]. DALYs are computed with no age weighting to follow standard cost-effectiveness practices[26]. The disability associated with anemia is assigned to the same time period as the malaria infections causing it.

Years of life lost (YLLs) and DALYs are calculated assuming age-specific life expectancies based on the life-table from Butajira, Ethiopia, with an average life expectancy of 46.6 years at birth[27]. This life-table represents that of an East African setting with low malaria transmission and is very similar to that for Hai District, a high altitude and low malaria prevalence site in Tanzania[28]. YLLs for

each simulated death are computed under the assumption that this life table would apply in the absence of malaria.

Vaccine delivery costs

The vaccine delivery costs are estimated using the methodology of a previous study by the authors[29], which was based on an ingredient approach requiring information on the quantities of physical inputs needed and their unit costs. The costs of introducing a malaria vaccine into the EPI in Tanzania include those related to an assumed range of vaccine purchase costs, and data collected from Tanzania on costs of distribution, cold chain, management, vaccine delivery by health facilities, training, and social mobilization[30] (Table 6.1). For booster doses, the per-dose delivery cost is assumed to be the same as that of routine EPI. The costs of vaccine campaigns are estimated by adding to the purchase costs, those costs associated with distribution, cold chain, management, specific programme activities, personnel, and other capital costs, estimated by a study in Tanzania on a campaign for Vitamin A supplementation[31] (Table 6.2).

Table 0.1 Vaccine delivery costs – routine EPI – US$ 2006

Item	*Source*	*Costs (US$)*		
Net vacc. purchase cost per dose	Derived	**1.23**	**2.45**	**12.25**
Vaccine price per dose		1	2	10
Freight	UNICEF estimates	0.0417	0.0417	0.0417
Wastage	WHO estimates	15%	15%	15%
Distribution per dose	[29]	**0.09**	**0.09**	**0.09**
Storage per dose	[29]	**0.03**	**0.03**	**0.03**
Management per dose	[29]	**0.003**	**0.003**	**0.003**
Delivery per dose	Derived	**0.13**	**0.13**	**0.13**
Syringes		0.06	0.06	0.06
Unit cost per dose	[30]	0.05	0.05	0.05
Freight	UNICEF estimates	0.0417	0.0417	0.0417
Wastage	WHO estimates	10%	10%	10%
Safety boxes		0.01	0.01	0.01
Unit cost per dose	[30]	0.0122	0.0122	0.0122
Freight	UNICEF estimates	0.0417	0.0417	0.0417
Wastage	WHO estimates	10%	10%	10%
Personnel facility level	[29]	0.06	0.06	0.06
Waste management				
Training over 5 years)	[29]	**0.03**	**0.03**	**0.03**
Social mobilization (av)	[29]	**0.12**	**0.12**	**0.12**
TOTAL COST PER DOSE	Derived	**1.63**	**2.86**	**12.66**

*adjusted for inflation

Table 0.2 Vaccine delivery costs – Campaign – US$ 2006

Item	*Source*	*Costs (US$)*		
Net vacc. purchase cost per dose	Derived	**1.23**	**2.45**	**12.25**
Vaccine price per dose		1	2	10
Freight	UNICEF estimates	0.0417	0.0417	0.0417
Wastage	WHO estimates	15%	15%	15%
Distribution per dose	[29]	**0.09**	**0.09**	**0.09**
Storage per dose	[29]	**0.03**	**0.03**	**0.03**
Management per dose	[29]	**0.003**	**0.003**	**0.003**
Delivery per dose	Derived	**0.07**	**0.07**	**0.07**
Syringes		0.06	0.06	0.06
Unit cost per dose	[30]	0.05	0.05	0.05
Freight	UNICEF estimates	0.0417	0.0417	0.0417
Wastage	WHO estimates	10%	10%	10%
Safety boxes		0.01	0.01	0.01
Unit cost per dose	[30]	0.0122	0.0122	0.0122
Freight	UNICEF estimates	0.0417	0.0417	0.0417
Wastage	WHO estimates	10%	10%	10%
Programme-specific costs		**0.07**	**0.07**	**0.07**
Allowances	[31]	0.1132	0.1132	0.1132
Fuel & Maintenance		0.0337	0.0337	0.0337
Fax & Telephone		0.0094	0.0094	0.0094
Refreshments		0.0058	0.0058	0.0058
Stationary & Postage		0.0056	0.0056	0.0056
Photocoping		0.0051	0.0051	0.0051
Transport		0.0050	0.0050	0.0050
Social mobilization		0.0048	0.0048	0.0048
Other		0.0005	0.0005	0.0005
Personnel cost		**0.42**	**0.42**	**0.42**
Government		0.3017	0.3017	0.3017
Non Government		0.1141	0.1141	0.1141
Capital cost		**0.07**	**0.07**	**0.07**
Vehicles		0.0410	0.0410	0.0410
Social mobilization		0.0156	0.0156	0.0156
Long term training & studies		0.0153	0.0153	0.0153
Other		0.0017	0.0017	0.0017
TOTAL COST PER DOSE	Derived	**1.98**	**3.20**	**13.01**

*adjusted for inflation

Potential cost savings of the interventions

The costs of treating those seeking health care for malaria episodes are calculated under the reference and the vaccine scenarios modeled. This allows calculation of expected cost savings associated with the introduction of an efficacious malaria vaccine. The case management cost inputs correspond to those published previously by the authors adjusted for inflation to 2007[24 32-36] (Table 6.3) and the first line treatment for uncomplicated malaria changed to an ACT (artemether/lumefantrine), for which the public sector price posted by WHO was used (Table 6.4).

The numbers of uncomplicated and severe malaria episodes averted due to vaccination are multiplied by the case management unit costs, as described above, to estimate the potential cost savings for both the health system and households. The cost savings are subtracted from the vaccine costs to compute the net costs of the interventions.

Table 0.3 Case management unit costs US$ 2006

	Costs (US$)	*Source*
Household average out of pocket costs per outpatient visit		
Travel costs	0.09	[32]
Medical supplies	0.03	[32]
Non medical supplies	0.22	[32]
Travel costs	0.09	[32]
Unit cost of outpatient visit	**0.7176**	**derived**
% of outpatient visits that take place at health centers	17%	[33]
% of outpatient visits that take place at dispensaries	72%	[33]
% of outpatient visits that take place at hospitals	10%	[33]
cost per outpatient visits at health centers	1.47	derived
cost per outpatient visits at dispensaries	1.18	derived
cost per outpatient visits at hospitals	2.54	derived
% of patients using Diagnostic Techniques	0.1	[34]
unit cost of Diagnostic Technique	0.3	[34]
% of outpatient visit cost that are recurrent	69%	[32]
% of outpatient visit cost that are fixed	0.25	[32]
Hospital costs of severe episodes		
Non drug cost per admission when patient fully recorvers	**14.4**	**derived**
Non drug cost per admission when patient recorvers with NS	**32**	**derived**
Non drug cost per admission when patient dies	**6.4**	**derived**
Non drug cost per day of stay	9.00	[36]
Capital	2.60	
Recurrent	6.40	
average length of stay when patient fully recovers	4.5	[37]
average length of stay when patient recovers with NS	10	[37]
average length of stay when patient dies	2	[37]
% of hospital cost that are recurrent	71.1	[35]
% of hospital recurrent costs that are fixed	50.0	[37]

Table 0.4 ACT costs

Age	*Cost/dose in $ (including 12% dist)*	*Cost per course in $ + 25% wastage*
<3 years - 5 to 14 Kg	1.008	1.260
3-9 years - 15 to 24 Kg	1.568	1.960
10-14 years 25 to 34 Kg	2.128	2.660
15+ years - Above 35 Kg	2.688	3.360

Source: http://www.who.int/malaria/cmc_upload/0/000/015/789/CoA_website5.pdf accessed 15 July 2008.

Calculating cost-effectiveness ratios and interpreting the results

The cost-effectiveness ratios presented are calculated for four health outcomes: uncomplicated and severe malaria episodes averted, DALYs averted, and deaths averted. Future costs and benefits are discounted at 3%. The cost-effectiveness ratios are presented for assumed vaccine prices of US$ 2 or US$ 10 per dose for all the vaccines and vaccine combinations. The results are presented as cost-effectiveness on a 10-year period.

The cost-effectiveness ratios are to be interpreted as incremental cost-effectiveness ratios of implementing the interventions in the simulated scenarios relative to a do-nothing scenario, which corresponds to maintaining only the case management model described above.

Accounting for uncertainty

The cost-effectiveness results are based on an advanced modeling methodology aimed at representing reality as accurately as possible. The large number of scenarios simulated includes some sensitivity analyses of results for key variables, for instance for vaccine efficacy levels. The likely impact on results of other key features of potential malaria vaccines is explored in the companion article[14].

However, many sources of uncertainty cannot be captured by these sensitivity analyses. Probabilistic sensitivity analysis and expected value of information analysis could serve to further assess the impact of uncertainty on the simulation results[38-41], but there are technical problems in implementing and presenting such analyses for a large set of interventions and scenarios. It has been, therefore, planned to run an expected value of information analysis on a sub-set of simulations that will be reported in another article.

6.3 Results

Pre-erythrocytic vaccines

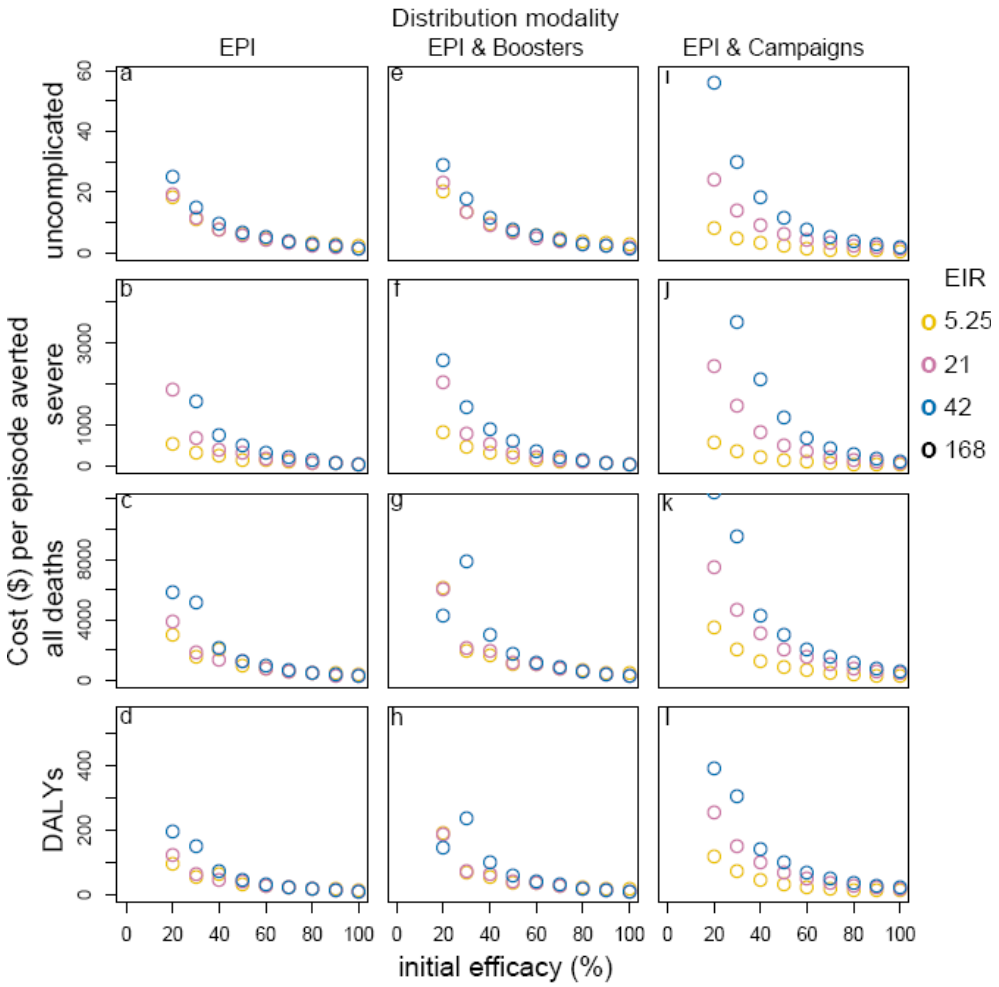
At a **reference transmission setting** with annual entomological inoculation rate (EIR) of 21, the simulations predict that a PEV with 52% initial efficacy could be very cost-effective when delivered via EPI alone. At a vaccine price of US$2 per dose, the cost per uncomplicated malaria episode averted would be around US$ 5, the cost per severe malaria episode averted US$ 269, the cost per DALY averted around US$ 35 and the cost per death averted US$1057 (see table 6.5 and 6.6, Annex). The cost-effectiveness ratios are lower for higher effectiveness levels (Figure 6.1). They increase almost proportionally with vaccine price reaching US$ 160 per DALY averted and US$ 4869 per death averted for a vaccine price of US$ 10 per dose (see table 6.7 and 6.8, Annex).

