Addressing implementation uncertainty in postdischarge malaria chemoprevention

Determinants of adherence, cost-effectiveness, and the value of further research in Malawi and other malaria-endemic African countries

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Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific Environment

I wrote this PhD as a PhD-fellow and researcher at University of Bergen's (UiB) Faculty of Medicine. At the Department of Global Public Health and Primary Care I worked in the Section for Ethics and Health Economics and in the Centre for International Health.

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Within UiB's Department of Global Public Health and Primary Care, collaborators were affiliated with different research groups: the Health Economics Leadership and Translational Ethics Research Group (HELTER), the Centre for International Health (CIH), and the Bergen Centre for Priority Setting (BCEPS).

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Lastly, I'm grateful to J. S. Bach, my daily companion throughout the years of reading and writing and deleting.

Abstract in English

Background: Malaria continues to be a leading cause of death and morbidity in children living in malaria-endemic areas of sub-Saharan Africa. The WHO recommends chemoprevention of malaria in vulnerable sub-populations as strategy to reduce the regionally stagnating malaria incidence and mortality rates. Postdischarge malaria chemoprevention (PDMC) comprises household-based oral antimalarial treatment of preschool children in endemic areas during the months of recovery after they were treated in hospital for severe anaemia. Three months of PDMC substantially reduce the risk of mortality and hospital readmission. Based on the available evidence, the WHO recently recommended that countries adopted PDMC in malaria-endemic areas. This thesis aimed to address remaining evidence gaps that policy-makers in sub-Saharan countries face when considering PDMC implementation. Namely, the determinants of caregivers' adherence to PDMC in Malawi, the economic evaluation of different delivery strategies of PDMC in south-eastern African settings, and the value of further information for sub-Saharan Africa were, analysed.

Data Sources: Data from an efficacy trial in Kenya and Uganda (n=1 040) and a delivery trial in Malawi (n = 375), conducted from 2016 to 2018, were used for the three analyses, and complemented with data from the literature. Both trials used three months with monthly dihydroartemisinin-piperaquine (DHAP) for PDMC. The efficacy trial compared PDMC to a placebo treatment. The delivery trial compared community-based PDMC delivery, where the full nine doses of DHAP were distributed to caregivers at hospital discharge, to facility-based PDMC delivery, where three monthly doses were collected monthly from the hospital.

Methods: Modified Poisson regression analysis was used to predict caregiver adherence based on child, caregiver, and household features (predictor analysis, Paper 1). Results are reported as relative risk for high adherence. The cost-effectiveness analysis (CEA, Paper 2) used Markov decision models to compare the two delivery strategies of PDMC with the standard of care for Malawi, Kenya, and Uganda. A societal costing perspective was assumed and results are reported as incremental cost-effectiveness ratios per quality-adjusted life-year gained. In a value of information analysis (VOI, Paper 3), we calculated the per-decision net monetary benefit (NMB) for Kenya, Uganda, and Malawi, of perfect and partial perfect information for the input variables of the CEA. A scenario with halved adherence rates to simulate real-world implementation conditions was included. Results were reported as per country annual NMB of perfect information, and applied to 27 other sub-Saharan countries, adjusted for variations in purchasing power and willingness to pay thresholds.

Results and Interpretation: No conclusive set of determinants for PDMC adherence could be found in the predictor study. A socio-economic index showed mixed associations across quintiles with poor adherence. Children with four or more malaria infections before admission were associated with reduced adherence. PDMC combines multiple factors that complicate adherence behaviour, and we suggest that established predictive factors for adherence to less complex regimens have weaker or more complex associations with adherence to PDMC. The CEA showed that PDMC was cost-saving and more effective than standard of care treatment. Community-based PDMC delivery was the cost-effective strategy in all countries, confirmed in sensitivity analyses. The robust results suggest that PDMC is cost-effective and that distributing a full course of PDMC at discharge is the optimal delivery strategy for malaria-endemic south-eastern African settings. The VOI analysis confirmed this result, identifying only two categories of model input with uncertainties that had a potential impact on the decision for the optimal delivery strategy: the relative mortality rate when receiving PDMC compared to standard of care, and the adherence rates. Perfect information on both parameters had a theoretical annual value of US$1 379, $7 979, and $4 840 for Malawi, Kenya, and Uganda, respectively. The scenario with reduced adherence rates generated comparable, overall lower, values of perfect information. Larger research projects to resolve these uncertainties may, thus, not be economically justifiable.

Abstract in Norwegian

Bakgrunn: Malaria fortsetter å være en ledende årsak til dødsfall og dødelighet for barn som bor i malaria-endemiske områder i Afrika sør for Sahara. Verdens helseorganisasjon (WHO) anbefaler chemoprevention av malaria for sårbare under-grupper som en strategi for å redusere forekomst av regional stagnerende malaria- og dødelighetsrater. Postdischarge malaria chemo-prevention (PDMC) består av husholdningsbasert oral antimalariabehandling for førskolebarn i endemiske områder i månedene etter recovery/bedring etter mottatt sykehusbehandling for alvorlig anemi. Tre måneder av PDMC reduserte risiko for dødelighet og readmission/gjeninnleggelse på sykehus substansielt. Basert på tilgjengelig bevis/funn/resultater anbefalte nylig WHO at land adopterer PDMC i malaria-endemiske områder. Denne avhandlingen hadde som mål å adressere de resterende kunnskapshull som lovgivere i afrikanske land sør for Sahara møter når de vurderer implementering av PDMC: faktorer for omsorgsgiveres adherence/etterlevelse til PDMC i Malawi, økonomisk evaluering av ulike delivery/leverings? strategier i sørøstlige afrikanske settinger, og verdien av videre informasjon for afrikanske land sør for Sahara ble analysert.

Datakilder: Data fra en efficacy trial i Kenya og Uganda (n=1040) og en delivery trial i Malawi (n=375), gjennomført fra 2016 til 2018 ble brukt til de tre analysene og komplimentert med data fra litteraturen. Begge trials brukte tre måneder med månedlig dihydroartemisinin-pipereaquine (DHAP) til PDMC. The efficacy trial/studien sammenlignet PDMC med placebobehandling. The delivery trial sammenlignet community-delivered PDMC, hvor den totale mengden på ni doser av DHAP ble distribuert til omsorgsgivere ved utskriving fra sykehus med 'facility-delivered' PDMC, hvor tre månedsdoser ble hentet månedlig fra sykehuset.

Metoder: Modified Poisson regresjonsanalyse ble brukt for å forutsi omsorgsgiveres adherence/etterlevelse basert på barn, omsorgsgiver, og husholdningskarakteristikker (predictor analyse, artikkel 1). Resultatene ble rapportert som relativ risiko for komplett etterlevelse. Kost-nytte-analysen (CEA, artikkel 2) brukte Markov decision modell for å sammenligne to leveringsstrategier av PDMC med standard of care for Malawi, Kenya og Uganda. Societal costing perspective ble tatt og resultatene ble rapportert som trinnvis kost-nytte ratio per kvalitets-justert liv-år oppnådd. I en value of information analyse (VOI, artikkel 3) kalkulerte vi per-decision net monetary benefit (NMB) for Kenya, Uganda og Malawi av perfekt og delvis perfekt informasjon for inputvariablene av CEA. Et scenario med halverte

etterlevelsesrater for å simulere implementeringsbetingelser fra real-world ble inkludert. Resultatene ble/er rapportert som årlig per land NMB av perfekt informasjon og anvendt til 27 andre afrikanske land sør for Sahara, justert for variasjon i terskel for kjøpekraft og villighet til å betale.

Resultater og tolkning: Det ble ikke funnet konkluderende sett av determinants/faktorer? for PDMC etterlevelse. En sosioøkonomisk indeks viste blandet assosiering på tvers av kvintiler med lav etterlevelse. Barn med fire eller fler malariainfeksjoner før innleggelse ble assosiert med redusert etterlevelse. PDMC kombinerer flere faktorer som kompliserer etterlevelsesatferd, og vi foreslår at etablerte spådde faktorer for adherence/etterlevelse av mindre komplekse regimer har svakere eller mer komplekse assosiasjoner med adherence/etterlevelse av PDMC. CEA viste at PDMC var kostnadsbesparende og mer effektivt enn standard of care. Community-delivered PDMC var den kostnadseffektive strategien i alle land, som ble bekreftet med sensitivitetsanalyse. Det robuste resultatet foreslår at PDMC er kostnadseffektivt og at å distribuere en komplett course av PDMC ved utskrivelse er den optimale delivery/leverings? strategien for malaria-endemiske sør-østlige afrikanske settinger. VOI analysen bekreftet dette resultatet ved å identifisere kun to kategorier av modellinput med usikkerheter som hadde en potensiell effekt på avgjørelsen av den optimale delivery/leverings? strategien: den relative dødelighetsraten ved å motta PDMC sammenlignet med standard of care og etterlevelsesraten. Perfekt informasjon ved begge parametere hadde en theoretical årlig verdi på US$ 1 379, US$7 979 og US$4 840 for henholdsvis Malawi, Kenya og Uganda. Scenarioet med redusert etterlevelsesrater genererte sammenlignbare, generelt lavere verdier av perfekt informasjon. Større forskningsprosjektet for å løse disse usikkerhetsmomentene kan derfor ikke være rettferdiggjøres økonomisk.

List of Publications

Kühl MJ, Nkosi-Gondwe T, ter Kuile FO, Phiri KS, Pannu M, Mukaka M, Robberstad B, Engebretsen IM. **Predicting adherence to postdischarge malaria chemoprevention in Malawian pre-school children: a prognostic multivariable analysis.** PLOS Global Public Health 3(4): e0001779. https://doi.org/10.1371/journal.pgph.0001779.

Kühl MJ, Nkosi-Gondwe T, Dhbangi A, Kwambai T, Mori AT, Opoka R et al. **Economic evaluation of postdischarge malaria chemoprevention in preschool children treated for severe anaemia in Malawi, Kenya, and Uganda: A cost-effectiveness analysis.** eClinical Medicine. 2022;52 (101669). doi.org/10.1016/j.eclinm.2022.101669.

Kühl MJ, Robberstad B, Mori AT, Okell L, Phiri KS, Griffin S. **Do we need to know more? An analysis of the value of further research on postdischarge malaria chemoprevention in preschool children in sub-Saharan Africa.** Unpublished.

Abbreviations and Acronyms

ACT	*Artemisinin-based combination therapies*
AL	*Artemether/lumefantrine*
ANC	*Antenatal care*
AS+AQ	*Artesunate amodiaquine*
AS+SP	*Artesunate/sulfadoxine/pyrimethamine*
DW	*Disability weight*
DHAP	*Dihydroartemisinin/piperaquine*
EHP	*Essential Health Package*
EVPI	*Expected value of perfect information*
EVPPI	*Expected value of partial perfect information*
GBD-study	*The Global Burden of Disease-study*
GDG	*Guideline Development Group*
GMP	*WHO's Global Malaria Programme*
GTS	*Global Technical Strategy for Malaria 2016-2030*
HBHI	*High Burden High Impact-initiative*
HAS	*Health Surveillance Assistant*
IMRAD	*Introduction, Methods, Results, and Discussion*;
IPD	*Inpatient department*
IPTi	*Intermittent preventive therapy - infants*
IPTp	*Intermittent preventive therapy - pregnant women*
IPTpd	*Intermittent preventive therapy - postdischarge*
IPTsc	*Intermittent preventive therapy - school children)*
IRS	*Indoor residual spraying*
ITN	*Insecticide-treated bed nets*
MDA	*Mass drug administration*
NMB	*Net monetary benefit*
OPD	*Outpatient department/clinic*
P	*Plasmodium*
PDMC	*Postdischarge malaria chemoprevention*
PMC	*Perennial Malaria Chemoprevention*
RBM	*Roll Back Malaria Partnership*
RTS	*RTS,S/AS01 (RTS,S);* WHO-approved malaria vaccine
SDG	*UN Sustainable Development Goals*
SMC	*Seasonal Malaria Chemoprevention*
SSA	*Sub-Saharan Africa*
UN	*United Nations*
UNICEF	*United Nations Children's Fund*
WHO	*World Health Organization*
ZCH	*Zomba Central Hospital*

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Background

This PhD thesis is organized along an extended IMRAD structure.[1] This Background chapter introduces the research context. It is followed by a short chapter summarizing the rationale behind this work, and introducing the objectives of the three research papers that make out the foundation of this thesis (and are attached in the Annex). In the Methods chapter, I describe the data sources and methods that were used in these three studies. The findings are briefly summarized in the Results chapter. Both methods and results are then critically reviewed in the Discussion chapter, and a few implications of the studies are presented. The thesis ends with a short Conclusion chapter.

This chapter consists of two thematic sections, the first introduces malaria and PDMC, the second describes the country contexts of interest. In the first section, I summarize how malaria and malaria-associated anaemia affect children in sub-Saharan Africa (SSA). Thereafter, I present an overview of the global response strategies and current trends to control both diseases, with emphasis on malaria prevention. Postdischarge malaria chemoprevention (PDMC) will then be introduced in more detail, covering the underlying rationale, and summarizing the evidence around PDMC to date. In the second section, Malawi, Kenya, and Uganda, the settings of the three studies, will be introduced. Next, the country-specific malaria burden and the national demand for PDMC will be described. Lastly, some features of the three health systems that are relevant to these studies in will be briefly presented.

Malaria and malaria prevention in African children

The burden of malaria and severe anaemia on children

Malaria is a tropical disease, carried by plasmodium parasites (P) in mosquitoes. As they bite humans, parasites are injected from the mosquito's salival gland into the human blood cycle.[2] The incidence of malaria depends on environmental factors that accommodate vector mosquitos as well as complex parasite and host factors.[3] Different malaria parasites cause different symptoms that vary in severity. P falciparum and P vivax are the most frequent parasites. The former reproduces at high rate in human blood and affects critical organs.[4] The latter causes a more subtle and often overlooked burden with a higher mortality rate.[5,6] P falciparum is most prevalent in sub-Saharan Africa, P vivax in all other endemic regions.[7–9]

Malaria is preventable. It was prevalent for millennia in most of the inhabited world before the transmission patterns became understood in the late 19th century.[10] Throughout the past century,

control efforts increasingly contained the disease to tropical and sub-tropical areas.[11,12] Today almost half of the global population lives in malaria transmission areas where the disease remains a leading cause of mortality and morbidity: in 2021, the WHO estimated 247 million cases of malaria globally, with an estimated 619 000 malaria deaths.[9,13] More than 95% of cases and deaths were located in sub-Saharan Africa, and African children are carrying the largest share of the burden. Eight of ten malaria deaths in 2021 were children younger than five years old.[9] Nigeria and the Democratic Republic of Congo together account for approximately 40% of both cases and deaths. Uganda shoulders more than 5% of the global cases and 3% of its deaths. The populations of Malawi and Kenya each contribute between 1% and 2% to the overall cases and deaths.[9]

In endemic areas, malaria is a leading cause of anaemia in children.[14] A Kenyan study estimated that severe anaemia contributed to half of the malaria-attributed child mortality.[15] Other country studies from sub-Saharan Africa show that approximately 30% of hospitalized children in high malaria transmission-areas are severely anaemic.[16,17] The relation of malaria and anaemia is, however, complicated. Both can co-exist and exacerbate one another, while, at the same time anaemia can also be caused by various other factors, mostly nutritional deficiencies or other infections.[18] The prevalence of anaemia in preschool children varies across the continent, depending on local epidemiological drivers and complex environmental factors. For example, in Western Africa, it correlates with larger humidity patterns, whereas in East Africa elevation is the dominant ecological predictor for anaemia in children.[19] The incidence of both paediatric malaria and anaemia are also independently associated with low socio-economic status and poor caregiver education.[18,20,21] Nonetheless, for malaria-endemic areas, there is overwhelming evidence that a malaria infection is a frequent cause of anaemia, and severe anaemia, in children.[22–25]

In mild forms, this interaction increases the risk of poor early childhood development, severe disease, and death.[23,26] Focusing on severe anaemia (SA), country studies in SSA found a high risk of mortality and morbidity in children, younger than 5 years old, during the months after they received treatment for SA and were discharged from hospital.[27–29] In this postdischarge period, children remain anaemic and highly vulnerable until their full hematologic recovery. A malaria infection before full recovery substantially increases their risk to die or to be readmitted.[29–31] A recent meta-analysis of predictors for postdischarge mortality and morbidity in children younger than 15 years, living in malaria-endemic African countries, found that the mortality by six months postdischarge in children admitted with severe anaemia (SA) was more

than double that of children without SA.[32] They also faced a higher risk of readmission during this period. It was recently estimated that in sub-Saharan Africa, annually, 134 000 children survive the acute treatment for SA, and enter the high-risk phase of recovery at home, in a malaria transmission area.[33]

The global response: eliminating malaria in the long term

The global long-term goal to eradicate malaria was first proclaimed by the WHO in 1955.[34] It has since been regularly re-affirmed, and at its core this remains the global vision today. Most notably, under the UN Sustainable Development Goal (SDG) 3, "to ensure healthy lives and promote well-being for all at all ages", the key target (SDG 3.3) to "end the epidemics of AIDS, tuberculosis, malaria (…)" by 2030 was declared.[9] The corresponding strategy is, in parallel, spelled out in the WHO's "Global Technical Strategy for Malaria 2016-2030" (GTS, with an updated version from 2021) and the Roll Back Malaria Partnership's (RBM) "Action and Investment to defeat Malaria 2016-2030". For a Malaria-Free World".[35,36] In both documents, four shared indicators for the SDG 3.3 are specified: a global reduction by 90% of (1) malaria deaths and (2) malaria cases, compared to 2015; in addition, (3) in 35 countries malaria should be eliminated since 2015, and (4) re-establishment of malaria should be prevented. These strategies also determine global milestones to monitor the progress towards each 2030-indicator for the years 2020 and 2025.[37]

Arguably, the goals were overambitious. They were defined under the impression of achieving the ambitious global malaria-related goals during the Millennium Development Goals-era, 2000 to 2015, when the malaria mortality rate was reduced by 65 and an initially growing case incidence by 37%.[38–40] The remaining malaria burden, however, has since proven to underly more resilient, complex patterns. It had further concentrated on sub-Saharan Africa, where the population at risk has been growing, while coverage of malaria control interventions plateaued, and access to primary health care remains compromised.[41,42] As a result, between 2015 and 2020, the reduction in mortality and cases in SSA nearly stagnated. Modest successes were superseded by population growth, and, within the Region, progress in countries with the highest malaria burden was slowest.[43] As a consequence, there is a high likelihood that the malaria-focused agenda under the SDGs may not be achieved by 2030. Other models, therefore, projected more time until the end of malaria.[44] The 2019 Lancet Commission on malaria eradication, for example, estimated that 2050 was a "bold but attainable goal" to eradicate malaria.[45]

In response, the WHO and the RBM Consortium launched the "High Burden High Impact-Initiative" (HBHI). It focused on the eleven countries with the highest malaria burden - with exception of India, they were located in SSA, and the group included Uganda.[46,47] The objective of this campaign is to support these countries by developing and implementing tailored strategies to get them "back on track" onto the path of the GTS milestones and to achieve the 2030 agenda.[40,48] This approach invited greater strategic involvement of national governments, however, it also appealed to their will and accountability to achieve this effort. Alongside, the campaign "Zero Malaria Starts With Me", a Regional campaign originating in Senegal, emphasized the individual's responsibility to contribute to vector control, and to demand better governance to promote this agenda. [47,49] Alongside, the global discourse has increasingly focused on the political economy to fight malaria, highlighting both the national economic gains from reduced malaria burdens, and the global economic benefits.[50] Malawi, Kenya, and Uganda, among other countries, have faced some challenges in increasing their national ownership over implementation and research strategies.[51]

The WHO's Global Malaria Programme (GMP) is the international expert body to supervise the adoption of the GTS and to globally coordinate countries' efforts to fight malaria.[52] It reviews evidence and recommends interventions and implementation strategies for policy makers and health systems to adopt. Moreover, it points out research gaps that hamper the global progress towards the set targets. The GMP supports countries in the formulation of policies and co-monitors their progress. It also conducts systematic surveillance of malaria, develops relevant capacities across sectors, and continuously scans for potential threats to malaria control. It generally advises that countries build their efforts to fight malaria on three strategic pillars of malaria control: case management, prevention, and surveillance of malaria.[9] Case management and prevention will be introduced separately below.