The proportion of events averted by PEV delivered via EPI with booster doses is slightly higher, but the cost per uncomplicated episode averted is 20% higher (see table 6.5, Annex), and cost per DALY and death averted is around 31% higher (see table 6.6, Annex).

With EPI and mass vaccination the proportion of events averted is 5% higher for mass vaccination coverage of 50% and 8% higher for coverage of 70%[14], and the cost per uncomplicated episode averted is slightly lower. However, the costs per DALY and death averted are around 60%-66% higher (see table 6.5 and 6.6, Annex). For higher efficacy levels the pattern is similar, showing that the incremental benefits of these deployment modalities, in this transmission setting, are modest (Figure 6.1).

Figure 0.1 Effect of initial efficacy on cost-effectiveness of PEV by transmission setting and delivery modality*

Results obtained assuming a vaccine half-life of 10 years, homogeneity value of 10, and vaccine price of US$2.
EPI & Campaigns means EPI with 70% mass vaccination.
*data for EIR in some cases are not shown in the figure due to a scale problem



In **low transmission settings**, while the cost per uncomplicated episode averted under EPI alone is similar to that in the reference transmission setting (see table 6.5 and 6.6, Annex), the cost per DALY and death averted are lower at US$ 31 per DALY averted and US$ 925 per death averted at a vaccine price of US$ 2 per dose (see table 6.6 and 6.8, Annex). Adding booster doses leads to higher cost-effectiveness ratios for efficacy levels up to around 60%, but at near 100% efficacy the cost-effectiveness ratios become similar (Figure 6.1). In contrast, when mass vaccination is added to EPI, the cost-effectiveness ratios decrease substantially, by around 70% for the cost per uncomplicated case averted (see

table 6.5 and 6.7, Annex), and by 24% to 28% for the cost per DALY and death averted (see table 6.6 and 6.8, Annex).

In **high transmission settings**, the effectiveness of PEV is low[14] and the cost-effectiveness ratios are therefore higher than in the other transmission settings irrespective of delivery modality. For some outcomes, vaccination even leads to an increase in the number of clinical events[14], and, therefore, to negative cost-effectiveness ratios and negative case management cost savings (see table 6.9, Annex).

Across all transmission settings, the incremental benefits of booster doses are small and the cost-effectiveness ratios are higher. Adding mass campaigns has little impact on overall effect when the primary efficacy is low. However, for high vaccine efficacy and high coverage, this strategy is predicted to lead to local elimination of the parasite in low transmission settings and substantially reduce transmission in medium transmission settings[14] at low additional costs. Under these conditions, because of the effects of the vaccine on transmission, delivery via mass campaigns plus EPI becomes a cost-effective alternative to EPI alone.

Blood-stage vaccines

At the **reference transmission intensity**, BSV of moderate efficacy with a price of US$ 2 per dose applied through EPI achieves a cost per uncomplicated episode averted of about US$ 9 (see table 6.5, Annex), which is higher than for the corresponding PEV, but the costs per DALY averted (US$ 21) and per death averted (US$ 630) are lower than for PEV (see table 6.6, Annex). At higher efficacy levels, the cost-effectiveness ratios decrease, following the same patterns as for PEV (Figure 6.2). Adding booster doses increases the cost-effectiveness ratios somewhat. Mass campaigns also increase the cost-effectiveness ratios except for uncomplicated episodes, where they decrease.

At **low transmission intensity** BSV averts a lower proportion of uncomplicated and severe cases and deaths than PEV[14] and the cost effectiveness ratios are higher for all outcomes. Adding booster doses leads to slightly higher costs per uncomplicated episode averted (see table 6.5 and 6.7, Annex), and much higher costs per DALY and death averted (see table 6.6 and 6.7, Annex, and Figure 6.2). Adding mass campaigns to EPI leads to a dramatic reduction in the cost per uncomplicated episode averted, but the costs per DALY and death averted are only slightly lower (see table 6.5, 6.6, 6.7, Annex, and Figure 6.3, 6.4).

Figure 0.2 Effect of initial efficacy on cost-effectiveness of BSV by transmission setting and delivery modality

Results obtained assuming a vaccine half-life of 10 years, homogeneity value of 10, and vaccine price of US$2.
EPI & Campaigns means EPI with 70% mass vaccination.

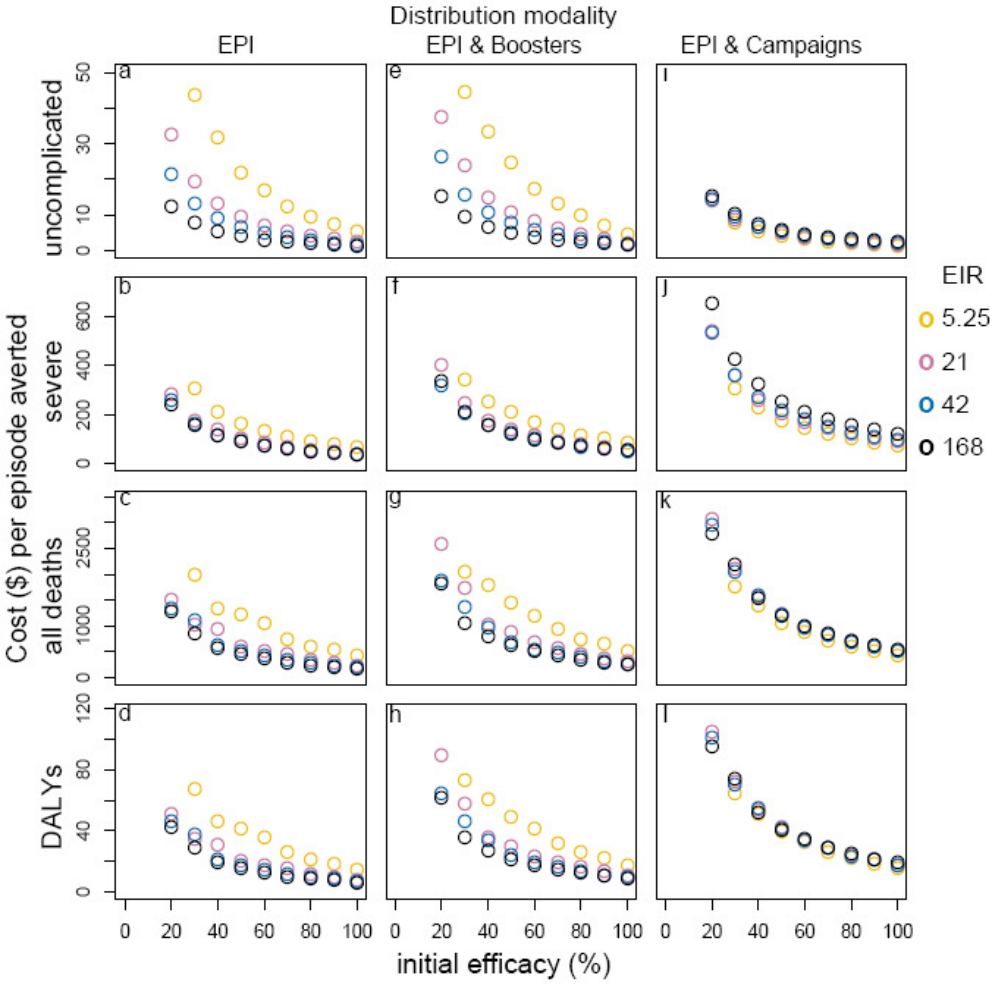


Figure 0.3 Effect of initial efficacy on cost-effectiveness of all vaccines delivered via EPI by transmission setting*

Results obtained assuming a vaccine half-life of 10 years and homogeneity value of 10, and vaccine price of US$2.
*data for EIR in some cases are not shown in the figure due to a scale problem

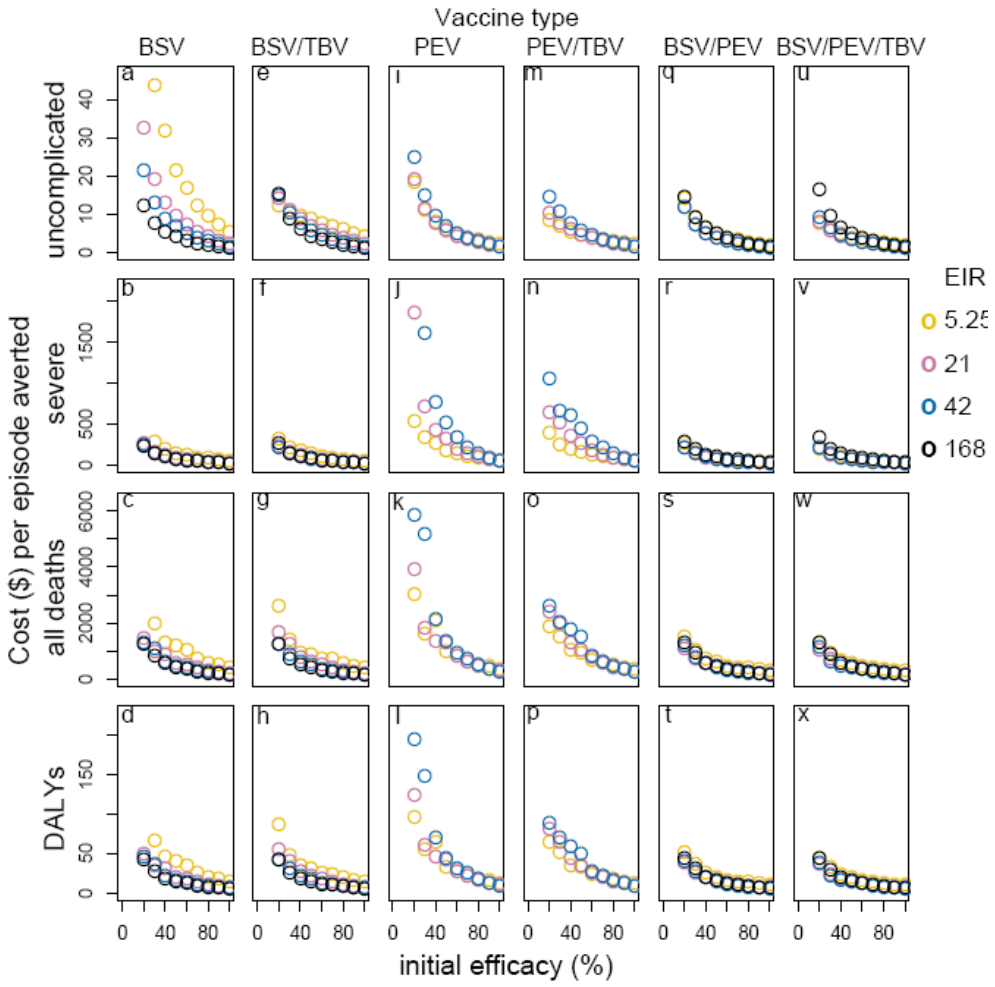
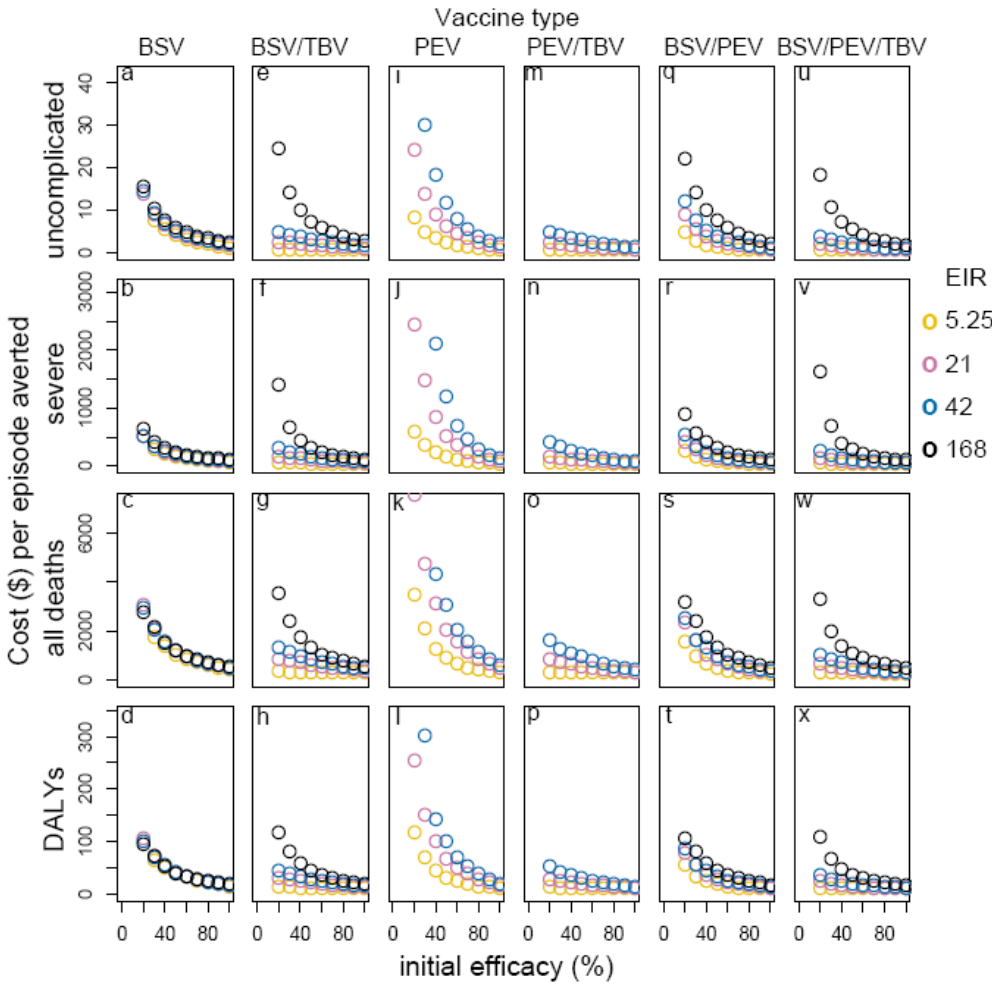


Figure 0.4 Effect of initial efficacy on cost-effectiveness of all vaccines delivered via EPI with 70-% mass vaccination by transmission setting*

Results obtained assuming a vaccine half-life of 10 years and homogeneity value of 10, and vaccine price of US$2.
*data for EIR in some cases are not shown in the figure due to a scale problem



In **high transmission settings** BSV is more effective than PEV especially in averting severe and mortality events[14] and it is also more efficient. Under EPI alone the cost per uncomplicated episode averted, in the highest transmission setting, is US$ 3.8, the cost per DALY averted is US$13.5 and the cost per death averted is US$401, at vaccine price US$ 2 per dose (see table 6.5 and 6.6, Annex, and Figure 6.3). Adding boosters or mass campaigns, leads to higher incremental costs than incremental benefits (see table 6.5, 6.6, 6.7, Annex, and Figure 6.2).

Across all transmission settings, the incremental costs of adding booster doses to EPI are higher than the incremental benefits and this is particularly true for severe episodes, DALYs, and mortality (see table 6.5, 6.6, 6.7, Annex, and Figure

6.2). In low transmission settings, campaigns improve cost-effectiveness for uncomplicated episodes averted, but do not change cost-effectiveness estimates for DALYs and deaths averted. However, in moderate to high transmission settings, the incremental costs of campaigns are higher than the incremental benefits (see table 6.5, 6.6, 6.7, Annex, and Figure 6.2).

Combination vaccines and MSTBV

Combining **BSV with PEV** (with matched efficacies) in general, improves or matches the cases averted over PEV alone for all transmission settings and vaccine delivery modalities[14]. The cost-effectiveness ratios for this combination are lower than those of PEV in all transmission settings particularly for the cost per DALY and per death averted and in moderate to high transmission settings (see table 6.5, 6.6, 6.7 in Annex, and Figure 6.3, 6.4). Compared to BSV alone, the cost-effectiveness ratios of combining BSV with PEV are lower, though the difference is smaller than for PEV and in this case it is higher in moderate to lower transmission settings than in high transmission settings. Adding booster doses to EPI leads to higher cost-effectiveness ratios across all transmission settings for this combination - the costs per uncomplicated episode averted increases by around 19%-23% while those per DALY and death averted show even larger increases (around 30%-40%).

Adding mass campaigns in low to moderate settings lead to incremental uncomplicated episodes averted that are higher than the incremental costs. However, in terms of DALYs and deaths averted the benefits exceed the costs only in the lowest transmission setting, while they are significantly lower in the reference and in high transmission settings. In high transmission settings even the additional uncomplicated episodes averted are lower than the additional costs.

Combinations of MS**TBV with PEV or BSV** and the **triple combination** do not improve the effectiveness of the vaccines alone when delivered via EPI or EPI with boosters[14]. However, adding mass campaigns leads to greater effectiveness in all transmission settings (Figure 6.4). The additional benefits of these combination vaccines are then much higher than the additional costs compared to delivering the vaccines under EPI alone and to all delivery modalities of PEV and BSV alone. In the reference transmission setting, for instance, the cost per uncomplicated episode averted of combining BSV with MSTBV, delivered via EPI and mass campaigns, is (at a vaccine price of US$2) US$1.8 and US$2.3 for 70% and 50% coverage (see table 6.5, Annex), while the cost per DALY averted is US$20 and US$ 22 for 70% and 50% coverage (see table 6.6, Annex). The

costs per DALY averted vary between US$ 12 and US$40 across transmission settings with the lowest value in the lowest transmission setting where the greatest improvement to effectiveness is observed. The very favourable cost-effectiveness ratios in low transmission settings are related to the case-management cost savings, which may compensate up to more than 50% of the costs of the vaccine intervention (see table 6.8, Annex).

Effect of delivery modalities

Adding boosters to EPI does not improve effectiveness or cases averted over EPI alone by very much even at the very high coverage level modeled, but it does incur additional costs. This delivery modality does therefore not represent a cost-effective alternative to EPI alone in any scenario (see table 6.5, 6.6, 6.7, Annex).

Delivering all vaccines and combinations via population based campaigns improves the effectiveness at mass vaccination coverage of 50%, especially in low transmission settings[14]. Depending on the transmission setting and the vaccine type considered, the incremental costs of delivering vaccines via population based campaigns can be lower than the incremental benefits, leading to a significant reduction in the cost-effectiveness ratios (see table 6.5, 6.7, 6.8, Annex, and Figure 6.4). Disseminating vaccines via population-based campaign in these cases is predicted to be a more cost-effective way of delivering malaria vaccines than EPI alone. Increasing the coverage of the mass vaccination campaigns increases the effectiveness and cases averted for all vaccine and vaccine combinations under most transmission settings[14]. However, the incremental benefits of increasing coverage are often lower than the incremental costs of achieving it (Figure 6.5). In some cases, the predictions suggest an optimal cost-effectiveness ratio at intermediate values for the campaign coverage. This is not a consequence of non-proportionality of vaccine delivery costs as a function of coverage (which could be realistic, but not modeled in this study), but of the indirect effects of the vaccines.

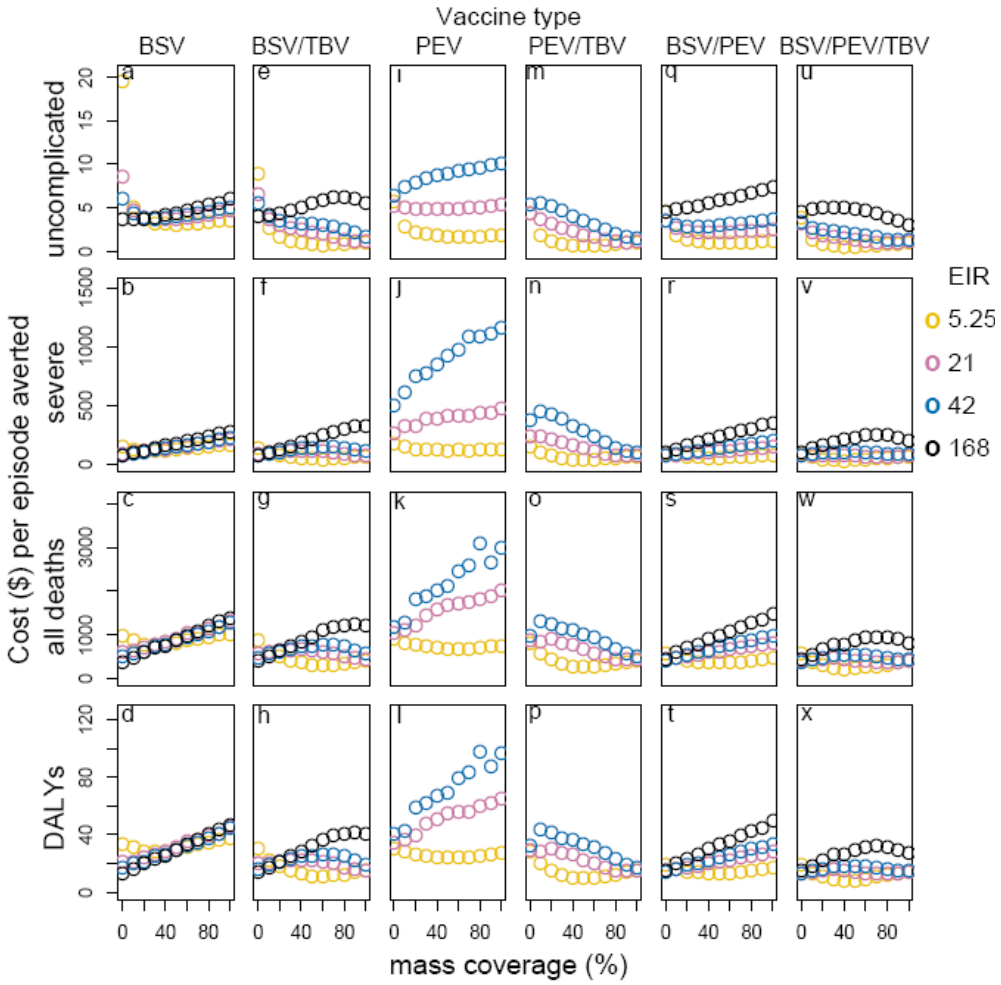
Effect of vaccine price

Although the simulations focus on comparative cost-effectiveness of different candidate malaria vaccines and delivery modalities, and not on the sensitivity of cost-effectiveness ratios to vaccine prices, which are hypothetical, it is evident that the cost-effectiveness results are almost directly proportional to the vaccine prices. In fact, at an assumed vaccine price of US$ 10 per dose, most cost-effectiveness ratios are between 4 and 7 times higher than those obtained at US$ 2 per dose (see table 6.5, 6.6, 6.7, Annex). At a vaccine price of US$ 2 per dose,

most vaccines and delivery modalities simulated present cost-effectiveness ratios comparable to those of other malaria interventions[9 10 37 42 43], while at a vaccine price of US$ 10 per dose in many of the simulated scenarios the cost-effectiveness ratios are higher.

Figure 0.5 Cost-effectiveness of vaccines given different levels of mass vaccination coverage by transmission setting*

Results obtained assuming a vaccine half-life of 10 years and homogeneity value of 10, and vaccine price of US$2.
*data for EIR in some cases are not shown in the figure due to a scale problem



6.4 Discussion

CEA is a method for evaluating the relative efficiency of alternative interventions and thus can provide important information for assessing the potential implications of the numerous malaria vaccine candidates. This study used stochastic simulations of *P. falciparum* malaria epidemiology, combined with a case management model, to simulate the cost-effectiveness of potential malaria vaccines under various transmission settings and delivered via different modalities. This is an extension of previous research on pre-erythrocytic vaccines delivered via the EPI[12].

The simulations presented suggest that the cost-effectiveness of candidate malaria vaccines is likely to differ substantially according to the transmission intensity and to the delivery modality adopted. They also suggest that alternative vaccine delivery modalities to the EPI may sometimes, but not always, be more cost-effective than the EPI. In general, at moderate vaccine prices, most vaccines and delivery modalities simulated are likely to present cost-effectiveness ratios, which compare favourably with those of other malaria interventions[37 42 43], making them potential attractive malaria control strategies, from an economic perspective, in malaria endemic countries.

These simulations have various limitations, as described in the companion article on the epidemiological effects[14]. For the economic analysis, one of the most important limitations is related to the relatively simple case management model used to assess the impact of malaria vaccines on the costs to the health system and to patients. As the case management model used is the same for all scenarios simulated, the relative cost-effectiveness of the vaccines modeled, and, therefore, the comparisons, should only be slightly affected by it. However, further research and modeling of health system characteristics in malaria endemic settings is required. Additionally, the vaccine delivery modalities modeled may not be feasible to implement in all settings as the coverage and the effectiveness of malaria vaccines is likely to depend strongly on the characteristics of the health systems where they will be implemented, including any other malaria intervention being delivered. For instance, the simulations assumed an EPI coverage rate of 89%, which is probably higher than found in some malaria-endemic countries. Lower EPI coverage rates could have an impact on the comparisons between different delivery modalities.

Other limitations of this study include that the comparisons of malaria vaccines – or of combinations of them- with different characteristics, are based on the same assumed vaccine price. In practice, the price might vary according to the characteristics of the vaccines, in particular for combinations of vaccines. This

might be important for the result that MSTBV combinations were more efficient than vaccines without MSTBV, especially when delivered via EPI with mass campaigns.