Malaria case management

Malaria has been treated for centuries in endemic areas, using traditional treatment methods. Appropriating indigenous knowledge that quinine was effective against malaria-caused intermittent fevers, Western scientists isolated it in the 1820s and later on cultivated it.[53] The WHO recommends that a suspected infection be tested to confirm the diagnosis and specific parasite. Confirmed cases should receive antimalarial drugs that kill the parasite and, therewith, prevent the complicating of the symptoms towards more severe disease or death. P falciparum infections should be treated with artemisinin-based combination therapies (ACT), combinations of different artemisinins with lumefantrine (AL), amodiaquine (AS+AQ),

sulfadoxine-pyrimethamine, (AS+SP), or piperaquine (DHAP). They are indicated dependent on contextual and patient features, as well as availability.[54] The use of ACT is standard of care and widely prescribed, and most have a treatment efficacy above 95%.[55] In 2020, for example, almost 10 million courses of ACT were used in Malawi's population of then less than 20 million.[56] In addition to general treatment, special guidelines have been formulated for special risk groups, like pregnant women, young children and infants, and patients co-infected with HIV, among others.[54]

Key barriers to the effective use of antimalarial treatment are late and inaccurate diagnoses, drug resistance, and, particularly in sub-Saharan Africa, substandard quality drugs.[9,57] Widely used for treatment, ACT play an increasingly important role in prevention strategies for specific groups, like PDMC.[58]

Malaria prevention

Given the complex interaction between parasites, hosts, humans, and their environment, an effective prevention strategy to eliminate malaria needs to be multifaceted.[59] Preventive interventions include various vector control efforts and the use of preventive antimalarials in vulnerable populations, such as PDMC.[3] These areas of prevention will be briefly presented below, leading towards postdischarge malaria chemoprevention. This section will end with a brief mention of the first malaria-preventing vaccine that was recently recommended by the WHO for widespread use.[60]

Vector control is a summary term for interventions that control the mosquito population, in any developmental stage, or prevent its contact with humans. The most widely used interventions are using insecticide-treated bed nets (ITN) and indoor residual spraying (IRS). The WHO recommends both for malaria endemic areas.[9] Especially the mass distribution of ITN that kill or deter mosquitoes and prevent their bites at night time has been attributed with substantial reductions in malaria incidence over the past decades.[61] The effectiveness of IRS has also been widely proven, however, it depends on various interdependent factors.[62]

Meanwhile mosquitos developing resistance against the insecticides used in these interventions, or their changing the biting behaviour, threaten successful vector control.[63,64] Vector monitoring is, therefore, important to remain responsive to a changing threat and be able to adjust control decisions accordingly.[9] The WHO's vector control strategy includes other interventions complementary to ITN and IRS, like larval source management. It has high

potential to reduce the malaria incidence – but a successful implementation strongly depends on the environmental context and local participation in the interventions.[65,66] Meanwhile, house improvement, genetically modified mosquitos, and different forms of poisoning are still being tested.[59] In conclusion, a comprehensive vector control strategy should consist of various, often combined, interventions and their continuous evaluation and improvement.

In recent years the reduction of malaria incidence in SSA has slowed down and partly stagnated.[43,67–70] In order to further reduce the burden of malaria, new control strategies were developed to target vulnerable sub-populations, generally using single antimalarials or, more common, different ACT for chemoprevention of malaria in these groups.[71] Often, these strategies would focus on treatment of these populations during specific periods of high transmission risk and vulnerability, such as rainy seasons or during infancy and pregnancy. They were therefore often called intermittent preventive therapies (IPTs).[58,72] These measures should generally be implemented alongside a wider malaria control strategy that includes population-wide measures.[9]

IPT for pregnant women (IPTp) was proven an efficacious, feasible, and cost-effective intervention and the WHO recommends it in its Guidelines for malaria control since 1998.[73,74] IPTp uses SP as antimalarial agent. In most countries, the delivery has been aligned with regularly scheduled antenatal care (ANC) visits. However, due to often interrupted or incomplete ANC, IPTp adherence has been compromised and alternative delivery strategies are currently evaluated, among them community-based delivery.[75–77] Another example of IPT delivery aligned with routine care schedules is IPT for infants (IPTi; increasingly called Perennial Malaria Chemoprevention, PMC). It was pragmatically aligned with established immunization schedules of infants when it was adopted to the WHO Guidelines in 2010.[72,78]

Seasonal malaria chemoprevention (SMC, previously also called IPT for children, IPTc), is the antimalarial treatment of asymptomatic children, aged 3 to 59 months, during malaria season in high transmission areas. The WHO recommends SMC since 2012.The purpose is to protect these children during a high transmission-period from malaria infections and to reduce the burden in their households.[79–81] Here, too, the safety and efficacy was proven and various delivery options were tested, and are continuously explored to increase relatively low uptake rates.[82,83] The scope of IPT-strategies expanded, including the development of postdischarge chemoprevention (PDMC), the topic of this thesis, which will be described in detail below. IPTsc (IPT for school children) is currently researched, with acceptability and feasibility

proven, but some uncertainty about both the optimal regimen and delivery path.[54,84–86] Mass drug administration, which is a summary term for treatment of larger populations, generally, irrespective of their risk, is currently recommended only in specific situations of either immanent emergencies or final measures towards national malaria elimination.[87]

Drug quality and drug resistance are likewise important concerns to rolling out effective chemoprevention programs. In addition, it remains unclear, if IPT negatively affects immunity building in children.[88] Based on "imperfect evidence", a recent review concluded that malaria chemoprevention interventions did not meaningfully increase resistance and that they, in fact, remain relatively effective in presence of higher resistance in the targeted populations.[89] Nonetheless, these measures' efficacy would inevitably be reduced by an increased overall resistance against any ACT used for IPT. Hence, in order to ensure the lasting effectiveness of chemoprevention measures in spite of complex resistance patterns, the constant development of new, safe and effective malaria drugs and their effective delivery is needed.[90]

Malaria vaccines: a new hope?

In late 2021, the WHO adopted the first malaria vaccine, named RTS,S/AS01 (RTS), for malaria prevention in infants living in areas with moderate or high malaria transmission. Four doses are needed to obtain a 36% efficacy against malaria after four years in children aged between five and 17 months at vaccination. Documented outcomes include reduced malaria cases, all-cause hospital admissions, and fewer blood transfusions.[91] RTS has been administered to more than one million children in Malawi, Kenya, and Ghana as part of a pilot rollout-out.[92] The protective effect, long-term outcomes, and differences depending on transmission intensity, are researched alongside this roll-out, as well as different timings of the regimen.[93,94] Notably, in the case of SMC, the use of the vaccine was not superior to standard SMC; however, combining both showed significantly higher efficacy against malaria-related outcomes.[95]

RTS is a relatively affordable, conventional vaccine with moderate efficacy.[96] With a substantially higher expected efficacy, next-generation vaccines are currently researched. R21, for example, an antigen-based vaccine with a stimulant for immune response has shown an initial efficacy of at least 70% after the first year of research.[97] Monoclonal antibody-vaccines appear promising due to high initial efficacy and a single dose-regimen.[98,99] Likewise, in the wake of the Covid-19 vaccine development, different mRNA-based malaria vaccines are in

different phases of testing with indications of a comparably high expected efficacies, but potentially more complicated regimens and delivery logistics.[100]

These vaccines promise a potential breakthrough on the road to eradicate malaria. However, the expected relatively high cost – once approved – as well as logistical and local capacity challenges may nonetheless brake vaccine roll-out with national coverage in sub-Saharan countries.[101,102] Smaller, particularly vulnerable groups, however, such as the children currently recommended to receive PDMC, may benefit early on from combined regimens or obtain vaccine access faster than the general populations.[58,88,95]

Postdischarge malaria chemoprevention (PDMC)

The observation of high postdischarge mortality and morbidity in children who were hospitalized and received a blood transfusion as treatment of severe anaemia motivated the development of two RCTs in the early 2000s. In the Gambia, Bojang et al assessed the effect of one month-lasting antimalarial protection, using SP, on child morbidity throughout the transmission season.[103] The results, published in 2010, were mixed: a reduction in malaria was found while no significant differences in the occurrence of anaemia was detected between the intervention and control groups. Alongside, Phiri et al conducted a similar RCT in Malawi with a more inclusive outcome definition, published in 2012.[29] Children younger than 5 years, treated in hospital for severe anaemia, received either malaria chemoprevention or a placebo over an effective period of 3 months, passively followed-up for another three months. This trial used AL, and the intervention was then called IPTpd (postdischarge). It detected a protective effect of 31% against death or readmission with severe malaria or severe anaemia in this period. In view of these promising results, IPTpd was included in the catalogue of potential strategies to protect particularly vulnerable groups in areas of high malaria transmission, subject to further evidence. The abstracts ends with the recommendation that "studies to confirm these findings and to investigate different delivery mechanisms and cost-effectiveness are needed."[104]

The PDMC Consortium (see Scientific Environment, p. 5) gradually addressed this need, since 2014, with different trials and studies. During this period, IPTpd was re-named postdischarge malaria chemoprevention, initially with the acronym PMC and, since WHO adoption in June 2022, PDMC. Generally following the intervention design by Phiri et al, the Guideline Development Group on Malaria Chemoprevention (GDG) defined PDMC as "the

administration of a full antimalarial treatment course at regular intervals to children admitted with severe anaemia (…) during the period after hospital discharge when they are at high risk of re-admission or death. (…) PDMC should be given even when the cause(s) of severe anaemia in an individual cannot be identified".[54] The group issued a conditional recommendation in favour of PDMC for areas of moderate-to-high transmission, assessing the certainty of the evidence as moderate. The evidence comprised an interdisciplinary selection of research mainly produced by the Consortium, including one multicentred clinical efficacy trial, a delivery trial, and qualitative studies on the acceptability and feasibility, and a preprint of the cost-effectiveness analysis presented in the thesis (Paper 2).[28,54,105–107] The two trials provide elementary data to the research in this thesis. They are briefly described below, and in more detail in the beginning of the methods chapter.

In the PDMC "efficacy trial" Kwambai et al followed the rationale of Phiri et al and conducted a multi-centre randomized controlled trial (RCT) with the primary objective to confirm the protective effect found in Malawi for Uganda and Kenya, and thus expanding the initial evidence from Malawi to areas with moderate-to-intense perennial malaria transmission in Eastern Africa.[28] They used monthly 3-day treatment courses of DHAP, protecting against a malaria infection for approximately four weeks, and thus superior to the two weeks-lasting effect of AL. The trial confirmed the high postdischarge disease burden on these children. More than one third of children in the placebo group were readmitted or died within the six-month postdischarge period. The intervention had a protective effect of 70% against any-cause mortality and morbidity within 3 months of discharge, and 36% within the complete 6 months. This was largely due to the antimalarial treatment preventing events of severe malaria or severe malarial anaemia, the dominant diagnosis of readmission in the placebo arm. A reduction in deaths was observed, however not statistically significant. The adherence was estimated at 98%. Notably, the beneficial effect was restricted to the first three months postdischarge, during the observation period when the antimalarial had waned off, the intervention group showed a significantly higher occurrence of adverse health events than the placebo group. This "rebound"-effect informed new PDMC regimens and delivery designs that are currently researched.

Phiri and Kwambai's efficacy estimates likely overestimated the effectiveness of PDMC once delivered under routine conditions. In controlled trial environments, both reported near perfect adherence, an unrealistic assumption for the delivery of a household-based intervention at scale. With IPTpd proven safe and efficacious, Gondwe et al could conduct a delivery trial for

PDMC in Malawi, in parallel to the efficacy trial in Kenya and Uganda. Using a cluster-randomized design, it aimed to determine the adherence of caregivers to PDMC, likewise using DHAP, via two scalable delivery strategies.[105]

Like in the efficacy trial, at discharge, all children received the standard of care postdischarge treatment as in the efficacy trial: artemether-lumefantrine (AL), providing malaria prophylaxis for approximately 12 days after discharge. Community-based PDMC-delivery comprised of the same PDMC regimen as in Kwambai, with all three courses of three daily tablets were given to caregivers at discharge with instructions how and when to administer them to the child at home, hence called *community-based*. Facility-based PDMC-delivery used the same regimen, however, with the requirement that the caregivers collected each monthly course from the hospital's pharmacy individually.

Community-based PDMC delivery resulted in a substantially larger proportion of caregivers with high adherence than the facility-based strategy: 24% more caregivers administered 7 to 9 tablets. The results on whether SMS reminders, factorially added to the delivery strategies, were inconclusive. Qualitative studies nested in the trial confirmed the feasibility and the caregivers' acceptability of both delivery arms, with a preference for community-based delivery.[106,108]

Overall, the WHO recommending of PDMC sits well with a growing understanding of the postdischarge period in LMICs as much stronger contributor to child mortality and morbidity than widely known.[81,109–111] A predictive modelling study estimated that half of paediatric mortality in SSA occurred after discharge.[112] A recent international cohort study of child mortality covering among other countries, Kenya, Uganda, and Malawi, suggested that "almost half of mortality occurs following hospital discharge" and that "despite being highly predictable, these deaths are not addressed in current guidelines". The authors call for a fundamental shift to a "child-centered, risk-based approach to inpatient and postdischarge management (…) to further reduce childhood mortality".[113] This is mirrored by a recent call for a concerted international effort to address the complex reasons underlying the high postdischarge neonatal and child mortality.[111]

Currently ongoing research builds on these initial results aiming to test the effectiveness of different dosing regimens and durations, involving community health services in PDMC-delivery, as well as treatment combinations with antibiotics, and detailed implementation costing (unpublished protocols). Moreover, there are tentative discussions to recategorize

PDMC as treatment, rather than prevention, linking it directly to the SA-treatment received at the hospital until discharge. This “continuum of care”-suggestion would mitigate concerns in health systems to use a drug (DHAP) for prevention that is, at the same time, widely used for malaria treatment.

Study context: Malawi, Kenya, and Uganda

This section provides an overview of the wider research contexts of this thesis, and of the data used in it. The three research papers presented in this thesis are focused on Malawi, while only Paper 2 covers Kenya and Uganda, in addition to Malawi, in a cost-effectiveness analysis. Malawi will, therefore, be described in more detail, laying the ground for all three studies, while Kenya and Uganda will only be introduced with the economic evaluation in mind. The aim of this section is to briefly describe the populations’ structures, each country’s state of development, and their health care system. These are key factors for decisions on national PDMC implementation.

Geography, demography, and economic development

The Republic of Malawi is a landlocked country in southern Africa, dominated by mountainous terrain and plateaus with moderate continental climate at elevation and warmer climate in the lower areas in the south and plains around Lake Malawi. During the rainy season from November to April the climate is generally warmer.[114] Further north, Kenya and Uganda are neighbouring countries in East Africa. Kenya’s north and east are covered with large arid desert land with exception of the tropical coastline. Towards the high plateaus and mountainous territory in the southeast, the climate gets cooler with temperate climate at highest elevations, before the landscape descends to Lake Victoria’s shores, where a tropical climate dominates. Uganda’s is a landlocked country with more a homogenous climate that is, overall, more humid. Tropical rainforest along Lake Victoria transitions into tropical, continental savannah climate in most of the country, with sporadic temperate climate at high elevation.

Malawi has a fast-growing population with a total fertility rate of 4.1, resulting in more than 600 000 annual births in a population that recently exceeded 20 million people.[115] Nearly one half are younger than 14 years old.[116] The population’s proportion of rural dwellers is among the highest worldwide, estimated at 82%.[117] The agricultural sector provides livelihood to approximately 80% of the population while contributing one third to the GDP. Largely dependent on rainfed agriculture, the country’s economy and overall development depend on

subsistency-favorable growth conditions. In recent years climate change-related shocks, both drought and flooding, have stalled economic growth.[118] Structural economic reforms have been envisioned but implementation has lagged behind.[119]

While peaceful since its independence from Great Britain in 1964, and largely democratic and politically stable over the past decades, Malawi remains among the poorest countries in the world. The national poverty rate was estimated at above 50% for 2021, and has remained unchanged since 2010.[119] The number of people in poverty, accounting for population growth, has grown by 2 million people during the last decade. The World Bank's internationally comparable poverty headcount-ratio ranks Malawi as the sixth poorest nation, estimating that over 70% of the population in 2021 lived of less than US$1.90 daily.[119] Poverty and food insecurity are more prevalent in the rural than in the urban areas. Populations in Southern Malawi are more affected than those in the Central region. Northern Malawi has the lowest incidence of poverty and food insecurity. An estimated 20% of the population (3.8 million) faced food insecurity between November 2022 and April 2023.[120] Notably, some improvements have been achieved over the past years, notably a relative reduction of the "ultra poor", the overall development has stagnated. The national poverty rates are nonetheless alarming because they document a trend singular to Malawi. Neighbouring countries Tanzania and Mozambique had higher poverty rates than Malawi in the early 2000s whereas today both have lower poverty rates.[119]

Kenya is more populated with approximately 55 million people, Uganda's population counts 47 million people.[121,122] Comparing key development indicators of Kenya and Uganda, the life expectancy at birth of 67 years and 64 years, annual population growth of 2.2% and 3.0%, or the poverty headcount ratio indicating that 29.4% and 42.2% of the population dispose of less than at US$2.15 per day, respectively, Kenya has attained a higher overall development level than Uganda. This is mirrored in the UN's counting Uganda and Malawi among the 46 least developed countries, whereas Kenya has long "graduated" from this category.[123]

Malaria and anaemia in the (child) population

Malaria generates a high disease burden in Malawi. Approximately 7 million confirmed malaria cases were reported for 2022 in Malawi, while international projections were overall lower, between 4 and 6 million.[9,124] The risk of infection varies by season and depending on environmental factors, where the warmer, lower-lying areas generally offer a better habitat to

parasite-hosting mosquitoes. However, even during dry season and in Malawi's areas of lower infection risk, transmission occurs throughout the year.[56,125]

The 2019 Global Burden of Disease Study (GBD-study) estimated the annual mean malaria incidence rate of plasmodium falciparum among children 0-4 years old in Malawi between 53 800 in the Southern and 42 400 in the Northern Region (national mean: 50 900 per population of 100 000), resulting in more than 1.3 million annual cases in this population in Malawi.[126,127] The incidence rates have stagnated since 2015. Malaria-related annual deaths in this group were estimated to make out 13% of Malawi's total under five mortality of 31 820 in 2019. The number of girls both suffering or dying from malaria is significantly higher than that of boys in Malawi.[126–128]

It was recently estimated that at least 40% of preschool children in Malawi are anaemic, mostly attributed to malnutrition and malaria (P. falciparum).[127,129] The strong association between the presence of a malaria infection and the prevalence of anaemia has long been established, and was recently confirmed for this specific population in Malawi.[23,130,131] Aside from malaria, various causes of anaemia exist, and may co-exist, resulting in various sub-diagnoses.

Both Kenya's and Uganda's populations likewise carry a high burden of malaria infections, disproportionately disadvantaging the most vulnerable groups, who have limited access to quality health care.[132,133] In spite of large shares of the populations in both countries living at relatively high elevation, the risk of infection persists year-round, albeit with a generally increased risks following rainy seasons. The per capita case incidence and mortality in Uganda are the highest compared to both Kenya and Malawi. Due to population size, Uganda shoulders the highest absolute case incidence in East Africa, accounting for over 5% of global cases in 2021 (following Nigeria and the Democratic Republic of the Congo in SSA overall), whereas the more populated Kenya shoulders less than 2% of both global case incidence and mortality. Despite its substantially smaller population, Malawi caries a share of the global burden comparable to Kenya, due to the higher case incidence and mortality. Therewith, Uganda lies above the sub-Saharan average, whereas Kenya's burden is among the relatively lowest in the Region, however with large in-country variation.[9,134]

The demand for PDMC

Children who were successfully treated for any severe anaemia, with exception of specific causes of anaemia (mainly sickle cell disease, cancer, or trauma), are eligible for PDMC. A recent mathematical modelling study estimated the annual demand for PDMC in Malawi to be

around 1 524 cases, with a range between 651 to 3 571 children depending on variation in the modelled hospitalization rate. The demand for Kenya was comparable with 1 659 (range: 707 to 3 893) children eligible for PDMC, annually, while in Uganda this demand was substantially higher: approximately 6 962 (range: 2 963 to 16 356), respectively. Malawi and Kenya contribute slightly more than 1% to the estimated overall demand of PDMC in sub-Saharan Africa, while the population eligible to receive PDMC in Uganda make out 5% of the Regional total estimate of 133 719 (56 932 to 314 058).[33]

Health care systems and the policy frames of PDMC

Malawi's health system consists mainly of public and some private, faith-based or for-profit, health care facilities. The public system is structured along four delivery levels. At the lowest level, community-based care is provided by health surveillance assistants (HSAs) covering approximately 1 000 citizens in a radius of less than 10km.[135,136] Five central hospitals (including Zomba Mental Hospital) constitute the highest, tertiary level-care, meant to provide specialist care to the whole population, including paediatric treatment for severe anaemia.[136,137] Malawi's health care system stands out internationally with a tradition of providing "free" health care to patients, meaning services, equipment and medications disseminated are publicly subsidized and no user fees are levied in primary care.[138] However, the financial protection of users from catastrophic health care expenditure has multiple limitations and is de facto distributed inequitably as result of strong resource constraints within the public system.[139] In addition to the costs of care, rural populations' health seeking behaviour is often compromised by the cost and time to travel to relatively distant care facilities.[140] Recently, more equitable distribution mechanisms have been considered, which intend to facilitate a transition towards national universal health coverage (UHC)-provision.[141,142]

In the government's 2020 voluntary report to the UN, self-reporting the national performance towards the SDG targets, the Malawi government chose to not mention malaria.[143] However, it has been estimated in the Commonwealth Malaria Report 2022 that Malawi was falling behind the milestones of malaria-related target, most notably the two main indices, malaria mortality and incidence (using data from 2019).[144] For the next five years, it appears that the government plans to budget an annual per capita expenditure on health of less than US$10 from its tax revenue – almost the same it had spent annually since 2019 and only a fraction of what would be needed to deliver the envisioned essential health package (which includes only Malaria treatment to date, not prevention) at scale.[145–147] Malawi will thus continue to depend on external resources in the pursuit of malaria elimination.[148]

Kenya's and Uganda's health systems are both more devolved than Malawi's. Kenya has a highly decentralized structure with de facto decision powers delegated: the health care system is organized at six levels, of which the lower five are the responsibility of the 47 counties.[149,150] Approximately half the health facilities are public institutions. One third of the private facilities are not-for-profit-based, whereas two thirds are for-profit facilities.[151] Being a low middle income country, Kenya disposes of better means than Malawi and Uganda to finance its health care services. Kenya's government contributes on average US$38.90 per capita (2019) of the total annual per capita health expenditure of $83.41.[121,152] While no user fees are levied in Kenya, public institutions charge relatively small registration fee. Like in Malawi, in Uganda, user fees have been abolished and public primary healthcare is supposed to be provided free of charge by the public facilities. However, 70% of health care services in Uganda are delivered by private sector-facilities, half of them for profit institutions. Primary health care, especially in rural areas, remains largely provided by the public sector, and implementation decisions are, in fact, largely made at the centre. [153,154] The access to health care remains unequal in Uganda with the rural population often disadvantaged.[155–157] Uganda's general government health expenditure per capita for 2019 has been estimated to be $4.90.[122]

In line with the SDGs, Kenya has committed itself in the "Kenya Vision 2030" to eliminate malaria while introducing UHC. Among the chemoprevention programs, currently, only IPTp is included within the UHC-package.[82] In a 2020 report tracking its progress towards the SDGs, Kenya reported to be lagging substantially behind the malaria-related target under SDG3.3.[158,159] The counties' discretion in implementation decisions and their limited central accountability have reportedly frustrated both centralized performance monitoring and an equitable implementation of the 2030 health agenda.[160,161]Like in Kenya, the ambition to achieve universal health coverage dominates the discourse on priority setting and healthcare financing in Uganda.[143,150] There is no mention of malaria chemoprevention, aside from a planned increase of IPTp- and group-unspecific MDA-campaigns on National Malaria Days, twice annually. The latest tracking report of the SDG 3.3. showed a markedly increase between the last two reported years, 2018 and 2019.[162]

Summary

When considering PDMC for national implementation, each country presents individual features that should influence the decision whether to introduce PDMC but also, if yes, which delivery-path should be chosen. While it goes beyond the scope of this work to present, discuss, and compare these features comprehensively, the country overviews above offer a short

account of their relative level of poverty and its distribution, the burden malaria presents to their population, how it is domestically distributed, the health system structures, as well as their overall available resources, and their capacity to implement new malaria prevention programmes.

The following three papers in this thesis present research relevant for an informed deliberation on national PDMC adoption. They inform on implementation design matters, cost-effectiveness of different delivery strategies, and the qualities of remaining uncertainties around PDMC. The results must, however, always be seen through the lens of a specific country's context.

Rationale and Objectives

Rationale

Chemoprevention has become an elementary part of the global strategy to eradicate malaria. It encompasses a growing body of WHO-recommended interventions, PDMC being the latest addition in June 2022. Part of the work in this thesis was considered by the WHO to decide on adopting PDMC.[163] In addition to informing this process, the purpose of this thesis is to support decision-makers in sub-Saharan countries to evaluate and address remaining uncertainties during their deliberations on PDMC implementation. Three specific rationales, focused on PDMC delivery, undergird this justification.

Firstly, experience from implementing other IPT interventions showed that social and environmental risk factors for malaria in children were hardly included in implementation decisions.[21,135] In the past, dismissing the influence of socio-cultural factors on communities' policy uptake has compromised the effective implementation of malaria control efforts in Malawi.[164] This risk is particularly high for interventions like PDMC, because it cannot be easily integrated in existing routine care. Yet, the determinants that affect caregivers' adherence to PDMC remain widely unknown. Tailoring implementation designs according to these factors – once known – may increase adherence and equitable access to PDMC.

Secondly, as a precondition to consider PDMC for adoption, the WHO required an economic evaluation of PDMC. In the absence of any such analysis, a preprint of Paper 2 of this thesis was made available to the WHO. While the WHO was primarily concerned with the question of general cost-effectiveness, it was evident that for decision makers in Malawi, Kenya, and Uganda to consider the implementation of PDMC, country-specific cost-effectiveness analyses, adjusted for delivery strategies and local costs, would be more meaningful. In addition, the government of Malawi identified cost-effectiveness as a key selection criterion to evaluate interventions for inclusion in the national EHP.[146,165] A cost-effectiveness analysis of PDMC specific for Malawi would therefore provide the locally-informed evidence needed to decide on the inclusion as EHP-intervention – presuming a WHO-recommendation for PDMC was issued, as it was later on.

Thirdly, the Malawi's National Malaria Control Programme, through the International Centre of Excellence for Malaria Research (ICEMR), constantly compiles local evidence to inform the national policy to eradicate malaria. This role includes identifying research gaps that

complicate decision-making.[166–168] The cost of research to reduce these uncertainties varies depending on the method needed to close a specific knowledge gap. Likewise, the impact of research projects varies. In the case of an economic evaluation, some new data may have no bearing while another finding may cause a shift in what constitutes the optimal treatment. The potential value of new evidence, that is the value of perfect information on a currently uncertain question, can be estimated by means of a value of information (VOI) analysis. It calculates the monetary benefit of certainty on one or more questions to a health system. Yet, no VOI analysis of uncertainties surrounding PDMC delivery exists. Such a quantification of remaining research gaps around PDMC for Malawi, and for the wider sub-Saharan Region, may guide the ICEMR in Malawi, or the equivalent institutions in other countries, when prioritizing national research needs on PDMC.

Objectives

The WHO recommends PDMC in malaria-endemic areas because it offers children at risk a protected period to recover from severe anaemia. PDMC contributes to the multifaceted global effort to eliminate malaria. This thesis provides evidence for health systems to manage uncertainty and take informed decisions on whether and how to routinely provide children in need with this protected recovery period. The overall objective of this thesis is to enable health policy makers to effectively implement PDMC in malaria-endemic areas. In line with the presented rationale, three specific objectives guided this work.

The first objective was to identify predictive factors for caregivers' adherence to PDMC in Malawi (Paper 1). The second objective was to analyse the cost-effectiveness of PDMC delivery, community-based or facility-based, compared with the standard of care in Malawi, Kenya, and Uganda (Paper 2), adjusted for adherence behaviour, and tailored to each country's context. The third objective was to establish the value of obtaining perfect and partial perfect information on remaining uncertainties around PDMC for Malawi, and for the sub-Saharan Region.

Materials and Methods

Overview

In this chapter, the materials and methods used in the three studies will be summarized. The studies relied heavily on two separate PDMC trials as data sources: an efficacy trial in Kenya and Uganda, and a delivery trial in Malawi. The trial designs and data collection procedures will be summarized first, before presenting the methods used in each paper, separately, including the study-specific use of the trial data. Paper 1 (predictor analysis) is a secondary analysis of data collected in Malawi during the PDMC delivery trial. Papers 2 (cost-effectiveness analysis) and 3 (value of information analysis) use data from this delivery trial and data from the PDMC efficacy trial conducted in Uganda and Kenya. The cost-effectiveness analysis includes additional cost data from a costing study nested within the delivery trial, and from the literature. Paper 3 builds largely on materials and methods used in Paper 2. In addition, it uses data from two modelling studies to transfer results for Malawi, Kenya, and Uganda to other sub-Saharan countries. Table 1 summarizes the data sources per paper.

Table 1: Overview of objective, data, and country focus per paper.

Paper No.: Design	**Short Objective**	**Data Sources**	**Country focus**
Paper 1: Predictor Analysis	Determine predictive factors for adherence to PDMC	- Delivery trial (Malawi)	Malawi
Paper 2: Cost-Effectiveness Analysis (CEA)	Compare cost-effectiveness of PDMC delivery strategies and standard of care	- Efficacy trial (Kenya, Uganda) - Delivery trial (Malawi) - Literature	Malawi, Kenya, Uganda
Paper 3: Value of Information Analysis (VOI)	Identify research uncertainties around PDMC with the greatest impact if reduced	- Paper 2 (CEA), i.e.: o Efficacy trial (Kenya, Uganda) o Delivery trial (Malawi) - Literature o Okell et al, 2023 o Pichon-Riviere et al, 2023	Malawi, Kenya, Uganda; sub-Saharan Africa

Data sources

The PDMC efficacy trial in Kenya and Uganda

Aiming to assess whether PDMC could reduce postdischarge child morbidity and mortality, Kwambai et al conducted a parallel, two-group, individually randomized, double-blind, placebo-controlled, superiority trial from May 2016 until May 2018.[28] Children younger than five years old admitted to hospital with severe anaemia were eligible. In nine public and private Ugandan and Kenyan hospitals, 1 040 caregiver-child pairs were enrolled in the trial after the children had received standard inpatient treatment (blood transfusion(s), antimalarial treatment, and where indicated antibiotic therapy). Children with sickle cell disease, those with other known specific reasons for their anaemia (f. ex., trauma, cancer) other than malaria were excluded from recruitment. The randomization to the intervention or placebo arms were performed independently. The allocation to the trial arms was unknown to the caregivers, investigators including the statisticians and the wider Consortium, and all trial staff until the conclusion of the trial.[104]

The trial used DHAP for PDMC. At discharge, all children received a two-week lasting preventive antimalarial treatment (AL) in line with both the Kenyan and the Ugandan national standards of postdischarge care following treatment for severe anaemia in this age group. After this period, caregiver-child pairs were visited at home and started a randomly allocated PDMC or placebo treatment, with the administration of the first dose directly observed by the trial staff during the visit. For younger children this involved dissolving a tablet in water. Children that vomited were provided with an additional tablet. Identical to the first course, the second and third course, four and eight weeks later, respectively, comprised a directly observed first dose during community visits. Doses two and three on the following days were not observed, but participants were reminded of each dose via phone contact.[104]

A combined primary outcome was defined as any cause hospital readmission or death of treated children within six months from discharge. Children were followed-up for 26 weeks (two weeks of standard of care, 12 weeks of intervention period including an estimated four-week effect of the last course following administration at week eight, and 12 weeks of post-intervention period). Secondary outcomes included causes of hospital readmissions and outpatient clinic visits. Health outcomes were included in the analysis from 2 weeks postdischarge until the end of the follow-up period, 24 weeks later. Main outcomes were reported in hazard ratios and stratified by the intervention and post-intervention periods.[28]

As part of the trial procedure, households' direct and indirect costs were collected. During enrolment, caregivers were interviewed inquiring the duration and cost of transport of the child to the hospital, including the cost of other accompanying adults. The time spent at the hospital before enrolment, and all expenses at the hospital were likewise collected, for example for medications, food, equipment, and any other expected and unexpected expenses. At the exit interview of the trial, caregivers were interviewed about the intervention cost, including the average time spent to administer a monthly course of three tablets to their child, caring in case of potential side-effects like vomiting, and observing the child after each given tablet. At unscheduled hospital visits, the same procedure as during enrolment was followed to collect data on the household cost associated with a readmission and an outpatient department visit. In Kenya, standard hospital admission fees were added to the household costs. All cost were collected by study personnel in local languages and encoded in English using Open Data Kit software (ODK). Local currencies were used. The time spent by the caregivers and any other adults was valued using minimum national salaries. In this trial, no data were collected from the provider perspective.

The PDMC delivery research in Malawi

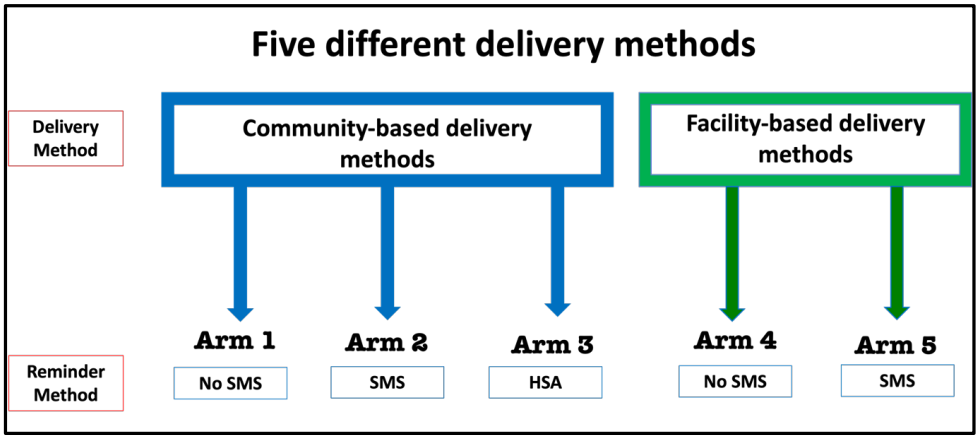
In parallel, the Consortium aimed to research the adherence of caregivers to PDMC, likewise using DHAP, via two scalable delivery strategies.[105] Gondwe et al conducted a single site, parallel-group five-arm, cluster-randomized trial between March 2016 and October 2018 in Zomba Central Hospital (ZCH), a tertiary care hospital covering Southern Malawi, the purposely selected catchment area for this trial.[108]

The eligibility criteria and enrolment procedure were the same as in the efficacy trial. To avoid contamination across the intervention arms, the villages in the catchment area were clustered and assigned to either of the two delivery strategies: (a) community-based PDMC delivery and (b) facility-based-delivery. The strategies were factorially combined with two and three reminder options, respectively, resulting in a total of five arms, into which a total of 375 caregiver-child couples were enrolled (Figure 1).[105] At discharge, all children received the national standard of care postdischarge treatment, providing protection against malaria for approximately 12 days.[108]

Community-based PDMC delivery comprised of the same PDMC regimen as in the efficacy trial, however with all three courses of three daily tablets given to caregivers at discharge with instructions how and when to administer them to the child at home. Factorially added reminder-

options were (a1) ´no reminder´, or (a2) a generic SMS reminder to the caregiver's phone, or to the phone of someone close to the household, reminding them before each course to administer it as instructed. Thirdly, (a3) the local health surveillance assistant (HSA, the equivalent of a village health worker elsewhere) would be reminded via SMS before each course to convey in person a reminder to the household.[107] *Facility-based PDMC delivery* used the same regimen, however, requiring that the caregivers collected each monthly course individually from the hospital's pharmacy. There was no HSA-reminder for this strategy. (Figure 3).

Figure 1: Overview of the delivery trial design, borrowed from Gondwe, 2021.[105]



As indicated in the background chapter, the trial results were not conclusive on the effect of the added reminders. In the studies presented here, we therefore pooled the reminder arms per delivery strategy. Once pooled, 223 caregiver-child pairs provided data for the community-based delivery, and 152 were allocated to facility-based delivery of PDMC (Table 2).

The primary outcome of the trial was caregivers' *high adherence* defined as seven to nine of nine possible doses given to a child vs adherence to less than seven tablets. Aside from health outcomes, secondary trial outcomes included a categorical adherence outcome, grouping adherence in four adherence ranges (*full*: all 9 tablets; *medium*: six to eight; *low:* three to five, and *no or very low*: two tables or fewer, including zero taken tablets. Outcome data on adherence was collected and encoded during unannounced monthly household visits shortly after each monthly PDMC course was scheduled to be completed. The number of empty blisters per returned DHAP-blister pack determined caregivers' adherence, with zero of three returned tablets indicating full adherence to one course. If caregivers allocated to facility-based delivery

failed to collect a PDMC course they were recoded as non-adherent for that monthly course without visit. All data was collected by trial personnel in Chichewa, and directly encoded in English using Open Data Kit software (ODK).