While modeling the costs of different vaccine delivery modalities, the fact that vaccine delivery costs might vary as a function of coverage (as it is the case for other interventions[44 45]) was not taken into account. This aspect was not considered due to the lack of solid evidence on vaccine delivery costs by coverage levels, especially for mass campaigns.

Despite these limitations, the simulations presented provide interesting information for vaccine developers on the potentials of different candidate malaria vaccines. Previous simulation of the cost-effectiveness of PEV[12] suggested that at moderate to low vaccine prices, a vaccine providing partial protection, and delivered via the EPI, may be a cost-effective intervention in countries where malaria is endemic. The simulations presented in this article, also show that these types of vaccines are more effective and cost-effective in low transmission settings, and that the additional costs of delivering a PEV under other modalities than the EPI are likely to be higher than the additional health benefits. The only exception is for the scenario of mass vaccination (added to routine EPI) in low transmission and for high vaccine efficacies and high coverage. In contrast to PEV, BSV are predicted to be more effective and cost-effective at higher transmission settings than low transmission.

Combinations of BSV and PEV are predicted to be more efficient than PEV, in particular in moderate to high transmission settings, but compared to BSV, combinations are more cost-effective in mostly moderate to low transmission settings. The cost-effectiveness ratios of the other delivery modalities simulated are higher than those for EPI alone in almost all scenarios, with the exception of adding mass campaigns to EPI in the lowest transmission setting.

Combinations of MSTBV and PEV or PEV and BSV do not increase the effectiveness or the cost-effectiveness compared to PEV and BSV alone when delivered through the EPI (including with the addition of booster doses). However, when applied with EPI and mass vaccinations, combinations with MSTBV provide substantial incremental health benefits and low incremental costs in all transmission settings. These combination vaccines are therefore predicted to be interesting only for the settings where mass vaccination achieving relatively high coverage rates would be feasible.

According to these simulations, adding booster doses to the EPI is unlikely to be a cost-effective alternative to delivering vaccines via the EPI for any vaccine and transmission setting – i.e. the incremental health benefits are rather low despite the additional costs.

Mass vaccination improves effectiveness, especially in low transmission settings, and in some scenario the cost-effectiveness ratios compare favourably with those of delivering the vaccine via the EPI only - the incremental costs are lower than the incremental health benefits. However, increasing the coverage of mass vaccination over 50%, often leads to incremental costs that exceed the incremental health benefits. In some scenarios, the lowest cost-effectiveness ratios are reached at intermediate coverage rates of campaigns. This result is particularly relevant as it is due to the indirect effect of the vaccines, and not to the increasing vaccine delivery costs of achieving high coverage rates.

In some of the mass vaccination scenarios the simulations predict that local elimination of the parasite would be, in principle, possible. In some of these cases, at moderate vaccine prices, the simulations also predict that the cost-effectiveness ratios of achieving local elimination might be relatively low despite the fact that often the incremental costs of achieving high vaccine coverage are higher than the incremental benefits. However, the cost-effectiveness analyses of these simulations include only part of the economic implications of malaria elimination.

If local elimination were feasible, it might be desirable to achieve high vaccine coverage rates even if the incremental costs are high (compared to the incremental health benefits) as elimination would bring future benefits, however to sustain elimination over time, once elimination is achieved there would be a need for strong surveillance and case detection, which would incur substantial additional costs that are not included in our simulations. An assessment of the economic implications of achieving and sustaining local elimination is planned in the next stage of the project.

6.5 Conclusions

The simulations presented supports that cost-effectiveness analyses of candidate malaria vaccines may help guide policy makers and vaccine developers, by providing additional evidence that malaria vaccines may be efficient malaria control interventions. The results also indicate that the transmission setting and the vaccine delivery modality adopted are important determinants of the cost-effectiveness of malaria vaccines. While adding booster doses to the EPI is not a cost-effective alternative to the EPI, mass vaccination is predicted to provide substantial health benefits, in particular in low transmission settings, at low additional costs making such a delivery mode, in principle, attractive and feasible, and in some cases lead to local elimination. Nevertheless, achieving high coverage rates can lead to substantial incremental costs compared to the health

benefits, while intermediate coverage rates may be a more efficient use of the resources.

While modeling studies such as this one are useful for exploring the potential impact of malaria vaccines at early stages of development, vaccine development and implementation decisions should be also informed by cost-effectiveness studies carefully tailored to the settings where the vaccines are likely to be adopted.

Ultimately, the relative efficiency of malaria vaccines will depend not only on the characteristics of them but also on the other malaria control interventions implemented. As malaria vaccines will eventually be deployed as part of integrated control strategies, the costs and effects of the interactions of vaccine programmes with those of other malaria control interventions should also be evaluated.

6.6 Annex

Table 0.5 Cost-effectiveness of different vaccination strategies in US$ per clinical event averted for a range of initial transmission intensities - a vaccine purchase price of 2 US$ per dose is assumed.

		Uncomplicated episodes					Severe episodes				
	EIR	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign
BSV	5.25	19.7	22.3	3.3	3.1	3.3	156.5	200.0	152.9	136.4	128.4
	21	8.7	10.0	4.1	3.8	3.8	99.4	130.9	183.4	155.8	131.4
	84	4.6	5.6	4.7	4.2	3.9	84.5	116.0	209.6	170.8	137.8
	168	3.8	4.7	5.1	4.5	4.0	85.8	117.3	226.4	187.3	147.8
BSV TBV	5.25	8.9	10.2	0.8	0.8	1.3	143.4	176.1	60.3	56.7	75.0
	21	6.6	7.8	1.8	2.3	2.7	97.9	126.2	111.3	124.2	120.7
	84	4.6	5.6	4.3	4.3	4.1	84.1	116.5	217.7	186.1	146.8
	168	4.1	5.1	6.2	5.6	4.8	87.5	122.8	284.3	224.1	162.4
PEV	5.25	5.8	6.8	1.8	1.8	2.0	191.8	228.3	129.2	128.5	135.0
	21	5.3	6.3	5.1	4.9	4.9	268.8	341.9	426.6	421.2	393.9
	84	9.9	10.8	26.9	24.7	21.0	neg.	4'911.5	neg.	neg.	8'964.9
	168	29.2	26.7	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
PEV TBV	5.25	4.4	5.6	0.8	0.7	0.9	162.1	206.9	59.6	49.3	65.2
	21	4.5	5.3	1.4	2.0	2.8	243.6	272.0	99.7	148.2	202.7
	84	8.4	9.2	5.0	7.6	10.4	4'436.7	2'339.1	514.0	1'209.2	5'559.8
	168	25.0	22.5	12.7	29.7	116.0	neg.	neg.	neg.	neg.	neg.
BSV PEV	5.25	4.7	5.8	1.1	1.0	1.2	102.4	130.8	72.5	67.1	69.0
	21	3.6	4.4	2.3	2.2	2.3	82.9	106.9	136.3	122.8	106.9
	84	3.9	4.7	4.6	4.2	3.9	94.7	121.7	225.0	189.2	155.2
	168	4.7	5.6	6.5	5.9	5.4	112.1	147.3	292.3	244.5	196.4
BSV PEV TBV	5.25	3.9	4.9	0.8	0.6	0.7	97.1	122.3	57.2	44.4	44.4
	21	3.3	4.1	1.0	1.3	1.7	81.0	102.7	72.1	83.6	90.2
	84	3.8	4.6	2.8	3.2	3.4	93.5	122.8	167.2	169.7	151.7
	168	4.7	5.5	4.4	5.0	5.2	112.2	144.9	257.9	239.4	201.5

Table 0.6 Cost-effectiveness of different vaccination strategies in US$ per DALYs and deaths averted for a range of initial transmission intensities - A vaccine purchase price of 2 US$ per dose is assumed.

		DALYs					Deaths				
	EIR	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign
BSV	5.25	33.6	47.4	33.7	29.6	29.0	976.4	1'380.7	923.7	817.9	804.9
	21	21.4	25.6	36.8	31.8	26.7	629.7	755.6	1'073.3	921.2	783.5
	84	14.8	20.3	36.7	31.2	24.0	436.0	601.3	1'084.1	922.4	708.3
	168	13.5	19.3	37.4	29.9	23.8	400.9	572.6	1'106.4	886.0	707.8
BSV TBV	5.25	30.6	39.9	11.9	11.6	15.4	880.5	1'146.9	329.2	323.0	433.9
	21	20.3	26.2	20.1	22.6	22.7	591.8	770.9	593.4	666.0	669.9
	84	14.7	20.9	33.4	30.6	24.1	435.9	618.9	995.8	912.7	714.5
	168	14.1	19.3	39.8	32.6	25.5	417.6	572.1	1'187.8	970.5	757.9
PEV	5.25	31.1	41.7	24.6	24.3	25.7	925.6	1'219.3	695.5	697.2	752.5
	21	34.8	45.9	56.9	55.7	47.9	1'057.4	1'382.6	1'748.6	1'707.2	1'467.0
	84	63.7	109.7	182.3	134.7	122.8	1'936.7	3'328.2	5'675.0	4'173.4	3'910.5
	168	302.6	140.8	8'658.1	325.2	438.0	15'601.5	4'279.4	neg.	11'050.7	15'568.2
PEV TBV	5.25	28.5	37.5	11.6	9.9	12.8	834.9	1'101.5	321.1	275.4	362.0
	21	29.7	36.3	17.1	22.9	27.8	904.2	1'084.0	508.1	691.1	840.3
	84	61.7	70.2	49.2	56.9	74.3	1'867.9	2'095.4	1'511.9	1'738.7	2'280.4
	168	422.5	353.9	95.1	163.1	277.3	20'445.9	19'392.0	2'967.8	5'400.1	9'418.8
BSV PEV	5.25	19.7	27.6	14.5	13.4	14.2	581.3	825.4	402.1	373.4	400.1
	21	15.1	19.5	24.3	21.5	18.8	445.6	579.0	717.3	638.0	555.0
	84	15.3	19.9	33.7	28.7	23.9	455.9	591.2	1'004.5	860.3	712.0
	168	15.2	20.7	40.1	33.4	27.1	453.1	615.5	1'196.4	998.7	804.9
BSV PEV TBV	5.25	20.0	25.3	11.0	8.7	8.9	586.5	742.4	303.3	241.4	249.8
	21	13.8	18.1	12.9	14.7	16.2	409.2	535.6	379.1	433.0	482.5
	84	14.6	18.6	24.4	24.0	22.4	434.5	552.5	731.7	717.7	668.5
	168	15.5	20.4	32.4	29.8	26.5	463.1	606.1	974.9	892.4	792.7

Table 0.7 Cost-effectiveness of different vaccination strategies in US$ per clinical event averted for a range of initial transmission intensities - a vaccine purchase price of 10 US$ per dose is assumed.

		Uncomplicated					Severe episodes				
	EIR	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign
BSV	5.25	91.6	102.8	15.2	14.7	15.7	729.5	923.2	702.6	635.6	605.7
	21	41.8	47.4	18.5	17.5	17.6	477.1	618.2	821.3	709.1	609.8
	84	22.6	27.0	20.9	19.1	17.9	414.7	555.0	926.3	767.7	633.6
	168	18.8	22.7	22.3	19.9	18.1	421.0	562.1	995.5	836.3	675.9
BSV TBV	5.25	42.2	47.7	4.6	4.7	6.8	677.5	823.4	330.1	313.2	386.1
	21	31.8	37.0	8.4	10.8	12.8	471.7	599.0	522.5	576.0	564.2
	84	22.7	26.9	19.0	19.3	18.7	412.2	556.6	954.2	828.2	668.4
	168	20.1	24.4	27.0	24.7	21.6	427.6	585.4	1'230.0	986.0	733.2
PEV	5.25	27.2	31.7	8.5	8.5	9.6	897.2	1'061.4	613.7	613.9	643.0
	21	24.4	28.9	21.7	21.2	21.4	1'238.0	1'564.3	1'835.1	1'824.9	1'725.9
	84	43.9	47.8	111.8	103.3	88.9	neg.	21'797.5	neg.	neg.	37'938.5
	168	126.8	117.0	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
PEV TBV	5.25	21.0	26.4	4.5	4.0	5.0	768.7	967.4	328.0	285.0	351.8
	21	20.9	24.6	6.7	9.2	12.5	1'129.4	1'253.8	479.0	680.6	914.0
	84	37.4	41.0	21.5	31.9	43.9	19'645.3	10'396.4	2'186.7	5'107.2	23'544.5
	168	108.3	98.1	52.8	122.7	483.9	neg.	neg.	neg.	neg.	neg.
BSV PEV	5.25	22.7	27.4	5.6	5.5	6.2	495.9	623.7	378.6	355.1	361.4
	21	17.8	21.3	10.8	10.4	10.7	406.5	513.2	624.3	569.9	504.3
	84	18.9	22.4	20.1	18.7	17.7	456.8	577.5	983.9	838.5	701.3
	168	22.3	26.1	28.1	25.7	23.8	532.4	689.9	1'261.7	1'068.4	873.9
BSV PEV TBV	5.25	19.1	23.7	4.4	3.7	4.0	475.2	586.7	318.4	265.2	262.9
	21	16.2	19.6	5.2	6.6	8.2	398.4	495.3	365.8	409.3	435.4
	84	18.2	21.7	12.3	14.2	15.6	450.7	581.8	745.0	756.6	685.9
	168	22.2	25.9	19.2	21.9	23.0	532.1	678.8	1'117.7	1'044.5	892.5

Table 0.8 Cost-effectiveness of different vaccination strategies in US$ per DALYs and deaths averted for a range of initial transmission intensities - a vaccine purchase price of 10 US$ per dose is assumed.