Table 2: Data for the five arms used in the implementation trial (Gondwe et al, 2021) were pooled in two arms: community- and facility-based PDMC delivery, thus removing the factorially added reminder options.[105] *This table is borrowed from the supplementary material of Paper 2.*[169]

	Community-based delivery of PDMC					**Facility-based delivery of PDMC**			
	3 arms in Gondwe et al (2021)					**2 arms in Gondwe et al (2021)**			
Category of adherence/Reminder	**Com -SMS**	**Com +SMS**	**Com +HSA**	**pooled total**	**percent (%)**	**Fac -SMS**	**Fac +SMS**	**pooled total**	**percent (%)**
No or very low	1	2	2	**5**	**2.3**	4	2	**6**	**4.0**
Low	8	4	6	**18**	**8.1**	12	14	**26**	**17.3**
Medium	16	9	17	**42**	**19.0**	21	19	**40**	**26.7**
High	43	59	54	**156**	**70.6**	39	39	**78**	**52.0**
Total	**68 (100)**	**74 (100)**	**79 (100)**	**221**	**100.0**	**76 (100)**	**74 (100)**	**150.0**	**100.0**

In the studies presented in this thesis, we used this stricter outcome definition for adherence by four categories to the trial data. The justifications for this vary between the studies and are described separately. In short, the largest proportion of caregivers, in both strategies, adhered to all nine tablets. Community-based PDMC resulted in higher adherence than the facility-based strategy with 71% and 52% adherence, respectively, to the full three courses.[105] Given the large size of this group, regardless of strategy, it was useful to maintain the strictest definition for the fully adherent group. On the one hand, this allowed a comparison with all caregivers who did not adhere to at least one tablet, which was done in the predictor study (Paper 1). In Papers 2 and 3, on the other hand, using these four categories that reflect, in practice, the three courses and zero adherence, was useful to assess more sensitively the differences in cost and effectiveness depending on adherence.

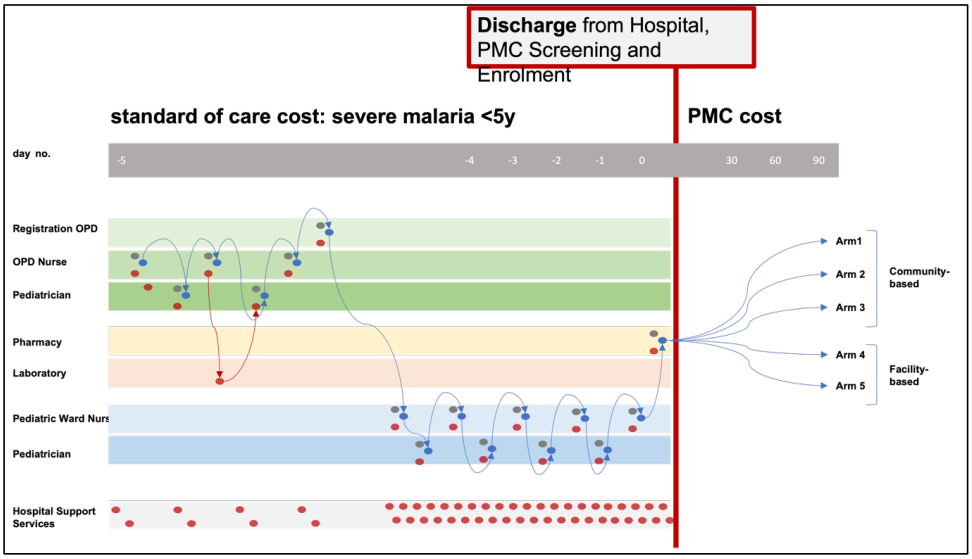
In this trial, direct and indirect household costs associated with the PDMC intervention were collected in a similar process as described in the efficacy trial. However, in addition, we included the differences related with the allocation to either delivery strategy. This covered the financial costs, as well as the time spent, to repeatedly obtain the monthly DHAP courses (facility-based delivery), while the costs of the community-based delivery were limited to the financial and economic costs of obtaining all three monthly courses from the pharmacy at discharge. Data on household costs of adverse health events in Malawi, i.e., a readmission or an outpatient clinic visit, were obtained similarly as described for the efficacy trial.

In addition to household costs, in Malawi, we collected the direct and indirect provider costs associated with PDMC delivery and estimated costs of readmissions within six months of discharge. These costs were collected between June and September 2018 at ZCH by the PhD candidate. To determine the provider cost of delivering PDMC, we inquired the procurement costs of DHAP, including the standard surcharge for handling and wastage at the hospital. Two pharmacists instructing mothers on PDMC administration were observed and interviewed about the time they took to instruct a mother once, and, separately, to repeat the procedure twice in subsequent months for those allocated to facility-based PDMC delivery. The pharmacists' time used was valued by the real average salaries that the hospital paid pharmacists in this position, which were extracted from an overview of all salaries paid in June 2018. Additional annual or one time-payments were added to the average monthly salaries, proportional to one month. All payment information were limited to the hospitals' costs and did not include secondments or third-party subsidies.

The providers costs of adverse health events were collected at the same time. The basic cost components for an outpatient department visit (moderate disease) and for a hospital readmission (severe disease) was determined by means of observing a proxy process: the initial hospital admission with severe anaemia of trial participants later on enrolled in the trial, which was, according to hospital procedure, preceded by an assessment at the outpatient department.

In summary, the provider's average direct and indirect costs of treating a severe anaemia in a child younger than 5 years were established along four cost categories: health personnel, medication and medical equipment, hospital support services. Health personnel and equipment cost were collected based on an average caregiver-child pair's pathway from initial reception at the outpatient department until discharge (Figure 2). Observing patient-provider contacts, along the pathway, we inquired the average duration and the equipment used per contact. Personnel costs were determined per position, valuing the average time spent per readmission based the average monthly salary of each of the involved positions. Equipment used was determined on the basis of the interviews and average medication use was determined based on 50 random medical journal of patients that were enrolled in the trial. Medication prices were adopted from Malawi's national procurement system with the same 30% surcharge for handling and wastage. Unit cost per readmission were then weighted by the average use according to the journals' average. The same procedure was used to determine the cost for an outpatient department's visit, restricted to the contacts before admission (Figure 2).

Figure 2: Patient pathway of a child-caregiver pair treated for severe anæmia (child), based on observations done at ZCH.



Both departments' share of hospital-wide provided support services (including water provision, maintenance services, and security costs, among others) were estimated as a per-patient share of the hospital's annual expenses for these services. The inpatient- and outpatient departments' annual number of patients in the preceding year (2017) were available. However, the hospital's total number of patient days could not be determined and, instead, the roof surface of the IPD and OPD wards was calculated relative to the overall surface of all clinical buildings. Based on this ratio, the wards' shares of the total costs of support services was then distributed evenly across all patient days, and multiplied by the average duration of an admission for SA in Malawi. An overview of the collected costs is provided in the methods section of Paper 2, and in more detail the costs a summarized in Tables 3 to 8 of the supplementary materials of Paper 2.[169]

Lastly, the cost of blood transfusions were reported among the medication and equipment costs, however, they make out the highest single cost component and were therefore estimated and modelled separately. In Malawi, the cost of blood transfusion and associated laboratory costs were determined based on the literature and interviews of laboratory personnel. There are two main sources for blood transfusion packs in Malawi: a central blood bank and locally donated blood. The ratio of centrally and locally produced transfusion packs used in the ZCH was considered.

Notably, these average costs are based on a single diagnosis, severe anaemia, and therefore not representative of the outcomes of interest in this thesis: any cause readmission. While all children admitted with severe anaemia received blood transfusions, the cost estimates for any-cause readmissions needed to allow for other diagnoses without transfusion need. Using the readmission diagnoses from the efficacy trial data, we thus determined the true need for blood transfusions per readmission. This was further adjusted for the PDMC vs. placebo allocation, as both the overall number of readmissions and the per readmission need for transfusions was higher in the placebo arm. Regarding mortality, we did not collect any provider or household cost incurred after the death of a child.

In absence of provider cost data from Kenya and Uganda, we adjusted the costs from Malawi to these settings using the mean official national salaries for the involved positions. Blood cost and costs of DHAP were determined by literature review and officially reported costs. In addition, we adjusted to cost to the variations in mean length of readmissions between Malawi (SA: 4.6 days), Kenya (5.5 days), and Uganda (3.9 days).[28]

Ethical considerations

The PDMC efficacy trial protocol was approved by the relevant research ethics committees in Kenya, Uganda, the United Kingdom, and Norway (Regional Ethics Committee of Western Norway (REC-Vest): 2014/1911).[104] The protocol of the delivery trial was approved by the authorities in Malawi and Norway (REC-Vest: 2015/537).[107] The approvals include the data use and collection for the three studies conducted in this PhD project.

Role of the funding source

The three studies presented in this thesis were funded by the Research Council of Norway through the Global Health and Vaccination (GLOBVAC) Programme (Papers 1 and 2: project number 234487; Paper 3: 326107). GLOBVAC is part of the European and Developing Countries Clinical Trials Partnership (EDCTP2), supported by the European Union. The funder had no role in designing the study, in the collection, analysis, and interpretation of data, or in the writing and submission for publication of these studies.

Paper 1: predicting adherence to PDMC

Overview

The objective of Paper 1, titled, “Predicting adherence to postdischarge malaria chemoprevention in Malawian pre-school children: a prognostic multivariable analysis” (here

also “the predictor analysis” or “Paper 1”) was to identify potential determinants of caregivers’ adherence behaviour to PDMC in rural communities of Malawi.[170] We developed a prognostic multivariable model to assess correlations between potential predictors and caregivers’ adherence, grouped in four categories, using data from the delivery trial, pooled for the two delivery strategies, community- and facility-based delivery, irrespective of allocated reminder.[170]

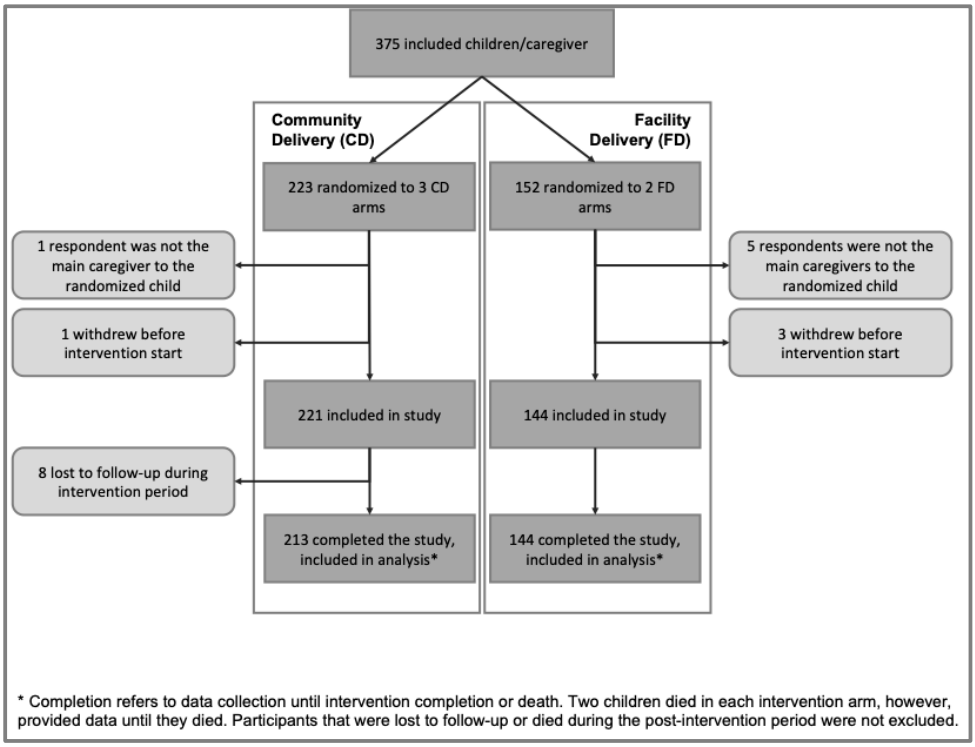
Population

For this analysis, we exclusively used data from the delivery trial and, initially, adopted the inclusion criteria: children under 5 years old at enrolment and their caregivers, residing in the predominantly rural and malaria-endemic hospital catchment area in Southern Malawi, who were successfully treated for severe anaemia. A few specific types of anaemia were excluded. However, for the predictor analysis we applied stricter criteria, creating a subsample subject to three further selection criteria. This was done to obtain a fitting sample for the study’s objective. Described below, the first additional exclusion criterion focused on potentially predictive (independent) variables; the second and third criteria were concerned with the outcome (dependent) variable.

Firstly, we excluded data from all children that were not accompanied by their main caregiver at enrolment. Reliable responses to the baseline questionnaire of potential predictive factors on the child’s medical history, and the caregiver’s and their household’s characteristics could only be provided by a main caregiver. We consequently excluded six children from the trial’s 375. Secondly, we removed caregivers who withdrew from the study before the intervention started. Without outcome data, including them in a study of correlations was irrelevant. For the same reason, thirdly, we excluded the eight participants that were lost to follow-up during the intervention. While questionable in an intention to treat-analysis, for this analysis we prioritized high certainty on the outcome behaviour.

The adjusted trial profile, applying our additional criteria, is shown in Figure 3, borrowed from the Paper 1. Data from 357 children, their caregivers, households, and communities were finally included in the analysis. Notably, we did not from the outset exclude the four children that died during the trial. We censored their data after the last course when they were still alive and included their adherence information up to that course. A child that, for example, received the full first PDMC course and died before the second, would accordingly be categorized as fully “adherent”, accounting for the caregivers’ adherence behaviour within the relevant period.

Figure 3: PDMC delivery trial-profile, adjusted for predictor analysis (borrowed from Paper 1).



Data collection and management

We conducted a prognostic predictor analysis, meaning that data on the considered predictors had to be collected before the trial's intervention had any possible bearing on them. Baseline data were collected at the hospital, immediately after child discharge and trial enrolment of the caregiver-child pair. This process included a medical check of the child and data collection on socio-economic characteristics, parenting practices, and cultural affiliations. Data on all potential predictors considered in our analysis were collected at this point, before the intervention. Only data on the outcome and on loss to follow-up were used from the body of data collected during and after PDMC delivery.

Potential predictors

All potential predictors, extracted from the trial's baseline data, were categorized according to the UNICEF Extended Model of Care, which starts with the child at the centre, then the caregiver, and lastly their household and community.[171,172] With the trial design in mind, where all caregivers were given access to the same treatment through two different delivery arms of

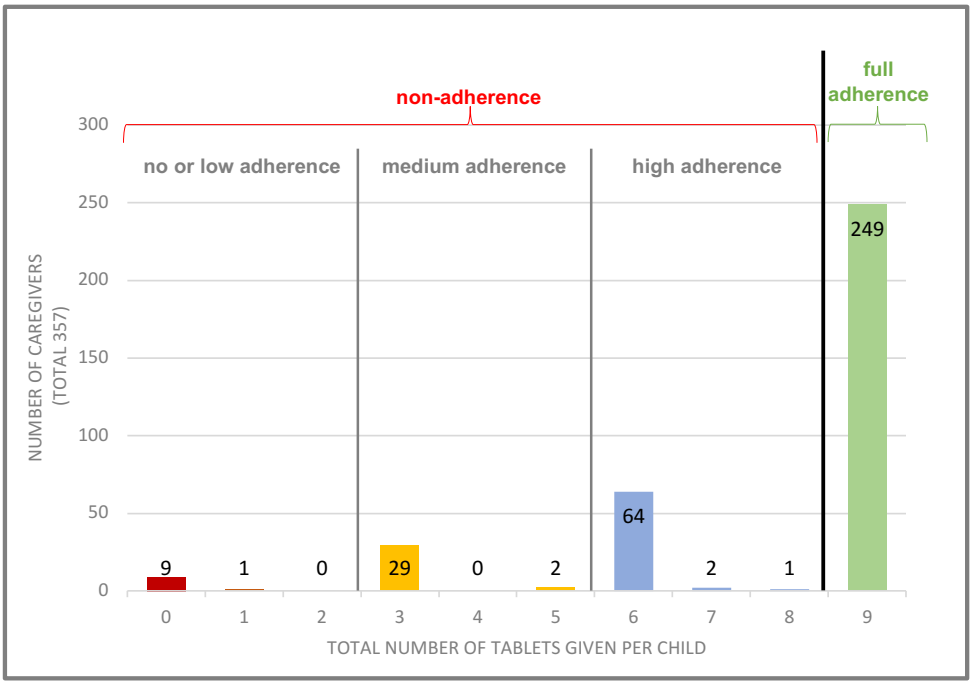
PDMC, we maintained the allocation to the delivery mechanism as separate predictor, outside of the grouping according to the UNICEF framework. The predictors will be summarized below, while Paper 1 provides an overview of all predictors by group, and their variable expression.[170]

Child-related predictors covered their demographic and health details, including age, sex, weight, height, and haemoglobin level. With a focus on malaria, past infections and hospital admissions due to malaria were included. Caregiver information covered their socio-economic status, education and literacy, their tribe and religion, their relationship to a partner, and whether they were a single parent. The number of their children, and how many of them were alive were also included. Covering the caring practices for the child, the question whether the child in question slept under an ITN was included. At the wider household-level, we included an index of their socio-economic status, grouped in quintiles, relative to the households of all other caregiver-child pairs we included. The index was generated based on a principal component analysis (PCA) that initially included 88 household assets and features. Details on the PCA method and its results are provided in the supplementary materials of paper 1.[170] Core aspects of wealth such as owning a bank account, having a regular income, and owning their dwelling were excluded from the assets-list and analysed as independent potential predictors at household-level. This groups also covered community level-variables, like the source of drinking water and its distance from the dwelling, as well as whether a community had received indoor residual spraying. The study hospital's distance to the community was likewise included.

Outcome definition

We expressed a stricter outcome than the primary trial outcome, defining *adherence* as giving a child all nine DHAP doses as prescribed: three monthly courses of a once-daily tablet for three days. *Non-adherence* was defined as administering fewer than nine tablets, that is missing one tablet or more. This binary outcome was determined by the "hard" metric of the tablet count upon blister pack collection. We disregarded data on self-reported adherence due to the risk of introducing bias. With the majority of caregivers categorized as adherent when applying the strict "hard" outcome definition of blister pack collection, it was unnecessary to soften the definition and include the less reliable self-reported adherence behaviour (Figure 4). If the overall observed adherence had been lower, self-reported adherence might have merited more weight in the analysis.

Figure 4: Distribution of adherence behaviour: the total number of tablets administered per caregiver for the subsample in the predictor analysis (borrowed from paper 1).



Analysis

Our main analysis consisted of three steps, summarized in the columns of Table 5. We firstly produced descriptive statistics for each predictor, tabulating it by the adherence outcome. We reported either means with standard deviation (continuous variables) or frequencies with corresponding percentages (categorical predictors). Secondly, we used modified Poisson regression for clustered data to obtain for each potential predictor the relative risks of non-adherence to PDMC over three months. This model was selected in consideration of the binary outcome, to control for a clustering effect, and to prevent a risk of overestimation based on the frequent outcome "full adherence".[173–175] The study arm allocation and the cluster effect were forced into these analyses. In the case of categorical variables, we tested their significance both for each variable as a whole (global significance) using a Wald test, as well as for the stratified subgroups. For each predictor, we reported the relative risk associated with the outcome, and the 95% confidence interval for these estimates. Thirdly, we developed a multivariable model including clustering and treatment arm, as well as all individually statistically significant predictor variables. We reported the relative risks for those remaining significant throughout

this adjusted calculation. Our results are reported in line with the "Tripod Statement.", a reporting guideline for predictor analysis by the equator Network.[176]

In the initial analysis per predictor, we conducted interaction testing for the age and sex variables of the children and caregivers. All predictors in the adjusted model were tested for multicollinearity. We calculated the k-fold cross-validated area under the receiver operating characteristic (ROC)-curve to assess the model's performance.[177]

Considering the trial design and the potent treatment effect, we also stratified the data by PDMC delivery strategy and conducted the same analytical steps independently for each arm's population. The non-adherent group had large variation in tablet counts (0 to 8 tablets). In a sensitivity analysis, we therefore tested our results adopting the four adherence categories described above (full, high, medium, and low or now adherence). We used an ordered logistic regression analysis with this alternative, ordered outcome.