		DALYs					Deaths				
	EIR	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign
BSV	5.25	156.7	218.8	154.9	138.1	136.6	4'550.1	6'371.6	4'244.1	3'811.6	3'797.5
	21	102.5	121.1	164.8	144.5	123.7	3'022.8	3'567.7	4'807.3	4'191.1	3'635.6
	84	72.5	97.2	162.1	140.1	110.2	2'140.5	2'877.6	4'792.2	4'146.7	3'257.2
	168	66.4	92.4	164.3	133.4	108.7	1'968.1	2'745.1	4'864.2	3'956.9	3'236.2
BSV TBV	5.25	144.3	186.3	65.2	64.3	79.5	4'158.8	5'361.1	1'801.3	1'782.5	2'233.9
	21	97.6	124.6	94.4	104.6	106.3	2'851.7	3'660.0	2'786.3	3'087.3	3'131.1
	84	72.2	99.9	146.3	136.3	109.9	2'136.7	2'958.4	4'365.6	4'061.3	3'253.3
	168	68.9	91.8	172.3	143.6	115.1	2'042.0	2'727.9	5'139.1	4'271.0	3'421.6
PEV	5.25	145.7	193.7	116.8	116.0	122.6	4'328.7	5'669.8	3'304.2	3'329.5	3'583.2
	21	160.2	210.2	244.7	241.2	209.9	4'869.9	6'327.3	7'522.9	7'396.8	6'429.6
	84	281.9	486.8	757.8	563.1	518.3	8'564.8	14'776.1	23'590.3	17'448.8	16'506.1
	168	1'314.1	616.9	35'637.1	1'344.9	1'827.5	67'815.3	18'744.6	neg.	45'698.5	64'956.9
PEV TBV	5.25	135.3	175.6	63.9	57.4	69.0	3'958.6	5'151.2	1'768.3	1'593.7	1'952.6
	21	137.8	167.3	82.2	105.3	125.3	4'193.4	4'996.4	2'441.7	3'174.4	3'788.9
	84	273.2	312.4	209.2	240.2	315.2	8'274.7	9'330.0	6'433.3	7'345.5	9'671.0
	168	1'829.4	1'545.4	394.7	674.7	1'155.2	88'498.2	84'676.3	12'317.4	22'343.9	39'230.8
BSV PEV	5.25	95.5	131.4	75.8	71.0	74.3	2'813.1	3'934.7	2'098.9	1'974.8	2'095.1
	21	74.2	93.8	111.2	100.0	88.6	2'185.5	2'780.8	3'285.9	2'961.3	2'618.3
	84	74.0	94.5	147.2	127.3	108.0	2'200.0	2'806.4	4'393.0	3'812.9	3'216.3
	168	72.1	97.1	173.1	146.2	120.4	2'151.6	2'883.4	5'164.4	4'364.3	3'581.7
BSV PEV TBV	5.25	97.9	121.2	61.1	52.2	52.9	2'869.6	3'560.7	1'689.1	1'442.9	1'477.8
	21	68.0	87.4	65.6	71.7	78.2	2'013.4	2'583.7	1'922.0	2'119.2	2'329.1
	84	70.2	88.2	108.9	106.9	101.1	2'094.7	2'617.3	3'260.0	3'199.3	3'022.8
	168	73.7	95.5	140.3	130.0	117.5	2'196.0	2'838.8	4'225.6	3'894.2	3'511.0

Table 0.9 Net cost and cost savings of different vaccination strategies - A vaccine purchase price of 2 US$ per dose is assumed –values discounted at 3%

		Net cost					Cost savings				
	EIR	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign	EPI	EPI booster	EPI 70% campaign	EPI 50% campaign	EPI 30% campaign
BSV	5.25	392.9	554.8	1'119.2	898.4	685.5	27.0	30.7	144.5	125.3	96.7
	21	378.3	539.6	1'156.0	925.0	699.7	41.3	46.5	107.3	97.2	82.0
	84	367.6	530.3	1'175.9	939.8	707.8	51.8	55.6	87.4	82.8	74.0
	168	368.0	529.5	1'184.2	947.1	712.2	51.8	56.7	79.1	74.8	68.6
BSV TBV	5.25	386.5	545.6	899.6	726.4	613.8	33.6	39.6	363.8	295.4	167.8
	21	376.7	535.2	1'088.4	902.9	692.8	43.1	50.3	174.9	119.1	88.4
	84	368.7	531.2	1'188.6	951.0	716.4	51.1	54.8	74.8	70.3	64.8
	168	369.6	532.5	1'209.0	964.9	724.5	50.0	53.1	54.3	56.6	57.0
PEV	5.25	390.6	550.1	1'072.3	870.3	677.3	28.8	35.9	191.0	152.7	104.7
	21	398.4	561.3	1'217.4	984.7	752.9	21.0	24.6	45.3	37.0	28.8
	84	420.3	583.5	1'274.3	1'033.0	790.7	(0.5)	2.2	(11.0)	(10.3)	(8.5)
	168	431.3	594.1	1'289.8	1'046.6	803.0	(11.6)	(8.4)	(27.3)	(25.5)	(20.9)
PEV TBV	5.25	384.0	546.1	892.6	686.0	579.4	35.4	39.9	370.9	336.2	202.1
	21	395.3	556.0	1'056.4	914.5	724.9	24.5	29.7	206.3	108.5	55.7
	84	419.5	581.1	1'235.0	1'017.9	785.8	0.3	4.4	27.7	3.9	(4.1)
	168	430.8	596.3	1'276.4	1'046.4	804.0	(11.1)	(10.4)	(13.4)	(24.1)	(21.6)
BSV PEV	5.25	374.8	532.6	952.3	765.7	601.2	45.5	53.1	310.1	256.6	180.6
	21	368.5	528.1	1'122.8	901.7	684.2	51.4	57.9	140.2	120.5	96.4
	84	376.1	535.8	1'192.4	956.4	723.2	43.9	50.1	71.0	65.4	57.5
	168	383.4	545.2	1'212.5	974.1	738.7	36.0	41.0	50.6	47.8	43.3
BSV PEV TBV	5.25	369.8	529.2	880.8	659.8	518.0	50.3	57.1	383.2	362.8	263.7
	21	366.8	525.4	987.6	842.2	664.6	52.9	61.0	275.1	178.8	115.9
	84	376.3	536.7	1'163.1	949.3	722.0	43.4	48.7	99.4	72.5	58.3
	168	384.4	545.4	1'206.1	977.1	742.8	35.4	41.0	57.1	46.1	39.1

The total cost is the net cost of the intervention, considering the cost savings due to the aversion of clinical episodes as shown in the right-hand side of the table. Negative numbers indicate higher costs (for case management) in the intervention scenario. The numbers are given per 1000 simulated person-years.

6.7 References

1. Snow R, Guerra C, Noor A, Myint H, Hay S. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature* 2005;434(7030):214-217.

2. Greenwood B, Bojang K, Whitty C, Targett G. Malaria. *Lancet* 2005:1487-1498.

3. Breman JG, Alilio M, Mills A. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. *Am J Trop Med Hyg* 2004;71 (2 Suppl)(2 Suppl):1-15.

4. Bojang K MP, Pinder M, Vigneron L, Alloueche A, Kester KE, Ballou WR, Conway D, Reece WHH, Gothard P, Yamuah L, Delchambre M, Voss G, Greenwood BM, Hill A, McAdam KP, Tornieporth N, Cohen JD, Doherty T. Efficacy of RTS,S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: a randomised trial. *Lancet* 2001;358:1927-1934.

5. Alonso P, Sacarlal J, Aponte J, Leach A, Macete E, Milman J, et al. Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomised controlled trial. *Lancet* 2004;364(9443):1411-1420.

6. Edejer Tan Torres T. Improving the use of research evidence in guideline development: 11. Incorporating considerations of cost-effectiveness, affordability and resource implications. *Health Res Policy Syst.* 2006;Dec 5;4:23.

7. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes.* New York: Oxford University Press. Second edition, 1997.

8. Gold M, Gold S, Weinstein M. *Cost-effectiveness in health and medicine.* Oxford: Oxford University Press, 1996.

9. Goodman C, Mills A. The evidence base on the cost-effectiveness of malaria control measures in Africa. *Health Policy Plan* 1999;14(4):301-12.

10. Goodman CA, Coleman PG, Mills A. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999;354(9176):378-385.

11. Maire N, Tediosi F, Ross A, Smith T. Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the expanded program on immunization in sub-Saharan Africa. *Am.J.Trop.Med.Hyg.* 2006;75(2 Suppl):111-118.

12. Tediosi F, Hutton G, Maire N, Smith TA, Ross A, Tanner M. Predicting the cost-effectiveness of introducing a pre-erythrocytic malaria vaccine into the expanded program on immunization in Tanzania. *Am J Trop Med Hyg.* 2006;75(2 Suppl):131-143.

13. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, et al. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: Overview. *Am.J.Trop.Med.Hyg.* 2006;75(2 Suppl):1-10.

14. Penny M, Maire N, Studer A, Smith T. What should Vaccine Developers Ask? Simulation of the Effectiveness of Malaria Vaccines *PLoS ONE* 2008;3 (9):e3193.

15. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, et al. *Making choices in health: WHO guide to cost-effectiveness analysis*: World Health Organization, Geneva, 2003.

16. Olsen JA Richardson J. Production gains from health care: what should be included in cost-effectiveness analyses? *Soc Sci Med.* 1999;Jul; 49(1):17-26.

17. Drummond M, O'Brien B, Stoddart GL, Torrance G. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1997.

18. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic sumissions to the BMJ *BMJ* 1996;313(3 August):275-283.

19. Luce BR, Elixhauser A. Estimating costs in the economic evaluation of medical technologies. *International Journal of Technology Assessment in Health Care* 1990;6:57-75.

20. Weinstein M, Siegel J, Gold M, Kamlet M, Russell L. Recommendations of the panel of cost-effectiveness in medicine. *JAMA* 1996;276(15):1253-1341.

21. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice of decision analytic modeling in health care evaluation: Report of the ISPOR Task Force on Good Research Practices-Modeling Studies. *Value Health* 2003;6:9-17.

22. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, Molineaux L. A model for natural immunity to asexual blood stages of Plasmodium falciparum malaria in endemic areas. *Am J Trop Med Hyg* 2006;75(2 Suppl):19-31.

23. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, et al. Towards a comprehensive simulation model of malaria epidemiology and control. *Parasitology* 2008;Aug 11:1-10.

24. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, et al. An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa. *Am.J.Trop.Med.Hyg.* 2006;75(2 Suppl):90-103.

25. Murray CJL, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Harvard: Harvard University Press, 1996.

26. Fox-Rushby J, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy Plan* 2001;16:326-331.

27. Indepth Network. *Model Life Tables for Sub-Saharan Africa*. Aldershot, England: Ashgate, 2004.

28. Indepth Network. *Population, Health and Survival at INDEPTH Sites*. Ottawa: IDRC, 2002.

29. Hutton G, Tediosi F. The costs of introducing a malaria vaccine through the expanded program on immunization in Tanzania. *Am.J.Trop.Med.Hyg.* 2006;75(2 Suppl):119-130.

30. Msd. Medical Store Department price Catalogue 2006. http://www.msd.or.tz., 2006.

31. Most. Cost analysis of the national twice-yearly vitamin A supplementation program in Tanzania. Arlington VA: USAID, 2005.

32. Adam T, Kakundwa C, Manzi F, Schellenberg JA, Mgalula L, de Savigny D, et al. Analysis report on the costs of IMCI in Tanzania. Multi-country evaluation of the Integrated Management of Childhood Illness (IMCI). , World Health Organization. Geneva: Department of Child and Adolescent Health and Development, World Health Organisation, 2004.

33. National Malaria Control Program. Global Fund 4th round Proposal. Introducing Artemisin Combination Therapy in Tanzania. 2004.

34. National Malaria Control Programme. Monitoring Malaria Situation and Control Activities in Tanzania 2001–2003. Health Facility and Community Survey. In: Dar es Salaam TNMCPMaE, Programme. UNMC, editors, 2004.

35. Health Research for Action. Health care financing in Tanzania: Costing study of health services. Final Report. Laarstraat, Belgium, 1999.

36. Alonso-Gonzalez M, Menendez C, Font F, Kahigwa E, Kimario J, Mshinda H, et al. Cost-effectiveness of iron supplementation and malaria chemoprophylaxis in the prevention of anaemia and malaria among Tanzanian infants. *Bull World Health Organ* 2000;78(1):97-107.

37. Goodman CA, Coleman PG, Mills A. *Economic analysis of malaria control in sub-Saharan Africa*. Geneva: Global Forum for Health Research, 2000.

38. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics.* , 2008:781-98.

39. Brennan A Kharroubi S O'hagan A Chilcott J. Calculating partial expected value of perfect information via Monte Carlo sampling algorithms. *Med Decis Making.* , 2007:448-70.

40. Fenwick E Claxton K Sculpher MJ Briggs AH. Improving the efficiency and relevance of health technology assessment: The role of iterative decision analytic modelling. *University of York*, 2000.

41. Felli JC Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making.* 1998;Jan-Mar;18(1):95-109. Erratum in: Med Decis Making 2001 May-Jun;21(3):254. Med Decis Making. 2003 Jan-Feb;23(1):97.

42. Goodman CA, Coleman PG, Mills AJ. The cost-effectiveness of antenatal malaria prevention in sub-Saharan Africa. *Am J Trop Med Hyg* 2001;64(1-2 Suppl):45-56.

43. Morel CM, Lauer JA, Evans DB. Cost effectiveness analysis of strategies to combat malaria in developing countries. *BMJ* 2005;331 1299.

44. Johns B, Torres TT. Costs of scaling up health interventions: a systematic review. *Health Policy Plan.* 2005;20(1):1-13.

45. Johns B, Baltussen R. Accounting for the cost of scaling-up health interventions. *Health Econ.* 2004;13(11):1117-1124.

Chapter 7: Discussion and conclusions

Malaria control requires a mix of preventive and treatment strategies tailored to the specific conditions of each malaria endemic setting. Cost-effectiveness analyses showed that several efficacious strategies available to control malaria are also an efficient use of resources. Nevertheless, despite the growth in the literature on the cost-effectiveness of malaria control interventions, there is virtually no research on long term cost-effectiveness analyses employing dynamic modeling[1]. This type of research could, in principle, allow predicting the cost-effectiveness of malaria control interventions when transmission intensity changes, capturing also the effects of health systems dynamics and the potential synergies of integrated strategies. Dynamic modeling the epidemiological impact and the cost-effectiveness of malaria control interventions, could also inform policy makers' decisions regarding the implementation of the Global Malaria Action Plan issued recently by Roll Back Malaria calling for malaria elimination.

This thesis is part of a wider research project, conducted by the Swiss Tropical Institute, aimed at developing integrated mathematical models for predicting the epidemiologic and economic effects of malaria control interventions. The thesis specifically combines innovative mathematical models of malaria epidemiology with innovative modeling of the health system and of the costs and effects of malaria control interventions. These approaches are applied to simulate the epidemiological impact and the cost-effectiveness of hypothetical malaria vaccines.

Chapter 1 provides the rationale of the thesis, describing why malaria is a public health priority, the increasing relevance of conducting economic analyses in the health sector, the economic evaluation framework, and the economic consequences of malaria.

Chapter 2 presents an approach to dynamically modeling the case management of malaria in SSA. This model allows the simulation of different rates of treatment coverage and parasitologic cure rates, predicting thus how variations in transmission intensity might have an impact on the health system and on the cost of it. As the actual epidemiologic impact and the cost-effectiveness of an intervention depend on the health system in place, the case management model is

an important part of simulations predicting the consequences of other interventions. The model allows computing the eventual cost savings due to the reduction in the case load.

The first delivery modality that may be considered for a malaria vaccine, once it will be available, would be through the EPI. The delivery of a malaria vaccine through the EPI has not previously been modeled and costed. Chapter 3 describes an approach to costing the delivery of a hypothetical malaria vaccine through the EPI, on the basis of the information currently available on the likely characteristics of the vaccine most advanced in development, and on the EPI in Tanzania. The analysis presents the predicted cost per dose delivered and the cost per fully immunized child, which are key inputs to the cost-effectiveness analysis.
In this chapter the cost of interest is the incremental cost associated with the intervention to achieve the health effect. Given the range of information needs of decision makers in the health sector, two types of incremental cost have been selected for measurement: marginal cost and average cost. The former consists of the additional costs that would be incurred when introducing a malaria vaccine into the EPI schedule, based on new resources that would be used in the delivery of the intervention; the latter includes all those costs involved in delivering a health intervention, whether they are used specifically for a new intervention, whether resources are shifted away from other activities, or whether spare capacity is used. Average costing involves sharing the costs of existing capacity among all the interventions benefiting from those resources. The usefulness of presenting full economic cost through this analysis is that it enables comparison of intervention efficiency in the long-term, where all resources can (hypothetically) be redeployed in alternative uses. Therefore, average costs are useful for cost-effectiveness analyses for long-term planning decisions.
The costs included in the analysis are those related to purchase of the vaccine, taking into account the wastage rate; costs of distributing and storing the vaccine at the central, zonal, district, and facility levels; costs of managing the vaccination program; costs of delivery at the facility level (including personnel, syringes, safety boxes, and waste management); and costs of additional training of EPI personnel and of social mobilization activities.
The results show that, although the vaccine price determines most of the total delivery costs, other costs are relevant and should be taken into account before planning its inclusion into the EPI. For instance, at a vaccine price of US$1 per dose, at the assumed coverage rates, the total annual cost to the EPI would be more than 35% of the annual (in year 2002) EPI budget in Tanzania. When the vaccine price increases to US$4 per dose, the total annual cost would increase to

more than US$ 19 million, which is slightly more than the annual EPI budget. These results highlight how important would be investing in strengthening the EPI program if a malaria vaccine would become available.

Chapter 4 and 5 combine modeling of malaria transmission and control with predictions of parasitologic and clinical outcomes, to assess the epidemiological effects and the potential short and long term cost-effectiveness of a pre-erythrocytic vaccine delivered via the EPI. The results suggest a significant impact on morbidity and mortality for a range of assumptions about the vaccine characteristics, but only small effects on transmission intensities.

The cost-effectiveness analysis (Chapter 5) adopts a societal perspective for both costs and effects. Case management costs include all resource inputs irrespective of whether these are borne by government, the patient, or both. Vaccine delivery costs and case management costs include both the direct costs of service provision and costs directly associated with the service, which essentially means the costs for the patients accessing the services, covering additional transport and sustenance costs.

The results suggest that at moderate to low vaccine prices, a pre-erythrocytic vaccine providing partial protection, and delivered via the EPI, may be a cost-effective intervention in countries where malaria is endemic. Over the vaccine price range of US$1.0 to US $20 per dose, the cost-effectiveness ratio is almost proportional to the price per dose, ranging (in the reference analyses) between US$12 and US$190 per (discounted) DALY averted. In the SSA context, cost-effectiveness ratios towards the lower end of this range would be very attractive for health ministries[2 3].

The cost-effectiveness results show sometimes counter-intuitive behavior in cost-effectiveness ratios that corresponds to health effects in the model. When episodes are delayed rather than averted, they occur in older individuals who may require larger drug dosages. Thus, the health benefits of delaying illness may be partially offset by increased costs. Since the epidemiologic model also corresponds with field data that suggests a maximum incidence of clinical episodes (though not mortality) at intermediate transmission intensities[4 5], it is possible for reductions in malaria transmission to lead to increased case loads.

A societal perspective in cost-effectiveness analysis also requires that indirect economic impacts of the intervention should be taken into account. In the case of a vaccine that reduces morbidity episodes as well as mortality, there is a clear impact on productive time either leading to higher income (in the case of market work) or higher unsold production (in the case of non-market work). This can either be through a gain in production of the averted malaria case, or where the

patient is a child, the production gained of the care giver who would have cared for the averted malaria case. Therefore, Chapter 5 explores also the implications of including in the analysis productivity costs due to morbidity, showing a reduction in cost-effectiveness ratios. Nevertheless, despite the importance of indirect economic impact of malaria, there are many pitfalls in measuring it in the context of rural Africa where most of the population is subsistence farmers, child care is often performed by older siblings, work is seasonal, and work inputs may be shifted over time and between household members.

A major impact of malaria on productivity is likely to be by the effects on premature mortality, but it is inappropriate to include in a CEA the costs of mortality, as available from estimates of life-time earnings forgone or willingness to pay studies, since this would result in double counting of the benefits of averting deaths[6-8].

These conclusions reflect the reference case, but the cost-effectiveness ratios are sensitive to assumptions about the epidemiologic setting, the vaccine characteristics, the transmission intensity, and the efficacy and duration of protection. The cost-effectiveness ratios varied with the time since the start of the vaccination program because the epidemiologic model does not reach equilibrium within the time scale of the simulation[9]. In general, the cost per DALY averted is lower in the first phase of the vaccination program than later, with the highest cost per DALY in the third five-year time period after the start of the program. Extending the duration of protection increases the cost-effectiveness ratios in the third and fourth five-year time periods.

Chapter 6 is an extension of the research described in Chapter 5, simulating the cost-effectiveness of three different vaccine types: Pre-erythrocytic vaccines (PEV), Blood stage vaccines (BSV), mosquito-stage transmission-blocking vaccines (MSTBV), and combinations of these, each delivered via a range of delivery modalities (EPI, EPI with booster, and mass vaccination combined with EPI).

The simulations presented in this Chapter show that PEV are more effective and cost-effective in low transmission settings. In contrast to PEV, BSV are predicted to be more effective and cost-effective at higher transmission settings than low transmission. Combinations of BSV and PEV are predicted to be more efficient than PEV, in particular in moderate to high transmission settings, but compared to BSV, combinations are more cost-effective in mostly moderate to low transmission settings.

Combinations of MSTBV and PEV or PEV and BSV do not increase the effectiveness or the cost-effectiveness compared to PEV and BSV alone when

delivered through the EPI (including with the addition of booster doses). However, when applied with EPI and mass vaccinations, combinations with MSTBV provide substantial incremental health benefits and low incremental costs in all transmission settings. This highlights the importance of developing other vaccine candidates as they have potential to facilitate a PEV/BSV combination vaccine to be more beneficial. Nevertheless, these combination vaccines are predicted to be interesting only for the settings where mass vaccination achieving relatively high coverage rates would be feasible.

Chapter 6 simulations indicate that the transmission setting and the vaccine delivery modality adopted are important determinants of the cost-effectiveness of malaria vaccines. Adding booster doses to the EPI is unlikely to be a cost-effective alternative to delivering vaccines via the EPI for any vaccine and transmission setting. By contrast, mass vaccination improves effectiveness, especially in low transmission settings, and in some scenario the cost-effectiveness ratios compare favorably with those of delivering the vaccine via the EPI only. Nevertheless, increasing the coverage of mass vaccination over 50%, often leads to incremental costs that exceed the incremental health benefits (due to the indirect effect of the vaccines and not to the increasing vaccine delivery costs of achieving high coverage rates).

Thus alternative vaccine delivery modalities to the EPI may sometimes, but not always, be more cost-effective than the EPI. In general, at moderate vaccine prices, most vaccines and delivery modalities simulated are likely to present cost-effectiveness ratios, which compare favorably with those of other malaria interventions[10 11]. Further research would be required to evaluate the importance of alternative deployment strategies outside EPI.

In some of the mass vaccination scenarios the simulations predict that local elimination of the parasite might be possible, sometimes at relatively low costs (assuming moderate vaccine prices), although often the incremental costs of achieving high vaccine coverage rates are higher than the incremental benefits. Eliminating malaria would, however, have wider economic implications than those simulated in our cost-effectiveness analyses. In fact, if local elimination were feasible, it might be desirable to achieve high vaccine coverage rates even if the incremental costs would be high (compared to the incremental health benefits) as elimination would bring future benefits. However to sustain elimination over time, once elimination is achieved, there would be a need for strong surveillance and case detection, which would incur substantial additional costs that are not included in our simulations. The models presented in this thesis can be further refined to assess the economic implications of achieving and sustaining local elimination in specific settings.