Paper 2: a cost-effectiveness analysis of PDMC

Overview

The objective of paper 2 "Economic evaluation of postdischarge malaria chemoprevention in preschool children treated for severe anaemia in Malawi, Kenya, and Uganda: A cost-effectiveness analysis" was to determine separately for Malawi, Kenya, and Uganda the cost-effectiveness of two PDMC delivery strategies compared to the standard of care. This analysis used data from the two PDMC-trials described above.[169]

Study design

For each of the three countries, we created one decision-analytical discrete-time model (Markov) which we ran for six one month-long cycles. Three health states were expressed: healthy, severely sick (i.e., admitted to a hospital), and dead. Mild and moderate health events, recorded as outpatient visits at a hospital or health centre, were optional within the healthy state. Like the two trial populations, the three Markov cohorts entered the model at the start of the PDMC intervention, two weeks after discharge. While evidently vulnerable, they were assumed to be healthy. The models allowed for monthly transitions between the two alive states, and dying was possible from both of them. A state diagram for a Markov cohort is included in the illustration of the model structure (Figure 6). Results were reported for each country as incremental cost-effectiveness ratios (ICER) per strategy. The models report the incremental cost per incremental quality-adjusted life-year between the modelled interventions,

namely the two delivery arms from the delivery trial, and the standard of care. Costs and utilities were adjusted by a global discounting rate of 3 percent.

Data collection and model input

Data used in this analysis was pooled from the participants of both trials without additional exclusion criteria. We adopted data on adherence to different delivery strategies from the delivery trial. In addition, we used provider and household cost data from Malawi, collected during this trial. From the efficacy trial in Kenya and Uganda, we used data on the overall efficacy of PDMC and data on household costs.

We expressed different rewards per one month in the health states, informed by the 2019 Global Burden of Disease.[126] To determine the health related quality of life (HRQoL), we inverted annual disability weights (DW) to approximate the burden of 'severe sickness' (readmission) and ´moderate health events' (outpatient clinic visit), so that $HRQoL = 1 - DW$.[178,179] The reward for one month in the healthy state was the monthly equivalent of one full quality-adjusted life year (QALY). Any month in the dead state yielded no rewards. A moderate health event, occurring within the healthy state, resulted in an in-cycle reduction of the initial reward for a healthy month by the two week-equivalent of 0.046 QALY. This is the annual disability weight of the most frequently recorded diagnoses in the outpatient visits during the efficacy trial, moderate malaria.[28] Likewise, the disability burden in the severely sick state was defined based on the reasons for readmission recorded in the efficacy trial. Their weighted average disease burden was the monthly equivalent of 0.158 QALY, which was then likewise subtracted from the healthy states' reward.[28] We used no half-cycle-correction for these rewards due to the models' few and relatively short cycles. The proportion of children surviving the six cycles were awarded their 2018 national health-adjusted life expectancy, adjusted for their cohort's average age at that time.

Efficacy data for the initial transition probabilities between standard of care arms was and the relative risk of these transitions occurring when receiving PDMC were obtained from the efficacy trial data (Table 3). Adherence data were obtained from the delivery trial for two strategies: community-based and facility-based delivery. The transition probabilities and the relative risks, as well as the adherence rates from Malawi were used identically in the three models. We categorised adherence behaviour into the same four categories as described above, in Paper 1: *high*, *medium*, *low*, *very low or no* adherence. With these adherence rates we projected an adjusted efficacy of PDMC under implementation conditions as follows.

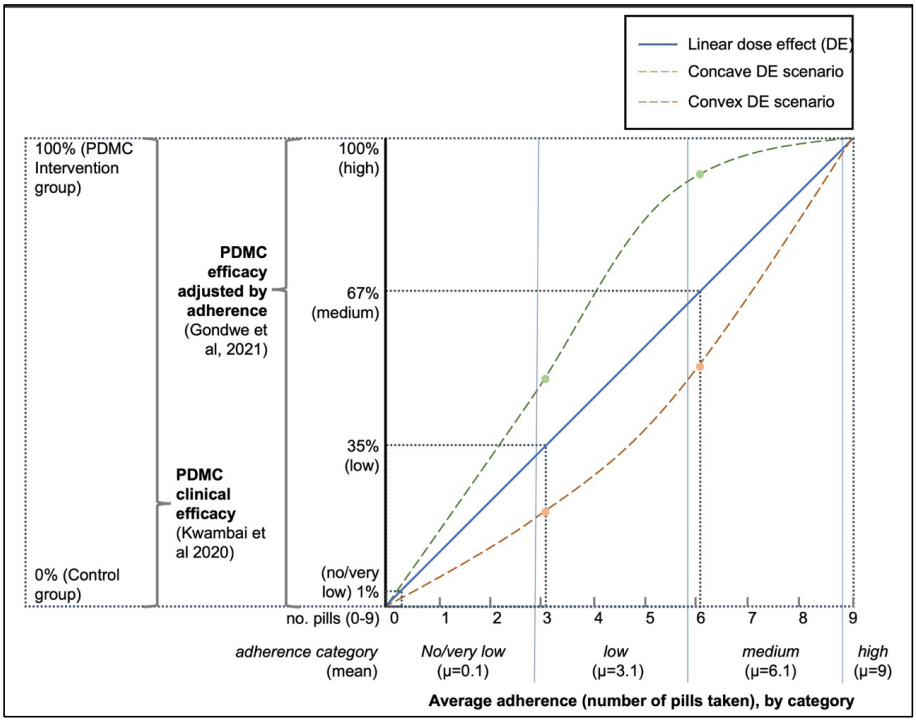
Table 3: Overview of transition probabilities used in the CEA, based on health outcomes reported in Kwambai, 2020.

Starting state	Trial arm allocation	Transition state		
		healthy	*severely sick*	*dead*
healthy	Standard of Care (base case)	0.8710	0.1238	0.0051
	Relative risk with PDMC	1.0954	0.3391	0.7490
severely sick	Standard of Care	0.9043	0.0891	0.0066
	Relative risk with PDMC	1.0121	0.8738	1.0472
dead	Standard of Care	-	-	1
	Probability PDMC	-	-	1

The health outcomes in the placebo treatment group of the efficacy trial were equated to 0% PDMC adherence, whereas we assumed the health outcomes observed in the PDMC-intervention arm to correspond to 100% adherence to PDMC. Between these values, we interpolated a linear dose-response and matched the four adherence categories with the efficacy estimate based on the mean number of tablets given per adherence category. These mean values were calculated from delivery trial data. All categories except *high adherence*, which yielded 100% efficacy at 9 tablets administered, thus combined a portion of the full effect with a portion of the placebo-effect – the specific ratio depending on the number of tablets administered on average (Figure 5).

Notably, like in paper 1, the order of tablets or courses adhered to was not considered in this model. While this is likely of some importance to better understand adherence, at this point, there was no evidence suggesting variations in the efficacy depending on the order of DHAP-tablets or -courses taken.

Figure 5: Adjusted dose-effectof PDMC based on adherence categories, using a linear interpolation and a convex and concave does effect (DE) scenario.



We assumed a limited societal costing perspective, combining the components of provider and household costs, but also report both provider and household perspectives, in order to allow an implementation-focused readership a choice of perspective.[180] We collected data on and include direct and indirect costs to both provider and households. The "household-perspective" includes the child receiving PDMC or the standard of care, her caregiver, and their family. We organized the cost as intervention cost and cost of adverse health events, making it easy to separate the preventive "treatment" given to all children from the varying effects across arms. We combined the household and the provider perspectives to report a relatively crude societal cost-perspective for each country. We used a pragmatic ingredients approach to determine costs, generally itemizing and valuing both financial and economic costs and summarizing them in aggregated costs components. All costs were converted to US$ (2018), and inflation adjusted if they were obtained from literature outside the trial years, 2016 to 2018.

Providers' intervention costs covered two main items: the cost of the antimalarials, with an added percentage for procurement and wastage; and the time spent by a pharmacist to instruct a mother on how to administer it. This time was adjusted for treatment arm and by the

corresponding adherence. Households' intervention costs were restricted to the additional time spent at the pharmacy for the community-based delivery. The facility-based delivery, however, required two travels to the hospital to collect monthly DHAP courses. These costs covered both transportation expenses and loss of productivity due to the travel. Caregiver time was valued with the minimum national salary of 2018 per country. Table 1 in Paper 2 summarizes theses costs.[169] Household costs were collected as primary data in the two trials. Pharmacists' time used to process a prescription and instruct caregivers in the administration were determined in time-and-motion observations, and interviews at Zomba Central Hospital in Malawi, and valued with the de facto average income the hospital paid its pharmacists. Pharmacists time in Kenya and Uganda was valued using the average national salaries for this cadre. An overview of all cost components is presented in Table 1 of Paper 2, and further details are provided in the Tables 4 to 8 of the supplemental materials.

Likewise, we assumed that the cost components of adverse health events in Kenya and Uganda were the same as in Malawi. Upon detailed observation of treatment of severe anaemia in ZCH, Malawi, the average personnel time used throughout the treatment per severely anaemic child were determined and valued with average salaries for each involved position. For Kenya and Uganda, salaries were adjusted with the national salaries for the involved cadres. In addition, these costs were adjusted for each country's average duration of readmissions, based on trial data. Equipment and medication cost were itemised, valued, and costed in Malawi using a sample of 50 patient files of children included in the trial. These were adopted in the other countries' models. We also included a proportionate handling and wastage surcharge (30%) for these items, as is practice in Malawi's public procurement system, and adopted it across the models.[181]

Notably, among these treatment costs, blood transfusions stand out as relatively costly and we therefore costed them separately, in more detail, based on literature for Kenya and Uganda, and additionally on hospital information and interviews of laboratory personnel in Malawi. While all children in their initial treatment for severe anaemia received blood transfusions, less than half of them needed this during readmissions in the efficacy trial. Notably, not only the overall number of readmissions was substantially lower in the PDMC-arm, but also the average need of transfusions per readmission: 29% of readmissions in the PDMC arm vs. 42% in the placebo arm required at least one transfusion. We adjusted the costs accordingly.

The costs of a hospital' s support services per readmission were estimated by adjusting the paediatric ward's annual share of these expenses for the proportion of malaria-related admissions among all admission causes. Hospital-wide maintenance costs that could not be attributed directly to the ward were estimated using an allocation key based on the roof area of the ward as a proportion of the entire hospital. Capital costs were disregarded, based on the amortised structures in ZCH in Malawi. These costs were adopted for Kenya and Uganda.

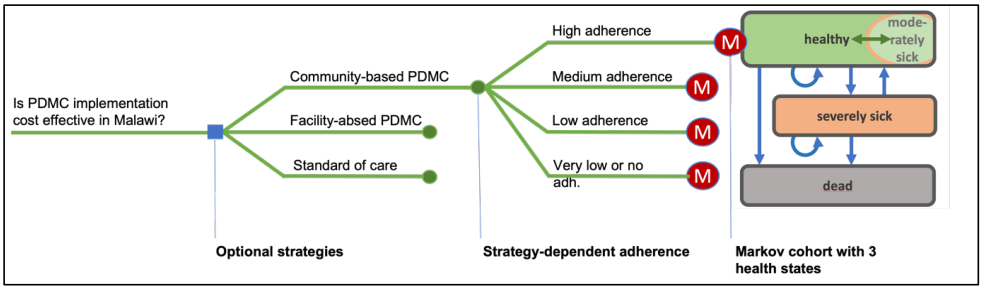
Household readmission costs were recorded as part of the trials' proceedings for each readmission in Kenya, Uganda, and Malawi. This included both households' expenses and opportunity costs for the duration of the admission and travel period. These costs also included the additional financial and economic costs if an adult had accompanied the mother. The admission duration was adjusted by country.

Cost for the moderate health events were collected following the same method. Detailed provider costs were determined for Malawi based on trial data and interviews at the outpatient paediatric department of ZCH, and adjusted for national salaries in Kenya and Uganda. Household costs for Kenya and Uganda were available from the efficacy trial data.

Analysis

We used Treeage Pro 2022 software to develop the model. Where inference data were available, distributions were specified using standard deviations. In their absence we created ranges, 50% higher and lower than any point estimate for costs, and 25% for all other variables. These ranges were used for univariate sensitivity analysis. For probabilistic sensitivity analysis (PSA), distributions were fitted to these ranges, using gamma-shaped distributions for cost data, beta-shaped distributions for all probabilities, and normal distributions, for other uncertain distributions, such as life expectancy. We specified 10 000 iterations of Monte Carlo simulations for the PSA.

Figure 6: Overview of the decision tree with Markov node



Paper 3: a value of information analysis of PDMC

Overview

The objective of paper 3 "Do we need to know more? An analysis of the value of further research on postdischarge malaria chemoprevention in preschool children in sub-Saharan Africa" was to determine the value of perfect and partial perfect information on the uncertain parameters in the CEA for Malawi, Kenya, and Uganda, and, on this basis, to estimate the annual value of perfect information on PDMC delivery for other sub-Saharan countries, where malaria is endemic. This analysis used data from the two PDMC-trials described above, and from two recent modelling studies.

Study design, model structure, and assumptions

We undertook a value of information (VOI) analysis based on the CEA model presented in paper 2, above: a decision-analytical discrete-time model (Markov).[169] In the VOI-analysis we compared community- and facility-based delivery of PDMC with the standard of care, as was done in the CEA. Likewise, all cohorts were modelled to receive the two weeks-lasting standard of care before they received PDMC, delivered according to either delivery arm, or no further treatment in the standard of care-cohort. We adopted all structural features of the model, and modelled the cohorts along the same three health states (i) *healthy*, (ii) *severely sick*, and (iii) *dead* for six months. As model input, we combined household cost and the efficacy data from the trial in Kenya and Uganda with adherence data, and household and provider cost data, from the delivery trial in Malawi.[28,105] We used, as base case for adherence-adjusted effectiveness of PDMC, the adherence estimates established for the CEA. They were based on an interpolated effectiveness estimate per adherence category, bound by the readmission rates of the placebo group (0% effectiveness) and the intervention group (100% effectiveness) from the efficacy trial (Figure 4). Survivors were then rewarded their average health adjusted life expectancy. The original model structure with input from source trials and assumptions are described above and in Paper 2.[169] The parametrized model input for this analysis is described in detail, below.

The delivery trial was designed to detect differences in adherence between the delivery strategies and some conventional bias inherent in clinical trials were minimized, for example, the unannounced outcome data collection during on the spot-visits for blister pack inspection. However, at the core it remained a trial design, thus framing the caregiver child-pairs in a relatively artificial health care provider environment, where they interacted with qualified and

dedicated trial personnel. This setting is associated with the risk of some bias in favour of adherence, compared to the "real" adherence that would be observed under routine care conditions. The caregiver information during the enrolment process, for example, included a formalized information and consenting process, likely providing higher quality information on the evidence of an intervention and consequences of non-adherence to the preventive regimen at home, compared to routine care information.[182] Moreover the desirability to adhere is, implicitly, communicated throughout the formalized interaction with qualified personnel of the study team, concluded by the signature to consent participation. The factors contribute to a generally established association that trial-based adherence is higher than adherence under routine care.[183–185] This was confirmed especially for LMIC with lower quality of care and trust in the public health care provider.[186] Discrepancies between trial-based and community-observed adherence have been documented for antimalarial-*treatment* of children in such settings.[187,188]

As PDMC is already recommended for implementation in endemic areas, and accordingly decision makers in health systems consider introducing it, producing implementation-tailored evidence is important. In view of this demand and the possibly overestimated adherence, carried over from the delivery trial, we developed an alternative scenario to the base case with reduced adherence that should reflect the true adherence under routine care delivery through a public health system. We assumed routine care adherence rates and adjusted the base case rates by the mean factor 0.5, parametrized in a beta distribution with a standard deviation of 0.25 (50% of the mean). Adherence rates in this scenario were thus, across all categories, on average half those observed in the trial.

Categories of inputs

Six initial categories of input were created, grouping all parametrized variables from the CEA (Table 4). The first category was intervention cost to both provider and household. Provider costs included the hospital's procurement costs of the antimalarial and the pharmacy cost of distributing it with instructions to the caregivers, according to the allocated delivery strategy. Household costs covered the financial and economic costs of collecting DHAP at the hospital, depending on delivery strategy, and giving the tablets to a child throughout the treatment period, adjusted by strategy-dependent adherence. The second category of cost inputs covered all costs associated with adverse moderate or severe health events during the six months postdischarge period, from both the provider and household perspectives. The cost components of treating a child in the inpatient or outpatient departments, with the related personnel and

medication costs, as well as laboratory, administration, and support services costs. The cost of blood transfusions, informed by the diagnoses at readmission in the efficacy trial, were included separately due to their relatively high costs. The households' perspective included financial costs of transport to the hospital and expenses during admission, as well as the care time on site, valued in national minimum salary.

The third input category included all probabilities for the modelled monthly transition between the two health states, and death. These probabilities describe these probabilities for the cohort allocated to the placebo-treatment in the efficacy trial, which was equated to the national standard of care. As measure of PDMC efficacy, relative to the placebo probabilities, this category also included the relative risk of each of these transitions occurring when receiving PDMC, compared to the standard of care.

The fourth category of inputs comprised the probabilities of adherence in the categories *high* (all nine tablets taken, three per course), *medium* (six to eight tablets), and *low* (three to five tablets), for each delivery strategy. The category *very low or no* adherence was excluded from probabilistic sensitivity analysis because it approximated 0; therefore, it was neither used in the VOI-analysis. The other six probabilities were adjusted, as described above, for the scenario with reduced adherence. In the fifth category, the assumption of a linear reduction of the dose-effect based on the number of non-administered tablets (by adherence category) was included, expressing uncertainty around the specific increase in the probability of a readmission, for example, caused by one tablet not administered.[169] The sixth category includes the health utilities of both a readmission with severe disease or a moderate disease, adjusted for the estimated duration of four weeks and two weeks, respectively. In addition, this category included the health-adjusted life expectancy awarded to the cohort surviving the six months postdischarge period.

Table 4: Parametrized variables based on the CEA, organized by category of input used in the VOI-analysis.