The approach used in this research represents, to our knowledge, the first attempt to develop dynamic models of malaria transmission and disease to evaluate the cost-effectiveness of malaria control interventions. The cost-effectiveness analyses are based on an approach to model the health system characteristics of the settings where a new intervention, such as a malaria vaccine, will be implemented, The rationale of this approach rests on: a) the need to capture the long term health and economic impact due to the interactions between malaria control interventions and the health system - e.g. the impact on the health system of variations in transmission intensity due to an intervention; b) the recognition that policy makers are more interested in cost-effectiveness predictions that are specifically tailored to their health system context rather than on a hypothetical one.

Nevertheless the approach followed by this research presents limitations that are being addressed in subsequent research at the Swiss Tropical Institute.

The case management model and the cost-effectiveness analysis presented are based on the characteristics of the health system of Tanzania with consequent limitations for the generalizability of results. The case management model developed is also still relatively simple. This is due to the difficulty of modeling the complexity of health systems in such a way that the models developed can be populated with data of good quality. Although this limitation is common to many modeling studies, being models simplified representation of reality by definition, more research should be carried out to refine this model in light also of the recent increase in availability of health system data from malaria endemic countries. Nevertheless, as the case management model used is the same for all scenarios simulated, the comparative cost-effectiveness of the vaccines modeled in Chapter 5 and 6 should only be slightly affected by it. Another limitation related to the case management model, is that it does not address the emerging problem of drug resistance, which would presumably increase the cost-effectiveness ratios.

The simulations considered only a limited set of sources of heterogeneity. In particular, it was assumed that each person in the simulation was exposed to the same entomologic challenge, and that the chances of being vaccinated were independent of individual susceptibility to disease. Over the time-horizon of the analysis, homogeneous probabilities of accessing health care were assumed. Nevertheless, over a long period, the introduction of a new malaria vaccine would have an impact on the health system and on the case management of malaria. These changes should ideally be taken into account when predicting the cost-effectiveness of a malaria vaccine. The models developed would make possible to

simulate more realistic patterns of heterogeneity, but the field data on which to base such models are very limited.

The cost-effectiveness analyses presented include a wide range of one and multi-way sensitivity analyses. However, they do not include a full probabilistic sensitivity analysis that would make possible to present results also in terms of cost-effectiveness acceptability curves and/or cost-effectiveness ratio ranges. This type of sensitivity analysis is not easily applicable when multiple scenarios are modeled without making hardly impossible to make sense of the results. An extension of the research presented in this thesis, is developing a methodology, based on value of perfect (and partial) information analysis, to run a full probabilistic sensitivity analysis on cost-effectiveness results of the pre-erythrocitic vaccine presented in Chapter 5. This analysis will explore the feasibility of using a full probabilistic sensitivity analysis to account for the uncertainty in cost-effectiveness results presented, assessing the incremental benefits compared to deterministic sensitivity analysis, and the potential benefits of conducting further research to reduce the uncertainty inherent in model parameters.

The interpretation of Chapter 6 results should take into account additional limitations. The vaccine delivery modalities modeled in Chapter 6 may not be feasible to implement in all simulated settings. Also, while it is now known that unit costs of health interventions vary with capacity utilization, as it has been shown also by a recent article on primary health care visit costs[12], in our analyses the costs of different vaccine delivery modalities are kept constant over the different coverage rates modeled. This was due to the lack of solid evidence specifically related to vaccine delivery costs by coverage levels, especially for mass vaccination campaigns. Including adjustments for variation in vaccine delivery costs would be particularly important when assessing the economic implications of scaling up coverage.

In addition, the comparisons of malaria vaccines – or of combinations of them- with different characteristics, are based on the same assumed vaccine price. In practice, the price might vary according to the characteristics of the vaccines, in particular for combinations of vaccines.

In this thesis, the epidemiological impact and the cost-effectiveness of hypothetical malaria vaccines are assessed versus an alternative of maintaining only the current case management practice in place. However, the relative efficiency of possible malaria vaccines will be affected by other malaria control interventions being concurrently implemented. Malaria vaccines will, eventually,

be deployed as part of integrated control strategies that should therefore be evaluated.

7.1 Conclusions

Malaria control strategies are complex interventions that should be carefully integrated, and adapted, to the health system and, more generally, to the socio economic context of the settings where they are implemented. Standard tools traditionally used to assess the public health and economic impact of malaria control interventions, such as efficacy trials and static cost-effectiveness analyses, capture only short term effects. They fail to take into account long term and dynamic effects due to the complex dynamic of malaria, and to the interactions between interventions effectiveness and health systems.

Combining advanced stochastic simulation modeling of malaria epidemiology with health system dynamic modeling is a crucial innovation proposed by the approaches presented in this thesis. In fact, while it is well known that the interactions between malaria and health systems take place under temporal and spatial heterogeneity, integration of health system metrics in epidemiological modeling is rarely done.

Simulating the effects of possible malaria vaccines showed that these approaches are a promising methodology to assess the short and long term effects of complex malaria control interventions. They provide a platform that could be used to model the effects of integrated strategies for malaria control. The increase in computer power available makes possible simulating complex scenarios with several dimensions/variables in a relatively short time. This, coupled with the increasing availability of information on malaria endemic countries health systems, should be exploited to further modeling health system dynamics, which is fundamental to assess integrated malaria control strategies.

An important aspect of the models developed is, in fact, that they can be adapted to the characteristics of local settings where malaria control interventions are implemented, including both the epidemiological and health system contexts. This allows thorough explorations of health system characteristics' impact on efficacy, effectiveness, and cost-effectiveness of the selected interventions.

The models and the approaches presented could be applied to inform decisions at several levels. Further applications might include simulating the epidemiology, the costs and consequences of packages of interventions, allowing estimating both effectiveness and (technical and allocative) efficiency. This would, thus, help policy makers to determine which intervention or, most likely, which package of interventions, might be most effective and efficient in a particular area.

Additionally, it would be possible to simulate the implications of coverage extension of malaria control interventions, and of different strategies and service delivery modalities that can reach the poorest.

The approaches developed could also allow identification of areas where intensified malaria control is the only feasible option, areas where malaria elimination is more likely to be achieved, the incremental cost-effectiveness of proceeding to elimination once a high level of control has been achieved, the optimal transmission levels at which to change strategy, and, in principle, economies of scope and or synergies in effectiveness and cost-effectiveness of new strategies. These are all research areas that have been identified as fundamental in the research agenda to be set up following the recent call for malaria elimination[1 13].

7.2 References

1. Mills A Lubell Y Hanson K. Malaria eradication: the economic, financial and institutional challenge. *Malaria Journal,* 2008;7(Suppl 1):S11.

2. Tan-Torres Edejer T, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, et al. *Making choices in health: WHO guide to cost-effectiveness analysis*: World Health Organization, Geneva, 2003.

3. Goodman CA, Coleman PG, Mills A. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999;354(9176):378-385.

4. Marsh K, Snow R. Malaria transmission and morbidity. *Parassitologia* 1999;41(1-3):241-246.

5. Trape JF, Rogier C. Combating malaria morbidity and mortality by reducing transmission. *Parasitol Today* 1996;12(6):236-240.

6. Drummond MB, O'Brien B, Stoddart GL, Torrance G. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1997.

7. Gold MR, Gold SR, Weinstein MC. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press, 1996.

8. Weinstein M, Siegel J, Gold M, Kamlet M, Russell L. Recommendations of the panel of cost-effectiveness in medicine. *Journal of the American Medical Association* 1996;276(15):1253-1341.

9. Maire N, Tediosi F, Ross A, Smith T. Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the expanded program on immunization in sub-Saharan Africa. *Am.J.Trop.Med.Hyg.* 2006;75(2 Suppl):111-118.

10. Morel CM, Lauer JA, Evans DB. Cost effectiveness analysis of strategies to combat malaria in developing countries. *BMJ* 2005;331 1299.

11. Goodman C, Coleman P, Mills A. *Economic analysis of malaria control in sub-Saharan Africa*. Geneva: Global Forum for Health Research, 2000.

12. Adam T Ebener S Johns B Evans DB. Capacity utilization and the cost of primary care visits: Implications for the costs of scaling up health interventions. *Cost Eff Resour Alloc.* 2008;Nov 13;6:22.

13. Hommel M. Towards a research agenda for global malaria elimination.;Malaria Journal 2008, 7(Suppl 1):S1.

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Publications

Peer reviewed journals and book chapters

Missoni E, Tediosi F, Pacileo G, Borgonovi E. *G8 Summit 2009: what approach will Italy take to health?* Lancet. 2009 Jul 4;374(9683):9-10

Tediosi F, Maire N, Penny N, Studer A, Smith T. *Simulation of the cost-effectiveness of malaria vaccines.* Malar J. 2009 Jun 8;8:127

Tediosi F, Gabriele S, Longo F. Governing decentralization in health care under tough budget constraint: What can we learn from the Italian experience? Health Policy. 2009 May;90(2-3):303-12. Epub 2008 Dec 5.

Yukich JO, Zerom M, Ghebremeskel T, Tediosi F, Lengeler C. *Costs and cost-effectiveness of vector control in Eritrea using insecticide-treated bed nets*. Malar J. 2009 Mar 30;8(1):51.

Hutton G., Schellenberg D, Tediosi F., et al. *Cost-effectiveness of intermittent preventive treatment for malaria control in infants (IPTi) in Tanzania and Mozambique.* Bull World Health Organ. 2009 Feb;87(2):123-9.

Murru M., Tediosi F (2009). *Development Assistance and health cooperation.* Third report of Italian Global Health Watch, (Salute globale e aiuti allo sviluppo Diritti, ideologie, inganni). Pisa, EDS, 2008.

Wiedenmayer KA, Weiss S, Chattopadhyay C, Mukherjee A, Kundu R, Ayé R, Tediosi F, Hetzel MW, Tanner M. *Simplifying paediatric immunization with a fully liquid DTP-HepB-Hib combination vaccine: evidence from a comparative time-motion study in India.* Vaccine. 2009 Jan 29;27(5):655-9. Epub 2008 Dec 3.

Yukich JO, Lengeler C, Tediosi et al.Costs and consequences of large-scale vector control for malaria. Malar J. 2008 Dec 17;7:258

Tediosi F, Aye R, Ibodova S, Thompson R, Wyss K. *Access to medicines and out of pocket payments for primary care: evidence from family medicine users in rural Tajikistan.* BMC Health Serv Res. 2008 May 23;8(1):109.

Hutton G., Rehfuess E., Tediosi F. *Evaluation of the costs and benefits of interventions to reduce indoor air pollution.* Energy for Sustainable Development. Vol. XI, No. 4 (December 2007).

Carinci F, Roti L, Francesconi P, Gini R, Tediosi F, Di Iorio T, Bartolacci S, Buiatti E. *The impact of different rehabilitation strategies after major events in the elderly: the case of stroke and hip fracture in the Tuscany region.* BMC Health Services Research 2007, 7:95

Magnussen J, Mihályi P, Tediosi F. *Effects of decentralization and recentralization on economic dimensions of health systems.* Decentralization in health care: strategies and outcomes. European Observatory on Health Care Systems. Open University Press, December 2006.

Maciocco G, Tediosi F. *Inequalities in health: the case of the USA (In Italian).* In "Inequalities in Health: II Report of the Italian Observatory on Global Health", ETS Press, November 2006.

Tediosi F, Hutton G, Maire N, Smith T, Ross A, Tanner M. *Predicting the cost-effectiveness of introducing a pre-erythrocytic malaria vaccine into the EPI schedule in Tanzania*. Am J Trop Med Hyg 2006 75: 131-143.

Smith T, Killeen G.F., Maire N., Ross A., Molineaux L, Tediosi F., Hutton G., Utzinger J., Dietz K, Tanner M. *Mathematical modeling of the impact of malaria vaccines on the*

clinical epidemiology and natural history of plasmodium falciparum malaria: overview. Am J Trop Med Hyg 2006 75: 1-10.

Tediosi F, Maire N, Smith T, Hutton G, Ross A, Utzinger J, Tanner M. *An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-Saharan Africa*. Am J Trop Med Hyg 2006 75: 90-103.

Hutton G, Tediosi F. *The costs of introducing a malaria vaccine through the Expanded Programme of Immunization in Tanzania.* Am J Trop Med Hyg 2006 75: 119-130.

Maire N, Tediosi F, Ross A, Smith T. *Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the expanded program on immunization in Sub-Saharan Africa.* Am J Trop Med Hyg 2006 75: 111-118.

Tediosi F. Roti L. *Community Hospitals in Tuscany: analysis of organization, activity, and costs (in Italian). Gli Ospedali di Comunità in Toscana: analisi degli aspetti strutturali, organizzativi, di attività e dei costi.* MECOSAN No. 51, 2004: :101-113.

Tediosi F., Bartolacci S., Roti L., Buiatti E. *Economic analysis of hospitalizations for osteoporotic fractures in Tuscany (in Italian). L'ospedalizzazione per fratture osteoporotiche in Toscana*. Politiche Sanitarie 2004, Vol. 5, No. 2; 61-69.