	Distribution shape	Point value/ mean	Standard deviation (SD) or minimum and maximum values (min; max)
1 Costs: PDMC Intervention (US$)			
Dihydroartemisinin−piperaquine, nine tablets	Gamma	2.36	SD: 1.18
pharmacy provide community-based PDMC	Gamma	0.12	SD: 0.06
pharmacy provide facility-based PDMC´	Gamma	0.24	SD: 0.12
household to obtain and administer community-based PDMC	Gamma	1.31	SD: 0.66
household to obtain and administer facility-based PDMC	Gamma	8.51	SD: 4.25
2 Costs: adverse health events (US$)			
Facility: treating one moderate malaria	Gamma	2.40	SD: 1.20
Facility: support services treating one moderate malaria	Gamma	0.04	SD: 0.02
Facility: blood transfusion	Gamma	65.93	SD: 32.97
Facility: medication per severe disease (readmission)	Gamma	18.67	SD: 9.34
Facility: personnel cost treating one severe disease (readmission)	Gamma	10.56	SD: 5.28
Facility: support services treating one severe disease (readmission)	Gamma	3.04	SD: 1.52
Household: moderate disease of child	Gamma	5.34	SD: 2.67
Household: severe disease of child (readmission)	Gamma	12.94	SD: 6.47
3 Efficacy: transition probabilities and relative efficacy (Placebo vs. PDMC)			
Standard of care: monthly probability to die while in the healthy state	Beta	0.005	SD: 0.001
Standard of care: monthly probability to become severely sick while healthy	Beta	0.12	SD: 0.03
Standard of care: monthly probability to die while severely sick	Beta	0.007	SD: 0.002
Standard of care: monthly probability to remain severely sick	Beta	0.089	SD: 0.022
Standard of care: probability of moderate disease while healthy	Beta	0.051	SD: 0.013
PDMC effect on monthly SOC probability to die while in the healthy state	Gamma	0.75	SD: 0.19
PDMC effect on monthly SOC probability to remain healthy	Gamma	1.10	SD: 0.27
PDMC effect on monthly SOC probability to become severely sick while healthy	Gamma	0.34	SD: 0.09
PDMC effect on monthly SOC probability to become severely sick while healthy	Gamma	0.83	SD: 0.21
PDMC effect on monthly SOC probability of a moderate disease while healthy	Gamma	1.05	SD: 0.26
PDMC effect on monthly SOC probability to recover from a severe sickness	Gamma	1.01	SD: 0.25
PDMC effect on monthly SOC probability to remain severely sick	Gamma	0.87	SD: 0.22
PDMC effect on monthly SOC probability of a moderate disease while healthy	Gamma	1.05	SD: 0.26
4 Effectiveness: Adherence to delivery strategies, base case			
cohort proportion with high adherence, community-based PDMC	Beta	0.71	SD: 0.18
cohort proportion with high adherence, facility-based PDMC	Beta	0.52	SD: 0.13
cohort proportion with low adherence, community-based PDMC*	Beta	0.78	SD: 0.20
cohort proportion with low adherence, facility-based PDMC*	Beta	0.81	SD: 0.20
cohort proportion with medium adherence, community-based PDMC*	Beta	0.65	SD: 0.16
cohort proportion with medium adherence, facility-based PDMC*	Beta	0.56	SD: 0.14
5 Effectiveness: dose effect at imperfect adherence			
efficacy factor for high adherence	Uniform	0.86	min: 0.75; max: 1
efficacy factor for low adherence	Uniform	0.35	min 0.26; max 0.44
efficacy factor for medium adherence	Uniform	0.67	min: 0.50; max: 0.84
efficacy factor for very low or no adherence	Uniform	0.010	min: 0.008; max: 0.013
6 Utilities: Transition and final rewards			
Disability weight of moderate disease, two weeks (DW)	Triangular	-0.0018	min: -0.0022; max: -0.0013
Disability weight of severe disease, one month (DW)	Beta	0.014	SD: 0.004
Life expectancy (HALE)	Normal	54.72	SD: 1.88

*conditional probabilities; owed to the tree structure, where we maintained two-armed nodes for probabilistic sensitivity analysis, the sums of the probabilities of the three (four) adherence categories listed here, are higher than 1 when summed up.

Analysis

We conducted a value of information analysis, initially calculating the per decision-value of eliminating uncertainties around single categories of input (the expected value of partial perfect

information (EVPPI)) for Malawi, Kenya, and Uganda, and the value of obtaining overall perfect information (EVPI) for these three and 27 other sub-Saharan countries.[189,190] They include the ten HBHI-countries, and 20 other malaria-endemic countries in sub-Saharan Africa, based on the selected countries in a recent mathematical modelling study that projected the annual demand for PDMC for each of the countries.[33] Table 8 in the Results chapter lists the countries. The willingness to pay-thresholds for the countries were adopted from a recent projection study, likewise listed in Table 8.[191]

The analysis was conducted using TreeAge Pro 2022 software. The EVPPI calculations used the CEA model for Malawi as a base case. Employing a two-level Monte Carlo method, we sampled 10 000 iterations in the "inner loop" combined with 5 000 iterations in the outer loop for each calculation. Included in the inner loop were all parameters, unless they were in the category of interest. Parameters from categories of interest were included in the outer loop. If a category-wide EVPPI was positive, subgroups or individual variables were analysed for their VOI. We report the per decision-EVPPI for Malawi, expressed as NMB per decision, using all model parameters. The same analytical process was followed for the EVPPI analyses for Kenya and Uganda, and for the EVPI-calculations for all countries.

We reported results for both EVPPI and EVPI as national annual net monetary benefit, assuming perfect national implementation, i.e., that all childrenin need of PDMC received it. Departing from the per-decision NMB in Malawi, we adjusted our initial calculations to the different country contexts, adopting data from two separate sources. Firstly, the differences in absolute purchasing power between the 30 countries were adjusted using the World Bank's 2021 purchasing power parity data (PPP), where we selected Malawi as base case (Table 8).[192] Secondly, we adopted the estimates of national annual demand for PDMC in these countries from the mathematical modelling study.[33] Using these data, we estimated the annual population value of perfect information, expressed as NMB, for the base case and the adherence-adjusted scenario for each of these countries. We report point estimates and ranges based on the variations in national hospitalization rates used in the modelling study (30% – 70%). For Malawi, Kenya and Uganda, we presented three time horizons: one year, five years, and ten years All projections were adjusted with an annual discounting rate of 5%.[193] For the other countries, we present the annual NMB, and a total regional NMB for the three time horizons, likewise adjusted for discounting. We focus on the annual perspective as it offers a useful point of departure for national decision makers to assume different time perspectives when planning further research.[33,194]

Results

Paper 1: predicting adherence to PDMC

In the predictor study, we aimed to identify patterns in the child, caregiver, and household characteristics that may allow conclusions on caregivers' adherence behaviour. We included 357 caregiver-child pairs, a description of their full characteristics is presented in the study.[170] In summary, more boys than girls were included, their mean age was 29 months. 40% of the children were stunted. Within the year before they were admitted, more than 60% of children had been diagnosed with malaria, almost 10% had at least four infections during that year. More than 20% of Caregivers reported that their child did had not slept under an ITN recently. Almost all caregivers were the mother to the sick child they accompanied, their average age was 29 years. More than 25% were single parents. More than 30% were illiterate, 14% had not completed primary school or any education at all. Only 2% of households had electricity. Approximately 15% of houses had access to piped water, while 5% of households used surface water as drinking water source.[170]

The 357 pairs were unevenly allocated to the two PDMC delivery-arms, due to the original trial design (Figure 1). Across both arms, a total 249 (70%) caregivers had administered all tablets to their child, thus being fully adherent. The remaining 30% had failed to administer at least one tablet, categorized as non-adherent. With this strict outcome definition, the analysis of our sub-sample confirmed the trial findings that there is a high risk of non-adherence connected to facility-based delivery (RR, 95% CI: 0.65, 0.55 to 0.76, Table 5), relative to community-based PDMC delivery. Table 5 shows only the final list of predictors included in the adjusted multivariable model. A comprehensive overview that also includes all potential predictors that were excluded throughout the steps of analysis is included in Paper 1.[170]

We considered the trial's allocation to the delivery strategies as separate predictor excluded from the predictor categories used in this analysis. Among the first of the three UNICEF categories of predictors, the child-related characteristics, only one significant predictor was identified: children with four or more diagnosed malaria infections in the past year, were associated with a higher risk of receiving an incomplete PDMC regimen (RR, 95% CI: 0.83, 0.71 to 0.97, Table 5) from their caregiver.

In the second category, only one caregiver-centred predictors could be identified. A caregiver's education, as a categorical variable of four education levels, does not predict caregivers'

behaviour. However, the two central categories that describe more than 80% of caregivers, having completed lower or having completed upper primary school, was associated with relatively poorer adherence (RR, 95% CI: 0.78, 0.64 to 0.95; and 0.79, 0.67 to 0.92, Table 5). The comparator, here, was not having completed any education level. The point estimate for the highest education category, while not statistically significant, was comparable to the reference estimate.

Adherence-specific prediction was likewise complicated, in the household-focused predictor category. The socio-economic index as global variable was not found to be a significant predictor. One index-category, belonging to the second poorest quintile, is associated with increased adherence (RR, 95% CI: 1.20, 1.04 to 1.42, Table 5). The overall picture of the quintiles as predictors is mixed, however: the poorest category served as reference, the second poorest was associated significantly with higher adherence, while the three less poor quintiles showed no significant association but indicated effects in opposing directions.

Table 5: Descriptive statistics and regression analysis of predictors in a multivariable model to predict high adherence to PDMC

Predictors		**Descriptive statistics by outcome** frequencies (percentages) - unless row indicated otherwise		**Generalized linear model-analysis**	
Predictor categories Included potential predictor variables	**Variable categories**	**Non-adherence** n=108	**Full adherence** n=249	**Crude relative risk** (95% CI)	**Adjusted relative risk** (95% CI)
Intervention allocation, PDMC trial (Gondwe, 2021)					
PDMC delivery	community-based	40 (37.0)	173 (69.5)	1	1
	facility-based	68 (63.0)	76 (30.5)	0.65 (0.55, 0.76)*	0.64 (0.55, 0.76)*
Characteristics of child at enrolment					
Four or more malaria infections, past year	yes	5 (4.6)	28 (11.2)	0.82 (0.70, 0.96)*	0.83 (0.71, 0.97)*
Characteristics of caregiver and caregiving behaviour at enrolment					
Caregiver's highest completed education level**	none	10 (9.3)	39 (15.7)	1	1
	lower primary	30 (27.8)	55 (22.9)	0.80 (0.66, 0.98)*	0.78 (0.64, 0.95)*
	upper primary	59 (54.6)	120 (48.2)	0.83 (0.70, 0.97)*	0.79 (0.67, 0.92)*
	lower secondary, higher	9 (8.3)	35 (14.1)	1.01 (0.84, 1.22)	0.98 (0.80, 1.21)
Household's caregiving resources					
Distribution by socioeconomic index in quintiles**	poorest quintile	31 (28.7)	59 (23.7)	1	1
	2nd quintile	10 (9.3)	50 (20.1)	1.20 (1.01, 1.42)*	1.23 (1.04, 1.42)*
	3rd quintile	32 (29.6)	42 (16.9)	0.83 (0.66, 1.05)	0.80 (0.64, 1.01)
	4th quintile	18 (16.7)	49 (19.7)	1.06 (0.87, 1.29)	1.04 (0.85, 1.26)
	richest quintile	17 (15.7)	49 (19.7)	1.15 (0.95, 1.39)	1.09 (0.89, 1.32)

* Predictors with p-values <0.05.
** Multilevel variables that were significant as entire variable (p<0.05), calculated using Wald-test.

The model's performance was low but acceptable, with a mean area under the ROC-curve of 0.65 (95% CI: 0.57 to 0.71), where 1 would signify a perfectly predicting model, while 0.5 describes a model predicting outcomes randomly.[195] The sensitivity analysis with the non-adherent group separated into non-adherent sub-categories (*medium*, *low*, and *low or no adherence*) did not yield significant predictors.

Paper 2: a cost-effectiveness analysis of PDMC

Taking the limited societal perspective, thus combining the provider's and households' costs of implementing PDMC and of adverse health events per child discharged from hospital, PDMC was found to be a less costly intervention than the standard of care. Compared to the costs of the national standards of care, in each country, the community-based delivery amounted to approximately half the costs: US$22.74 in Malawi, $37.87 in Kenya, and $29.78 in Uganda. The cost of facility-based delivery was located between these two strategies in all three countries (Table 6).

Table 6: Cost, Effectiveness, and incremental cost-effectiveness ratiosfpr Malawi, kenya, and Uganda, comparing community-based PDMC with facility-based PDMC, and with the national standard of care.

		Cost (US$)				Effectiveness (QALY)		Cost-effectiveness
Country	Strategy	Health care provider cost	Household cost	Total cost	Incremental cost	HALE	Incremental QALY	ICER
Malawi	Standard of care	36.00	8·91	44·84		52·65		negative
	PDMC Facility-delivered	19·50	11·65	31·11	-13·72	52·98	0·33	negative
	PDMC Community-delivered	16·95	5·83	22·74	-8·37	53·03	0·05	dominant
Kenya	Standard of care	46·63	29·98	76·40		53·86		negative
	PDMC Facility-delivered	26·27	23·47	51·49	-24·91	54·20	0·34	negative
	PDMC Community-delivered	22·54	15·72	37·87	-13·61	54·25	0·05	dominant
Uganda	Standard of care	41·95	14·16	56·00		53·84		negative
	PDMC Facility-delivered	22·46	18·44	40·84	-15·16	54·18	0·34	negative
	PDMC Community-delivered	19·33	10·50	29·78	-11·07	54·23	0·05	dominant

While we included no intervention costs for the standard of care, the significantly higher proportion of adverse health events, when not providing PDMC, caused markedly higher costs per child discharged than the additional intervention costs per child in either delivery strategy of PDMC combined with relatively fewer readmissions and moderate health events costs. When restricting the costing perspective to the provider, the ranking of strategies remained the same: intervention costs are relatively low for both PDMC delivery strategies compared to the substantially more frequent, costly readmissions when providing merely the standard of care. This was particularly influenced by the reduction in blood transfusions needed per-admission when children received PDMC. Assuming only the household perspective, community-based delivery remained optimal. Facility-based delivery, however, was estimated to be more costly to households than their receiving the standard of care. Caregivers have relatively high

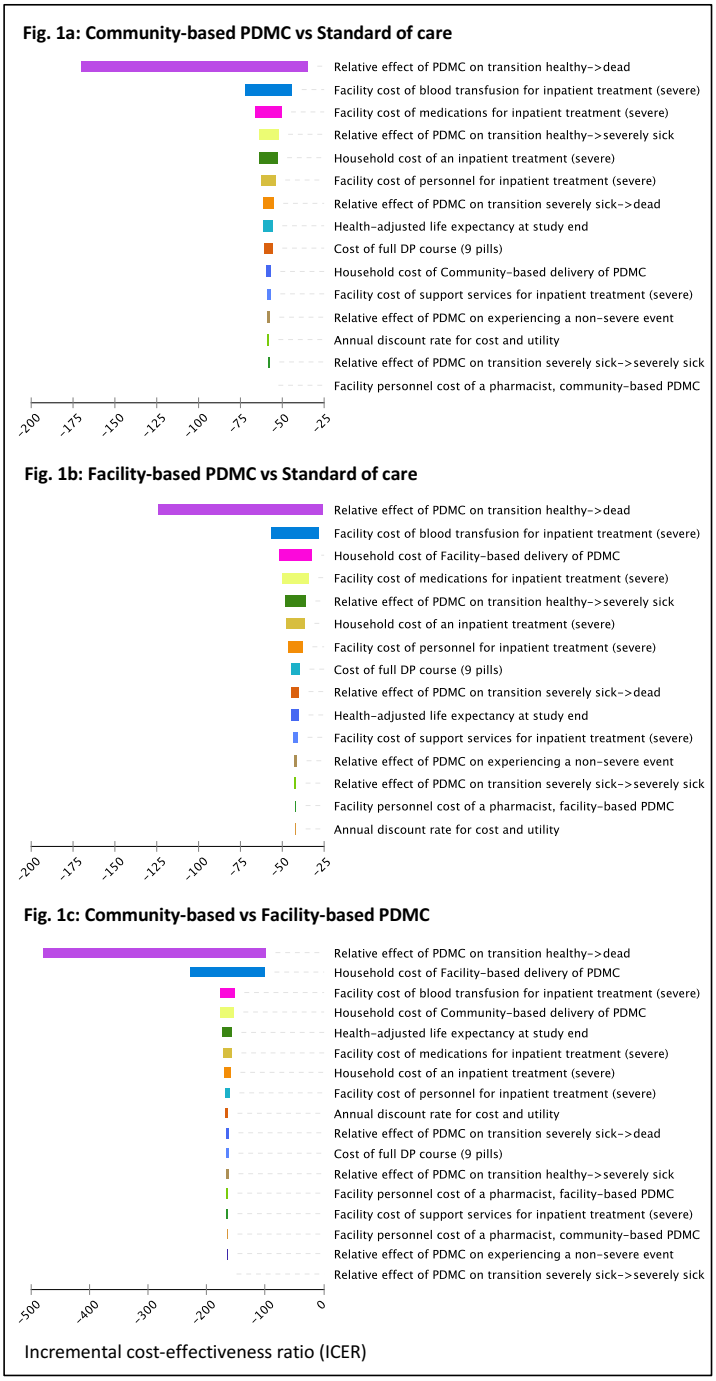
collection cost in this delivery strategy, while a large share of readmission cost are shouldered by the provider. Table 2 in Paper 2 summarizes the comparison of costs.[169]

While the differences in cost were quite pronounced, the effects did not differ substantially between the arms. Community- and facility-based PDMC delivery amounted to an estimated incremental 0.4 and 0.3 QALYs, respectively, compared to the standard of care arm. As we assumed the disability resulting from a readmission to last for one month, usually followed by a return to the healthy state, even a significant disability adjustment for this short duration becomes relatively weak when taking a lifetime perspective.

Combining cost and effectiveness results, we estimated with high certainty that PDMC is both more effective and less costly, thus cost-saving compared to the standard of care in all three countries. When comparing the two delivery options of PDMC, community-delivery was highly likely to be cost-effective: with higher adherence, it resulted in fewer readmissions and especially the household costs were substantially lower.

We summarized our univariate deterministic sensitivity analyses in a tornado diagram for Malawi. It illustrates that, assuming the parameter ranges we defined and all other variables constant, the relative difference between the children's mortality rate (probability to die) with and without PDMC has the largest potential to influence the ICERs for both the facility- and the community-based delivery strategy compared with the standard of care, but also compared among themselves. However, no value within these ranges was sufficiently powerful to affect the overall cost-effectiveness ranking of strategies. These results were comparable for Kenya and Uganda (Figure 7).

Figure 7: Tornado diagrams of community-delivered PDMC and facility-delivered PDMC versus standard of care (1a, 1b), and a comparison of both PDMC strategies (1c), as illustration of the deterministic sensitivity analysis for Malawi.



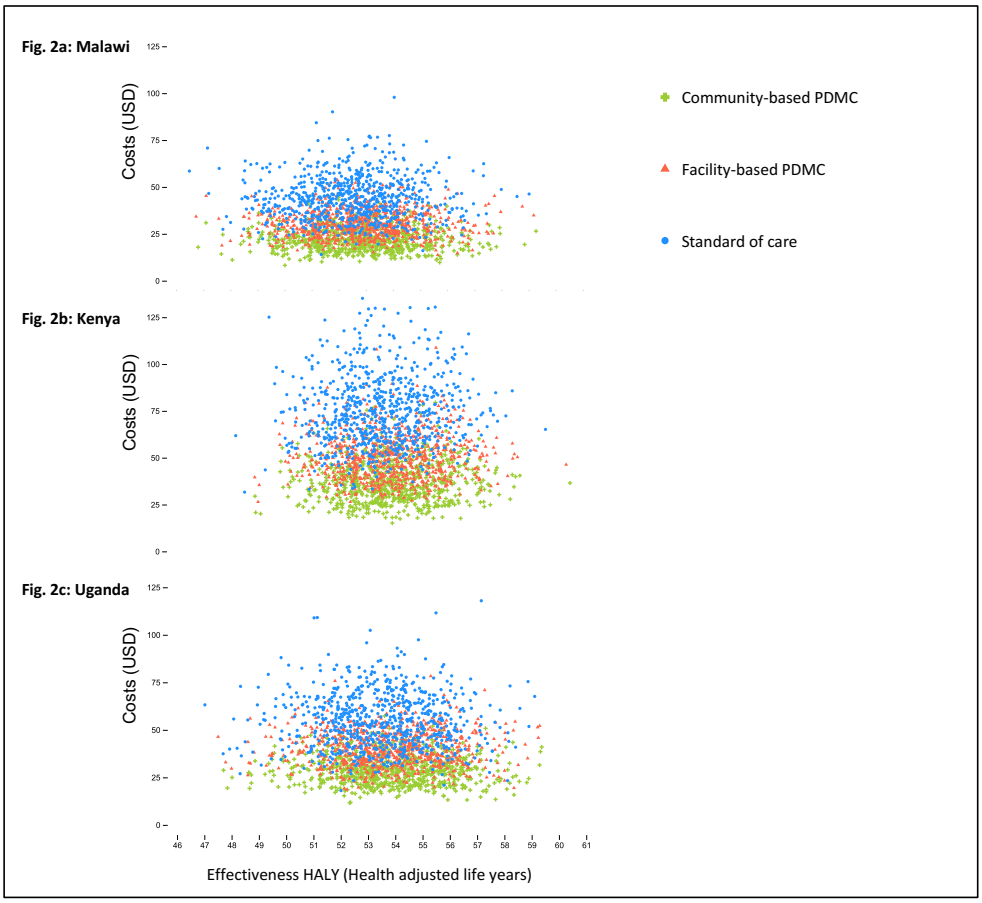
Results from the scenario analysis, where we assumed a convexly and a concavely-shaped dose-response curve to test the sensitivity of our assumption of a linear does effect, i.e., each dose of PDMC had an identical preventive effect, as illustrated in Figure 5. The scenarios, each calculated using 10 000 Monte Carlo simulations, confirmed our ranking of interventions (Table 7). As expected, in a concave scenario, the costs were lower as the effects per dose were higher than in the linear base case; when assuming a convex dose-effect relationship, PDMC was overall less efficacious with imperfect adherence, and, therefore, more expensive compared to the linear base case scenario.