Maciocco G, Tediosi F. *Is the American Health care system close to implosion? (in Italian). Il sistema sanitario americano. L'implosione dietro l'angolo.* Prospettive sociali e sanitarie. Speciale No.19: 2003: 1-25.

Toniolo F, Cislaghi C, Cobello F, Tediosi F. *Considerations on the interregional resource allocation mechanism in Italy (in Italian). Alcune considerazioni relative al "modello Fiuggi" per il riparto interregionale delle risorse sanitarie*. Politica Sanitaria N 2003 (**http://www.politichesanitarie.it/**).

Cislaghi C., Galanti C., Tediosi F. *Health care payment systems: principles and models (in Italian). La remunerazione delle prestazioni sanitarie: principi e modelli.* Annali di Igiene 2003**.**

Tediosi F., Bartolacci S., Roti L., Buiatti E. *Economic evaluation of clinical pathways of patients with stroke and hip fracture in Tuscany* (in Italian). *La valutazione economica dei percorsi assistenziali dei soggetti con Ictus e Frattura del femore in Toscana: risultati di uno studio pilota.* MECOSAN No. 48. 2003.

Cislaghi C., Pisani E., Tediosi F. *The resource allocation to Local Health Units in Tuscany. (in Italian). L'allocazione delle risorse alle Aziende Sanitarie Locali: il caso della regione Toscana*. Mecosan No.45 2002.

R. Campi, L. Garattini, F. Tediosi, M. Bonati. *Pharmacoeconomic analysis of prescriptions in Italian pediatric general practice*. Eur J Health Econom 3 (2002) 4, 261-266.

Tediosi F.*Investing in health of developing countries (in Italian). Investire in salute nei paesi poveri*. Prospettive Sociali e Sanitarie. No. 12 Luglio 2002.

Garattini L, Rossi C, Tediosi F, Cornaggia C, Covelli G, Barbui C, Parazzini F, Gruppo Studio SCORE *Direct costs of schizophrenia in mental health departments in Italy (in Italian). Costi diretti della schizofrenia nei dipartimenti di salute mentale italiani*. Pharmacoeconomics. Italian Research Articles 2002; 4/2: 81-89.

Bartolacci S., Berni. R., Forni S., Tediosi F., Cislaghi C. *The economic value of hospital care as function of distance from birth and death (in Italian). Il valore economico*

dell'ospedalizzazione in funzione del tempo dalla nascita e dalla morte. Politiche Sanitarie 2001; 4-6: 193-203.

Garattini L, Tediosi F et.al. *The Outpatient Cost of diabetes Care in Italian Diabetes Centres*. Value in Health 2001; 4: 251-257.

Garattini L, Cornago D, Tediosi F. *A comparative analysis of domiciliary oxygen therapy in five European countries*. Health Policy 58 (2001) 133-150.

Guerrini R, Battini R, Ferrari AR, Veggiotti P, Besana D, Gobbi G, Pezzani M, Berta E, Tetto A, Beghi E, Monticelli ML, Tediosi F, Garattini L, Russo S, Rasmini P, Amadi A, Quarti P, Fabrizzi R. *The costs of childhood epilepsy in Italy: comparative findings from three health care settings*. Epilepsia. 2001 May;42(5):641-6.

Tediosi F, Bertolini G, Parazzini F, Mecca G, Garattini L. *Cost analysis of dialysis modalities in Italy*. Health Serv Manage Res. 2001 Feb;14(1):9-17.

Garattini L, Rossi C, Tediosi F, Cornaggia C, Covelli G, Barbui C, Parazzini F. *Direct costs of schizophrenia in Italian Community Psychiatric Services*. Pharmacoeconomics 2001; 19: 1217-1225

Garattini L, Tediosi F, Di Cintio E, Yin D, Parazzini F. *Resource utilization and hospital cost of HIV/AIDS care in Italy in the era of highly active antiretroviral therapy*. AIDS Care 2001; 13: 733-741

Garattini L, Tediosi F. *A comparative analysis of generics markets in five European countries*. Health Policy 51 (2000) 149-162.

Tediosi F, Parazzini F, Bortolotti A, Garattini L. *The cost of urinary incontinence in Italian women. A cross-sectional study.* Pharmacoeconomics 2000; 17: 71-76.

Tediosi F, Parazzini F, Garattini L. *Cost of schizophrenia studies: a methodological review.* HEPAC Health Economics Prevention Care 2000; 1:14-19.

Garattini L, Tediosi F, Ghislandi S, Orzella L, Rossi C *How do Italian pharmacoeconomists evaluate indirect costs?* Value in Health 2000; 3: 270-276.

Ricci E, Ruggeri D, Tediosi F, Beghi E, Garattini L. *The cost of epilepsy care in referral centers in Italy*. HEPAC Health Economics Prevention Care 2000; 1: 111-115.

Tediosi F, Chiaffarino F, Parazzini F, Coscelli L,,Garattini L. *The costs of diabetic foot in Italy: data from Project RECORD (in Italian). I costi del piede diabetico in Italia: dati dal progetto RECORD.* PharmacoEconomics - Italian Research Articles 2000; Vol 2, No.1:23-28.

Garattini L, Ghislandi S, Tediosi F. *The evaluation of indirect costs in economic evaluations (in Italian). L'inclusione dei costi indiretti nelle valutazioni economiche: la situazione italiana*. Mecosan 2000;2;12-20.

Pagano E, Brunetti M, Tediosi F, Garattini L *Costs of diabetes. A methodological analysis of the literature*. Pharmacoeconomics 1999; 15: 583-595.

Orzella L, Tediosi F, Garattini L. *Direct costs of HIV/AIDS: a systematic review of the literature (in Italian). I costi diretti dell'infezione da HIV/AIDS: una revisione sistematica della letteratura*. Giornale Italiano di Malattie Infettive, 1999, n° 5/6, pag: 263-270.

Tediosi F, Pagano E, Garattini L. *The costs of schizophrenia: a literature review (in Italian). I costi della schizofrenia: un'analisi metodologica della letteratura esistente*. Bollettino Scientifico Informazione 1998; 5: 41-47.

Tediosi F, Garattini L. *The use of modeling in economic evaluations (in Italian). Utilizzo dei modelli nelle valutazioni economiche in sanità: cenni teorici e problemi pratici.* FarmacoEconomia 1998; n. 3: 21-30.

Lucca U, Tediosi F, Tettamanti M. *The epidemiological and economic dimension of dementia (in Italian). La dimensione epidemiologica ed economica della demenza*. Milan, July 2001. Publisher: Emme.

Garattini L, Tediosi F. *Health economics and generic drugs (in Italian). Economia sanitaria e farmaci generici*. Milan, May 2000. Publisher: K2.

Other journals

Yukich J, Tediosi F, Lengeler C. Comparative cost-effectiveness of ITNs or IRS in Sub-Saharan Africa. Malaria matters; 18: 2. July 2007.

Tediosi F. *The economic consequences of Malaria* (in Italian). *Le conseguenze economiche della Malaria*. Economia e Politica del Farmaco; 3: No. 8, July 2006.

Tediosi F. *The report "Macroeconomics and Health: investing in health for economic development" (In Italian)*. Salute e Sviluppo No. 1; 2002.

Tediosi F, Forni S, Cislaghi C. *Tuscany and Lombardy: comparing two health care systems (in Italian*). Toscana e Lombardia: due sistemi sanitari a confronto Toscana Medica. Ottobre 2001.

Tediosi F, Forni S, Cislaghi C. *Prevalence of prescription drugs consumption and drugs expenditure: a comparison at regional level (in Italian). Prevalenza di consumatori di farmaci e spesa farmaceutica: un confronto a livello regionale.* Ricerca & Pratica, 2002; 18: 218-227.

Orzella L, Tediosi F, Garattini L. *The evaluation of hospital costs of a infectious diseases department: the case of Bergamo's Hospital (in Italian*). *La valutazione dei costi ospedalieri in un reparto di malattie infettive: il caso degli Ospedali Riuniti di Bergamo*. ASI (Agenzia Sanitaria Italiana) 1999; n.40: 22-28.

Tediosi F, Garattini L. *The Danish Health care system (in Italian).* Il Servizio Sanitario Danese. ASI (Agenzia Sanitaria Italiana) 1999; n. 38: 6-9.

Tediosi F, Mallet J O, Garattini L. *The French Health care system (in Italian).* Il sistema sanitario francese (1a e 2a parte). ASI (Agenzia Sanitaria Italiana) 1999; n. 43: 20-26; n. 44: 22-30.

Tediosi F, Garattini L. *Medical devices in Europe (in Italian*). I dispositivi medici in Europa. ASI (Agenzia Sanitaria Italiana) 1999; n. 50: 12-18.

Tediosi F, Fattore G, Garattini L *Rationing of health care: reflection of some international experieces (in Italian). Il razionamento in sanità: riflessioni su alcune esperienze estere.* ASI (Agenzia Sanitaria Italiana) 1998; n. 35/36: 5-12.

Recent Reports

Tediosi F, Compagni A (2009). *Funding Health research in Italy (in Italian).* http://portale.unibocconi.it/wps/wcm/connect/Centro_CERGASit/Home/Eventi/07042009_CdR_CERGASit

Tediosi F, Longo F. (2009). Long term care in Italy: fragmented regional picture. The Institute for Studies and Economic Analyses (Istituto di Studi e Analisi Economica - ISAE) report on Public Finance and Institutions 2009 www.isae.it

Tediosi F, Paradiso M. (2008) *Health expenditure control in Italy and the credibility of Budgetary Balance Plans.* The Institute for Studies and Economic Analyses (Istituto di Studi e Analisi Economica - ISAE) report on Public Finance and Institutions 2008

Bernasconi JL, Tediosi F (2007). Current issues and future challenges in health SWAps: Fiduciary Risk Assessment & Financial Management – Issues Note. SDC Health SWAP Capitalisation Workshop.

Mahon J Tediosi F (2007). *Health SWAP in Tajikistan: Prospects and suggested next steps.* August 2007, Report to the Swiss Development Cooperation, Tajikistan.

Tediosi F (2007). *Exploring the potential financial and economic implications of a fully liquid DTP-HepB-Hib vaccine: an assessment for South Africa.* Report to Novartis Vaccines, August 2007.

Yukich J, Tediosi F, Lengeler C. (2007). *Operations, Costs and Cost-Effectiveness of Five Insecticide-Treated Net Programs Eritrea, Malawi,Tanzania, Togo, Senegal) and Two Indoor Residual Spraying Programs (Kwa-Zulu-Natal, Mozambique*). www.rollbackmalaria.org/partnership/wg/wg_itn/docs/Yukich2007.pdf).

Tediosi F. (2006). *Health financing reforms in Tajikistan: Capitated budget allocation for 2007 in project Sino pilot rayons*. Report to the Ministry of Health (November 2006).

Hutton G, Rehfuess E, Tediosi F, Weiss S (2006). *Evaluation of the costs and benefits of household energy and health interventions at global and regional levels.* World Health Organization 2006.

Tediosi F, Thompson R (2006). *Health financing reforms in Tajikistan: structures and systems at rayon level required for implementing capitated payments*. Report to the Ministry of Health (May 2006).

Wiedermayer K, Weiss S, Tediosi F (2006). *Time-motion study of a fully liquid pentavalent vaccine in Calcutta, India.* Report to Novartis Vaccines, November 2006.

Tediosi F, Wiedermayer K, Weiss S. *Economic Study on a fully liquid pentavalent vaccine*. Report to Novartis Vaccines, November 2006.

Tediosi F, Thompson R. *Recent Development in health financing reforms in Tajikistan and PHC capitation payments in Varzob and Dangara*. Report to the Ministry of Health (March 2006).

Tediosi F. *Revising co-payments for hospital care in Tajikistan.* Report to the Ministry of Health (December 2005).

Tediosi F et al. *Yellow Fever Stockpile Investment Case submitted by Yellow Fever Task Force (WHO) to The Global Alliance for Vaccines and Immunization (Economic analysis*); Geneva, December 2005.

Tediosi F. Aye R. *Patient satisfaction survey in the district of Varzob and Dangara*. Report to the Ministry of Health (September 2005)

Gabriele S, Cislaghi C, Costantini F, Innocenti F, Lepore V, Tediosi F, Valerio M, Zocchetti C. *Demographic factors and health expenditure profiles by age: the case of Italy.* ISAE Working paper N 3 2005 http://www.enepri.org/Ahead.htm

Tediosi F. *On implementing the Basic Benefit Package and the capitation system in Tajikistan*. Report to the Ministry of Health (August 2005).

Tediosi F, Costa J. *The financial and economic implications of implementing a Basic Benefit Package in Tajikistan*. Report to the Ministry of Health (April 2005).