Table 7 Comparison of cost-effectiveness analyses with concave and convex dose-effect scenarios.

	Cost (US$)			Effectiveness (HALY)			ICER		
Strategy/Dose-effect scenario	Base case	Concave	Convex	Base case	Concave	Convex	Base case	Concave	Convex
Community distribution	22	21	23	53.04	53.06	53.03			
Facility distribution	31	30	32	52.99	53.02	52.97	-162	-189	-143
Standard of Care	45	45	45	52.67	52.67	52.67	-60	-60	-60

Probabilistic sensitivity analyses (PSA) for all countries confirmed that, with a very high probability, community-based PDMC was the optimal strategy, followed by facility-based delivery, and the standard of care. The scatterplots of ICERs per delivery strategy in Figure 8 illustrate this. A high number of model iterations with probabilistic sampling from key variables confirmed, firstly, the ranking of strategies. Secondly, the iteration plots' layering along the y-axis point towards the cost as overall driver of the ranking, whereas the effectiveness between strategies varied relatively less, shown by small differences between strategies along the x-axis.

Figure 8: 750 iterations of Monte Carlo simulations, per country, illustrate the «layering» of the two PDMC strategies and the standard of care.



A pairwise comparison of strategies' of incremental costs and incremental effectiveness per iteration, illustrated in Figure 9 for Malawi but likewise calculated for Kenya and Uganda, resulted in comparable values for the three countries: Approximately 95% of iterations identified the community-based PDMC delivery as the optimal strategy, and nearly all of these showed this strategy to be both more effective and less costly than the standard of care. Compared with facility-based delivery, community-based delivery was optimal in over 80% of iterations in each of the three countries (Table 10, Supplementary materials, Paper 2).

Figure 9: Pairwise incremental cost effectiveness comparisons of the three PDMC strategies in 750 iterations, for Malawi,) each with a 95% confidence ellipse, and a willingness to pay-threshold of one GDP per capita in US$.

Fig. 3a: Incremental cost-effectiveness plot using 750 iterations, Community-based PDMC vs Standard of care (baseline), Malawi

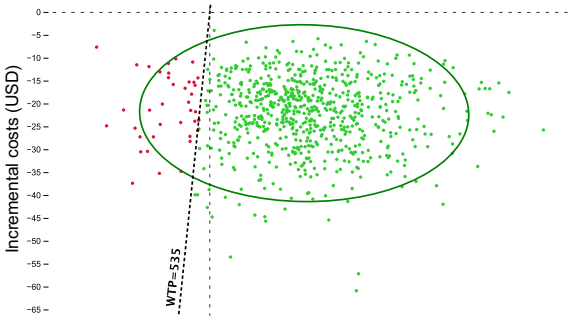


Fig. 3b: Incremental cost-effectiveness plot using 750 iterations, Facility-based PDMC vs Standard of care (baseline), Malawi

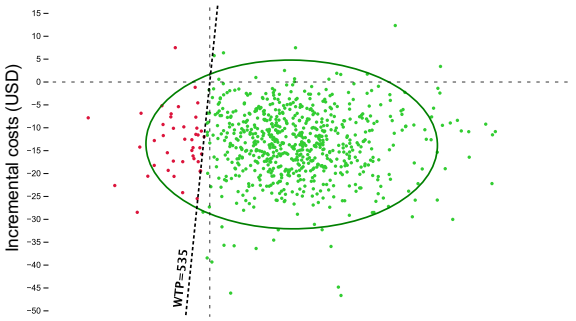
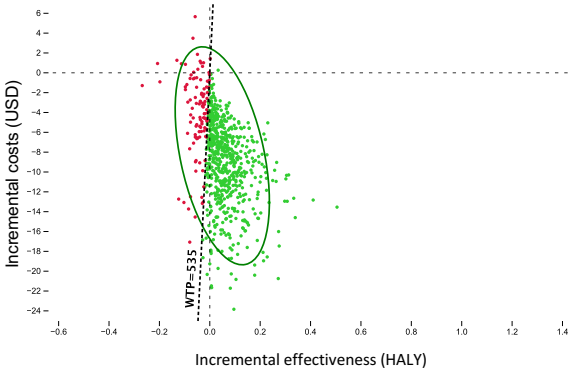


Fig. 3c: Incremental cost-effectiveness plot using 750 iterations, Community-based PDMC vs Facility-based PDMC (baseline), Malawi



Paper 3: a value of information analysis of PDMC

Among all categories of input, the probabilities to transition between health states in the control group and the relative risk of transition when receiving PDMC yielded the highest EVPPI, regardless of the adherence-scenario (3 Efficacy: transition probabilities and relative efficacy (Placebo vs. PDMC), Table 4). Within this category, the uncertainties around mortality, meaning the probability of death within the postdischarge period when receiving PDMC relative to the control group, and the mortality rate in the control group, drove this finding. They were the only probabilities with a positive EVPPI in this category of input. The EVPPI on mortality, per treatment decision, was estimated to be US$0.45, $2.83, and $0.25 for the base case scenario in Malawi, Kenya, and Uganda, respectively. In the adjusted scenario the estimated values were lower: $0.27, $1.71, and $0.15 for the respective countries. The second category of input with a positive EVPPI in this analysis contained the parameters describing the adherence rates to the PDMC delivery strategies (4 Effectiveness: Adherence to delivery strategies, not adjusted, Table 4). Eliminating the uncertainty around this category resulted in theoretical values per decision of $0.26 for Malawi, $1.37 for Kenya, and $0.20 for Uganda in the base case scenario. In the scenario with reduced adherence, the values were slightly lower: $0.23 (Kenya), $1.18 (Malawi), and $0.16 (Uganda). The other four categories of input generated no positive EVPPI for either scenario.

Assuming perfect implementation, that is providing PDMC to all children in need in each of the three countries, perfect information on child mortality in the base case scenario corresponded to an annual NMB of US$ 653 (range 279 – 1 530) in Malawi, $4 471 (range 1 906 – 10 493) in Kenya, and $1 658 (range 705 – 3 894) in Uganda. Perfect information on adherence rates was equated to $377 (range 161 – 884), $2 165 (range 922 – 5 079), and $1 326 (range 564 – 3 115) in theoretical annual NMB for these countries, respectively. The ranges reflect uncertainties in national rates of hospitalization with severe anaemia, ranging from 30% to 70%. These values are reported for one-, five-, and ten-year horizons in Table 2a in the manuscript of Paper 3. Table 2b reports comparable but slightly lower results for the scenario with reduced adherence.

The expected value of obtaining overall perfect information (EVPI), and thus eliminating all uncertainties, was equated to US$0.95 per treatment decision for Malawi, $5.05 for Kenya, and $0.79 for Uganda, when assuming trial-based adherence rates. With reduced adherence rates, we obtained lower values, respectively: $0.74, $3.86, and $0.56. In the base case scenario,

obtaining perfect information on all parameters corresponded to a theoretical annual NMB of $1 379 (range 589 – 3231), $7 979 (range 3 400 – 18 723), and $4 840 (range 2 060 – 11 371) for the three countries, with marginally lower annual values for the scenario with adjusted adherence: $1 074 (range 459 – 2517) for Malawi, $6 099 (range 2 599 – 14 311) for Kenya, and $3 912 (range 1 665 – 9 191) for Uganda.

Assuming perfect implementation across sub-Saharan Africa, Table 8 lists the national annual EVPI around PDMC with ranges based on hospitalization rates, and projections for five and ten-year horizons, with a 5% discounting rate. A product of a large population and a relatively high willingness to pay-threshold, Nigeria had the highest potential national annual NMB of US$106 573 (range 45 355 – 250 398) in the base case and $73 812 (range 31 412 – 173 424) with reduced adherence. Somalia and Guinea-Bissau had the lowest relative benefit from perfect information on PDMC, estimated at a theoretical annual NMB of $71 (30 – 167) and $48 (20 – 113) for the base case scenario. Kenya and Uganda are among the ten countries with the largest NMB from perfect information, while Malawi is among the ten countries with the lowest potential benefit. Depending on the scenario, overall perfect information in the entire Region corresponded to point values of $240 434 (base case) and $166 594 (reduced adherence) which translated to more than $1 million and 1.5 million, respectively, over 10 years.

Table 8: Estimated annual national net monetary benefit (NMB) of perfect information for Malawi, Kenya, and Uganda with adjusted and un-adjusted adherence rates to PDMC.

			Base case EVPI (adherence rates from Gondwe, 2021)					EVPI scenario for routine practice (reduced adherence rates)				
					national NMB of EVPI per year (US$)					national NMB of EVPI per year (US$)		
Country	**WTP (US$)**	**PPP-factor**	**NMB per PDMC decision**	**% sub-optimal strategies**	**expected value**	**low range bound**	**high range bound**	**NMB per PDMC decision**	**% sub-optimal strategies**	**expected value**	**low range bound**	**high range bound**
Angola	415	3.96	2.87	8.52	**9 927**	4 234	23 266	2.00	9.94	**6 918**	2 950	16 213
Benin	171	2.23	0.95	6.88	**3 605**	1 533	8 476	0.69	8.28	**2 618**	1 113	6 156
Burkina Faso	163	1.46	1.17	8.92	**2 537**	1 082	5 951	0.81	10.35	**1 757**	749	4 120
Burundi	79	0.47	0.73	11.48	**628**	268	1 473	0.49	12.86	**422**	180	988
Cameroon	304	2.48	2.33	9.55	**9 759**	4 165	22 870	1.60	10.97	**6 702**	2 860	15 704
Central African Republic	124	0.56	1.32	13.21	**2 155**	915	5 069	0.87	14.56	**1 420**	603	3 341
Chad	101	0.96	0.70	8.08	**414**	177	968	0.49	10.06	**290**	124	678
Cote d'Ivoire	413	3.57	3.05	9.11	**19 720**	8 392	46 348	2.11	10.58	**13 643**	5 806	32 064
Dem. Rep. of the Congo	78	0.72	0.55	8.76	**16 701**	7 107	39 245	0.38	10.21	**11 539**	4 910	27 115
Equatorial Guinea	1 688	9.82	15.88	11.65	**4 477**	1 906	10 541	10.62	13.09	**2 994**	1 274	7 050
Gabon	1 610	9.26	15.23	11.68	**6 991**	2 988	16 405	10.18	13.13	**4 673**	1 997	10 965
Ghana	115	3.65	0.40	3.70	**1 465**	625	3 434	0.33	5.02	**1 208**	515	2 833
Guinea	165	1.77	1.05	7.86	**1 977**	843	4 636	0.75	9.25	**1 412**	602	3 311
Guinea-Bissau	228	1.23	2.23	12.11	**19**	8	47	1.48	13.48	**13**	6	31
Kenya	529	3.18	5.05	11.43	**7 979**	3 400	18 723	3.86	12.87	**6 099**	2 599	14 311
Liberia	210	0.95	2.23	13.17	**2 625**	1 115	6 178	1.47	14.55	**1 730**	735	4 073
Malawi	122	1	0.95	9.53	**1 379**	589	3 231	0.74	10.50	**1 074**	459	2 517
Mali	127	1.42	0.79	7.61	**929**	397	2 174	0.56	9.03	**659**	282	1 541
Mauritania	357	3.56	2.40	8.25	**336**	144	786	1.68	9.76	**235**	101	550
Mozambique	150	0.82	1.45	12.01	**8 735**	3 713	20 544	0.97	13.39	**5 843**	2 484	13 744
Niger	122	0.80	1.08	10.91	**2 208**	942	5 176	0.73	12.38	**1 493**	637	3 498
Nigeria	372	3.30	2.70	8.94	**106 573**	45 355	250 398	1.87	10.40	**73 812**	31 412	173 424
Republic of Congo	298	2.17	2.46	10.29	**2 010**	855	4 726	1.67	11.80	**1 365**	581	3 208
Sierra Leone	158	1.08	1.35	10.58	**1 898**	806	4 464	0.92	12.07	**1 293**	549	3 042
Somalia	127	0.76	1.17	11.44	**71**	30	167	0.79	12.85	**48**	20	113
South Sudan	357	0.72	4.95	17.71	**12 747**	5 436	29 893	3.20	18.67	**8 241**	3 514	19 325
Tanzania	251	1.73	2.14	10.57	**1 500**	642	3 510	1.45	12.07	**1 016**	435	2 378
Togo	195	1.42	1.61	10.27	**2 073**	883	4 859	1.09	11.73	**1 404**	598	3 290
Uganda	128	1.51	0.73	7.30	**4 840**	2 060	11 371	0.59	8.82	**3 912**	1 665	9 191
Zambia	421	2.17	4.21	12.49	**4 154**	1 772	9 739	2.80	13.81	**2 763**	1 179	6 477
Total (US$) for 1 year (5% disc.)					**240 434**	102 384	564 669			**166 594**	70 940	391 251
Total (US$) for 5 years (5% disc.)					**989 028**	421 157	2 322 771			**685 286**	291 814	1 609 417
Total (US$) for 10 years (5% disc.)					**1 549 858**	659 974	3 639 904			**1 073 879**	457 288	2 522,041

Discussion

In three different papers, this thesis aimed to close important evidence gaps on PDMC, therewith removing a few obstacles on children's road to recovery after they received hospital treatment for severe anaemia; and at the systems level, enabling informed decision making regarding PDMC implementation as an effort to regain momentum in the global agenda to end malaria.

In Paper 1, we investigated predictive factors of Malawian caregivers' adherence to PDMC, using a prognostic multivariable model. To our knowledge, this was the first predictor analysis for adherence to PDMC. A secondary analysis of trial data, our study did not produce a coherent set of predictors in line with literature on either prevention or ACT-based malaria treatment.[142,187,188,196,197] Our results were, instead, mixed. Paper 2, the first economic evaluation of PDMC, established the cost effectiveness of PDMC over standard of care in Malawi, Kenya, and Uganda, and identified community-based delivery as the optimal delivery strategy among those tested. Paper 3 reviewed the uncertain parameters in this cost-effectiveness in order to quantify the value of engaging in further research to reduce these uncertainties. More generally, I conclude the discussion with thoughts on the reliability of our adherence data, which were elementary in all three papers, as well as the question whether current research and implementation on PDMC may be overlooking a simple mechanism to markedly increase adherence in rural communities in sub-Saharan Africa.

Paper 1: predicting adherence to PDMC

We aimed to predict caregivers' adherence behaviour to PDMC with child, caregiver, and household characteristics based on data from the delivery trial. Our results were mixed, only few predictors could be identified. In this discussion, we partly explain our mixed results with the complexity of factors underpinning caregivers' adherence to the PDMC regimen. We further suggest that the largely inconclusive findings are partly due to limitations in the study design, connected to sample size and the difficulties around the validity of adherence outcomes. Firstly, the complexity will be described against established adherence categories, and embedded the larger frame of this thesis. Secondly, in some depth, I review the validity of adherence data and how it may have influenced our outcome. Our findings prohibited us from articulating PDMC-specific advice how to target caregivers at risk of poor adherence. Instead, this discussion concludes with the pragmatic suggestion to identify children at relatively higher

risk of a malaria infection - rather than their caregivers' capacities to prevent that risk – and to tailor implementation to their needs.

Aside from overestimating adherence rates, generally not understanding adherence behaviour is a crucial and immensely complex problem in global health research. In a WHO-report on adherence behaviour to long-term therapies, the authors highlighted two important truisms in this under-researched field. They recognized, firstly, that "adherence is an important modifier of health system effectiveness".[198] This is, arguably, an understatement because imperfect adherence "modifies" system's performances in one direction only: the negative. It not only leads to sub-optimal therapy effectiveness for the non-adherent individual but also includes more systemically detrimental effects, like treatment costs or, in the case of malaria, the emergence of antimalarial resistances: a fundamental breaking block to the global progress on eradicating malaria and direct result of poor adherence within populations.[36,88,186]

Secondly, in the same report, the authors concede after a literature review that there are "no stable factors that reliably predict adherence". They then point towards the disease-, therapy- and context-specific factors that are elementary to consider when attempting to understand adherence behaviour.[198] Together, these two claims turn adherence into an uncomfortable black box in global public health research: it reduces established clinical effects while the real reduction is often unknown, or difficult to measure reliably; it is highly context-dependent; and the motivations behind it are multifaceted.[201,202] And, yet, the magnitude of the negative impact on health systems can hardly be overstated: adherence rates to long-term treatments are estimated to be around 50%, and generally lower in developing countries.[198]

The literature identifies as multiple factors that determine adherence, directly and indirectly, like age, socio-economic status, concerns about the treatment, and its expected or perceived benefit, as well as the perceived severity of disease, and mental health. Furthermore, provider-communication often plays an important role.[203–206] We considered these factors when studying PDMC adherence but we were not able to confirm them. We suggest that two key features may distinguish the adherence to PDMC from the more often studied and described behaviour in the literature.

Firstly, PDMC is a preventive treatment, it is not intended to be curative. Yet, it is a preventive treatment over a relatively short time. The evidence on adherence behaviour is generally better on curative treatment than on prevention. Those preventive treatments that have been researched for predictive factors are usually long-term treatments, often life-long.[198] Both

features are elementary drivers of adherence behaviour. Curative treatment promises a direct effect. Long-term preventive treatment allows to build a routine around the treatment in question, including reminder structures within households. Neither of these treatment features apply to PDMC, arguably creating a niche in which available evidence on adherence behaviour may have limited validity.

Secondly, most studied adherence patterns are focused on the person receiving the treatment and their adherence to a treatment. PDMC, however, is administered to young children (median age: 33 months) and, therefore, adherence is largely dependent on a child's caregiver. This relationship further distinguishes PDMC from the general literature. While it is not evident whether this may generally be a conducive feature or not, it has been established in the literature as distinguishing factor to adherence behaviour, generally. Specifically, in the context of ACT adherence in children, evidence from sub-Saharan Africa is focused on treatment, leaving us, again, with lacking evidence on the role the caregiver-child relationship plays in adherence to short-term prevention in children.

These two interdependent features may explain why established predictive factors for curative treatment or prevention in adults could not be confirmed as predictive factors for PDMC. We argue that the short-term preventive purpose, as well as the child-caregiver relationship, add complexity that may single out PDMC from treatment categories conventionally used in adherence research. A recent trial-based predictor analysis from Malawi and Uganda with a much larger sample aimed to assess the determinants of readmission of children discharged after treatment for severe anaemia, without receiving PDMC.[207] With similar findings, the authors concluded that they were not able to "identify specific predictors that would be easily amenable to clinical intervention". Interestingly, the authors tested adherence by caregivers to home-based postdischarge care of their child as potential predictor and found that poor adherence was highly predictive of readmissions.[207] The authors interpreted adherence as a proxy for quality of caregiver care at home. Overall, they could not determine actionable predictors and obtained an area under the ROC-curve comparable to the one of our model. This led the authors to conclude that key determinants had not been measured.

Adherence was described above as a black box, modifying treatment efficacy due to complex patterns, that are hard to measure or predict in community settings.[208] We designed the Malawi trial with some precaution, aiming to collect true adherence data. We measured the outcome using three unannounced visits, one after each DHAP-course's completion time. Arguably, we

did not consider sufficiently that caregivers likely predicted and expected the second and third visits - albeit unannounced. The clearly communicated, desirable behaviour in the trial context was that all tablets were administered as scheduled. There is a good chance that caregivers' adherence was influenced by their wish to display desirable behaviour combined with the growing expectation to be checked. This association has been shown for ACT-*treatment* in comparable settings.[187,188] A more practical aspect that may have led to our overestimating adherence rates was that pill collection occurred in the community setting with study personnel usually locating the caregiver at her home or in the village, and then waiting for them to fetch the blister pack to be checked.[105] This presented an opportunity to empty the pack before returning it. The incentive to do this would be, in addition to displaying desirable behaviour, the fear of losing valuable medication. The collection process allowed for caregivers to hold on to non-administered tablets.

Another potential bias we may have underestimated when measuring community-based adherence was the effect of information provided to caregivers during the consent process and study enrolment, including detailed administration instructions and demonstrations. Unless comparable desirability to adhere and knowledge about PDMC and associated risks of non-adherence can be expected in routine public care, these factors may have influenced caregivers' adherence – plausibly towards higher adherence than in a routine setting. In comparable settings, the quality of information on administration and effect of ACT *treatment* (not for prevention) have been associated with reduced adherence behaviour.[182]

Difficulties with indirectly assessing adherence are known, and the means of verification we chose in the trial is generally accepted as relatively reliable.[196,203,209,210] In addition, this trial was designed as a delivery trial, and it offered a methodologically robust comparison of adherence rates with a plausible ranking of the different delivery strategies. This critique is thus not addressed at the trial design but rather to the way the produced data were used in this thesis, in Paper 1 (and Paper 2, and with some adjustments in Paper 3). I assumed that the trial's absolute adherence numbers would reflect the rates to be found in the wider population under routine care. In view of the two arguments presented above, the de facto adherence to PDMC in Malawian communities should be expected to be on average lower than our data suggested; perhaps even the trial-based adherence was lower than we found.

The latter factor could have been minimized relatively easily by not collecting the non-given tablets but rather registering their number and leaving them with the caregiver for delayed

administration. Arguably, this may also be more ethical. The other points present epidemiological research dilemmas hard to address. “Smart” tablet containers are likely more reliable, and recommended, for future PDMC research, not last as they also allow for reliable monitoring of dose timing. However, they as well are prone to having an improving effect on adherence.[12,211]

In the predictor study, we expressed the strictest possible outcome definition, stricter than the trial paper, and more than half the caregivers in each delivery arm remained adherent, i.e. administered all tablets. It is difficult to assess the robustness of this rate against the literature, as adherence rates are hardly transferable across interventions and settings, and PDMC or comparable regimens are hardly researched in this regard. In summary, the presented factors, which we did not critically control for in paper 1, may have distorted our adherence data and therewith contributed to the mixed direction of conventional predictors for adherence to PDMC.

From an implementation perspective, the main purpose of understanding background factors that influence adherence behaviour is to tailor delivery strategies according to revealed risk patterns. In the case of PDMC, this could mean to routinely inquire about risk factors when communicating with caregivers and re-emphasize the importance of adherence, or set up specific reminder mechanism, for those caregivers that are at specific risk of poor adherence. While our study did not reveal any useful demographic or socio-economic factors, it still points towards one simple predictor: many malaria infections in the past year are indicative of a higher probability of poor adherence to PDMC in the future. A child’s medical history is easily obtained during hospital routine and may point towards a different, more pragmatic alternative to tailor PDMC delivery. The number of past malaria infections could be used, at discharge when PDMC is prescribed, as indicator for a potential higher risk of poor adherence to PDMC.

In addition, the factors predicting malaria infections in children have been well researched.[21,212–214] A recent study from Central Malawi analysed determinants of malaria infection among young children in rural communities in central Malawi, a region where the prevalence of infections among children is comparable to the national average.[21] Children of caregivers without formal education were found at substantially higher risk of infection (adjusted odds ratio: 2.77). Within the under 5-year-old cohort, older children were more likely to become infected. Another determinant for a higher risk of infection was recent intimate partner violence experienced by female caregivers. Assuming these results are true for the

postdischarge period in the community, it is thus possible to point out, beyond medical history, who is at relatively higher risk of malaria infections.

Until the distribution of adherence behaviour to PDMC across households is better understood, predictors for malaria may thus serve as useful intermediate proxies to tailor PDMC implementation to those at highest risk of a malaria infection during the postdischarge period. Depending on the cultural views, an inquiry on domestic violence experiences may be seen as invasive in the health context. In that case, relying mainly on education and child age in addition to medical history as predictors may be more constructive. Evidently, this singles out children at higher risk of a malaria infection, not of their caregivers' non- adherence. Yet, as an intermediate measure for PDMC implementation, it may be useful to consider the reliably predictable risk of infection, in addition to the weaker predictor for poor adherence, to reduce the overall risk the of child readmission due to malaria infections during the postdischarge period.

Paper 2: a cost-effectiveness analysis of PDMC

In the cost-effectiveness analysis we assumed a societal perspective, combining the provider and household cost perspectives. We found that in all three countries both PDMC-delivery strategies were cost-effective compared to the standard of care. PDMC has a high efficacy leading to substantial reduction in readmissions of children in the postdischarge period. Readmissions are costly, consuming resources from both the facility and the household over several days. Even a reduced protective effect, based on our linear assumption on the dose-effectiveness under compromised adherence, prevented a sufficient number of readmissions that both PDMC strategies were still highly probably cost-saving in all countries, meaning they are relatively less costly than the standard of care – in spite of the additional intervention costs – and marginally more effective. These results are confirmed in the sensitivity analyses we presented for the societal perspectives, separately for each country. The scenario of a convex dose-effect relation likewise confirmed the overall superiority of PDMC, delivered using either strategy, over the standard of care.

Comparing the two delivery strategies, community-based delivery is superior. It has higher adherence rates, which translates into an overall higher effectiveness of PDMC in the model, resulting in less adverse health events. This is shown in both a higher health utility, compared to facility-based delivery, and reduced cost in two ways: firstly, the relatively lower number of

readmissions saved the provider costs, as well as the households. The relatively lower household costs of administering fewer tablets, due to the lower relative adherence in the facility-based strategy, do not feature importantly. However, depending on strategy, the implementation cost had an impact. The repeated collection of monthly doses from the hospital pharmacy placed a significant additional burden on the rural families of children receiving the facility-based treatment. These costs are so important that, assuming only a household's costs perspective, this strategy would be inferior to the standard of care in Malawi and Uganda. Yet, the cost saved at the provider level with reduced readmissions are so influential, that they invert the ranking when both perspectives are combined in the societal perspective. Based on these driving factors, the superiority of the community-based strategy to deliver PDMC, over both the facility-based strategy and the standard of care, is plausible – and likewise confirmed in the incremental cost-effectiveness calculations where strategies are compared pairwise.

The delivery trial used five arms, factorially combining the two delivery strategies with SMS reminders, or no reminders, and adding one arm with a physical reminder to be provided by the local health surveillance assistant.[105] Unfortunately, the reported SMS delivered and received were few and inconclusive in association with adherence. The HSA reminder-mechanism was deemed by the caregivers too unreliable to depend on.[106] Therefore, we decided to compare only the two main delivery strategies in the cost-effectiveness analysis. Our results confirm the perhaps intuitive assumptions that repeated travelling of several hours to collect a monthly course would result, ultimately, in lower adherence and higher cost than having all needed courses at one's disposal at home. There is a potential benefit the facility-based delivery that was crudely disregarded in this analysis. If the monthly collection at the hospital was combined with a check of the child by a nurse or paediatrician, both the adherence rate and, independently, the health utility could have improved. In such a design, a cost-effectiveness analysis might result in somewhat more nuanced results than the absolute dominance of a less costly *and* more effective delivery strategy compared to a second strategy and the standard of care.

As discussed for Paper 1, a more critical reading of the factors behind the adherence outcome could have been advisable for this analysis, as well. Rather than scenarios about the dose-effectiveness, or in addition to them, a scenario applying a global reduction to the adherence rates as done in Paper 3, would have given this analysis more relevance for policy-development. Adjusting for the likely overestimated adherence for real-world conditions would have allowed us greater certainty on real implementation cost and effectiveness, once PDMC

is delivered as part of routine care. However, a second factor in this context may likewise merit further consideration. We assumed 100% adherence for the efficacy trial, with 98% being reported in the trial results. Recently, trial designs have become criticized for not assessing adherence sufficiently and consequently systematically underreporting non-adherence.[215] Considering that the second and third dose were taken without direct observation, but with a phone-based reminder, the reported 98% adherence to the trial may be optimistic. Self-reporting is generally prone to overestimate adherence in trials.[216] Assuming that the clinical outcome was achieved by 100% adherence, as we did in the CEA, may thus slightly underestimate the effect of actual 100% adherence; meanwhile the efficacy trial's intention to treat analysis may have introduced a similar or stronger bias in the same direction, if it underreported non-adherence.[217]

On the cost side, a wider consideration of training and other introduction costs would have been advisable. As we claim to present cost-effectiveness results for implemented strategies, such costs should be included, or their absence should be more explicitly addressed, not to mislead a reader to assume they are included. A recent analysis of the costs of introducing and implementing the RTS-vaccine found that introduction costs constituted up to 70% of the financial cost of implementation.[96] A comparably simpler intervention, like PDMC, would likely amount to lower introduction costs as it is added to the established patient pathways and discharge procedures of the standard of care. Nonetheless, the omission, combined with the explicit implementation focus, likely introduces a preventable bias in our interpretation in favour of the intervention. Notably, evidence reviewed by the WHO advisory groups for the vaccine cost-effectiveness, included cost estimates for these delivery factors and was estimated to be of overall higher quality than the evidence on the cost-effectiveness for PDMC.[218] It is therefore recommended to assume a more inclusive costing perspective when conducting implementation-focused economic evaluations of PDMC in the future.

Nonetheless, our CEA provides an evaluation of different delivery strategies of PDMC, and as such it is relatively more informative for policy development than an analysis simply comparing clinically proven efficacy with data from a placebo cohort. Integrating adherence data into the analysis added methodological robustness, which is often lacking in RCT-based economic evaluations without empirically determined adherence or fidelity estimates. Moreover, compared to many cost-effectiveness analyses, the robust patient-based costing of readmission cost, at least for Malawi, represents a strength of this study that allowed us to confidently determine in detail the cost of adverse events and focus on their frequency across

cohorts. Relying on these two strong features, and despite the discussed limitation, we could produce a robust recommendation in favour of PDMC.

Paper 3: a value of information analysis of PDMC

Employing the model for the cost-effectiveness analysis of PDMC in Malawi, we conducted a VOI analysis to quantify the theoretical gain from eliminated uncertainties around PDMC for Malawi, Kenya, Uganda, and a total of 30 malaria-endemic African countries. When considering further research to reduce uncertainties in the evidence, the population EVPI, or EVPPI, determine a theoretical ceiling that delineates the value of obtaining perfect information on the parameters in question. Reducing uncertainties around the probability to die and around adherence rates to PDMC offers a combined potential benefit, ranging between US$19 for Guinea-Bissau and $106 573 for Nigeria. In the scenario with more compromised adherence, the annual values of perfect information were lower, ranging from $13 to $73.812, respectively (Table 8).

The most important potential gain from partial perfect information would result from resolving the uncertainty around the probability of child mortality when receiving PDMC, or standard of care. The second category of inputs, caregivers' adherence rates to PDMC, offers overall less value, if resolved. All other uncertainties used in the CEA generated no positive EVPPI, including the uncertainties around cost or utilities.[189] Assuming an economic lens limited to PDMC in a particular context, and accepting the limitations inherent in the CEA model structure, further research on these uncertainties holds a minimal or no economic benefit that would justify a use of limited resources to address them.

Mortality is a relatively rare outcome, in general, and this is also the case for PDMC. Uncertainty around mortality is, therefore, not unusual in epidemiological studies, as certainty in mortality, compared to any more frequent health outcome, would demand a substantially higher sample size in a clinical trial. For this reason mortality was combined with readmissions into a composite outcome in the efficacy trial, allowing to consider mortality as outcome without the necessity to power the trial for a single mortality outcome. In addition, trial-based placebo- or standard of care- arms are often subject to "contextual effects" inherent to trials, such as enhanced care seeking behaviour due to easier access to care, or patient information above routine-level.[182] This is one reasons for a bias inherent in trial designs that may, as a result of their mere presence, lead to underestimated poor health outcomes in the general

population.[219,220] The authors of the efficacy trial presented this as a possible reason for the insignificant differences found in mortality between the arms, and mirrored these results with results of other trials in comparable settings that observed similar underestimates.[28] The persisting uncertainty around mortality associated with PDMC is, therefore, not surprising.

The uncertainty can be addressed through research of different methodologies. As indicated above, an identical RCT as the efficacy trial, however powered for a single mortality outcome, could produce certainty. The cost, however, would largely exceed the discussed ceilings for rationally-informed research funding. A meta-analysis of pooled, available trial data could produce a statistically significant effect size for child mortality in cohorts receiving PDMC vs. a placebo. Yet unpublished, such a study has been done. Recently, Phiri et al pooled and analysed data from three PDMC-trials from the Gambia; Malawi; and Kenya and Uganda, and found a significant reduction of the mortality rate of 1.6% in the control group's data by 1.2% to 0.4% in the PDMC-receiving group (RR 0.23, CI 95% 0.08-0.70) within the 3 months-intervention period.[221] Another trial -testing a different intervention, could provide further data on the survival of the same control group for Uganda and Malawi.[207,222] These data could be used to inform an updated CEA with more certainty on mortality input, which would, in turn, likely further reduce the value of eliminating the remaining smaller uncertainties around mortality. This approach would address the sample-size problem for mortality outcomes and it would cost a fraction of a large RCT. As this meta-analysis included only trial data, this approach does, however, not address the possible bias of underestimating mortality in the general population in need – outside of a trial environment. Pragmatically, as long an overestimation can be excluded, the risk of bias may be acceptable when deliberating over implementation strategies of PDMC. Alternatively, mortality estimates for the wider population in need of PDMC, as baseline, could be extracted from another meta-analysis that compares the risks of children admitted with severe anaemia compared to other admission reasons, and includes other designs than RCTs (20 studies).[32] Another retrospective option to obtain mortality rates would be to review sufficient patient history data, per country, to reliably determine the all-cause mortality rate of this population with a relatively small margin of error. The corresponding prospective design would be to document the population-wide mortality during a stepwise implementation with focus on areas where PDMC had not yet been introduced.

In view of the relatively low benefit from perfect information on mortality, the 10 year-NMB for Malawi, Kenya, and Uganda combined lies below US$50.000, updating the CEA with latest

literature results appears to be an economically rational and epidemiologically robust way to reduce the uncertainty on the difference in mortality when receiving PDMC compared to control groups.

Eliminating or reducing uncertainty around the second influential category of inputs, the adherence rates to PDMC, grouped by different categories of adherence, may require more contextualized research approaches. As discussed before, adherence behaviour is complex and, accordingly, estimating adherence rates for, for example, the entire sub-Saharan Africa or even just larger sub-populations than those in need of PDMC, would crudely ignore the Region's cultural heterogeneity. The factors influencing adherence behaviour have been shown for other treatments to vary strongly within and between sub-Saharan countries to the point that any claims of external validity would require justifying the underlying assumptions.[198,206,223–225] This limits the scope of populations in need of PDMC per research project. In turn, the total annual benefit of perfect information on adherence would be relatively lower than any results valid for the entire Region.[226] Using the same example as before, for the three countries the value of perfect information on adherence translates theoretically to less than US$25 000 and $21 000, depending on the scenario, over ten years. This funding ceiling a priori excludes larger research projects to address these uncertainties.

In addition, determining a longer time horizon for the benefit of perfect information on adherence, which is directly linked to specific delivery strategies, may be particularly difficult. It may well be that introducing SMS reminders may significantly reduce the number of caregivers that forget the later monthly doses of PDMC, and in such case it would likely be integrated into delivery strategies. Different regimen designs, combinations with antibiotic treatment, and, not last the option to use a vaccine for PDMC, are probable scenarios within this decade. Yet, nothing is certain and, therefore, determining a time horizon is always "an attempt to proxy an uncertain and complex process of future changes".[194] Still, it appears advisable to opt for a shorter horizon when projecting the benefits of perfect information on adherence, which is influenced by more complexly evolving factors, than to certainty on mortality outcomes, which rely primarily on bio-medical effects of a drug. Evidently, any such changes would equally devalue the CEA that underlies this VOI-analysis.

An interesting and, perhaps, unintuitive finding of this analysis lies in the comparison of values between the base case and the scenario with adjusted adherence. The values of perfect information are relatively lower when adherence is globally reduced. Yet, a reduction in

adherence increases uncertainty about the optimal strategy, which is shown in the relatively higher occurrence of error among the iterations with reduced adherence (Table 8). Therefore, one could expect the value of perfect information to increase accordingly in such scenario. However, with the relatively drastic reduction in adherence coincides an equally drastic reduction in effectiveness, in all adherence categories, bringing the arms closer together in their average utility. As a consequence, any error foregoes less health effects than in the base-case scenario with the larger differences in health effects, which outweighed in our case the increase in errors.

As we limited our results to reporting the EVPI for the other countries, a discussion for specific research designs is impossible. Even the highest national EVPPI, $106,573 per year, for Nigeria, would hardly cover the expenses of any novel research project to address mortality *and* adherence without any uncertainty remaining. However, an updated CEA, integrating the latest evidence would likely result in overall reduced uncertainty for each of these countries' VOI-estimates.

These EVPI-informed ceilings are theoretical in nature, serve only as a point of departure for research planning, and cannot predict economic gain to a health system in the long term if PDMC was perfectly implemented. On the one hand, the assumption of full coverage of PDMC – a theoretical requirement to quantify the population-based value - is a crude overestimation in practice. In addition to mere coverage, quality of care is an additional challenge: across sub-Saharan Africa, diagnosis accuracy and treatment according to guidelines are particularly lacking in the cases of malaria and anaemia routine treatment.[186] On the other hand, limiting the value of future research only to PDMC risks omitting the less predictable contribution it would likely make to other related interventions; moreover the benefits of improved health are strictly limited to a single utility, here, which omits other direct and indirect positive effects of good health beyond the CEA's utility. Only naming one complex of ignored consequences: malaria infections, related hospital readmissions and recovery cause short term developmental delays in children.[26] This is not considered in our presented calculation of the value of information and, therewith, does not figure in the estimated value of reducing remaining uncertainties.

Lastly, as we used the CEA for Malawi, Kenya, and Uganda, we carried over its limitations and assumptions into this analysis. The unpublished provider costing study for Malawi allowed for precise and robust cost estimates for Malawi. Adjusting them relatively crudely to Kenya

and Uganda signified a loss in the costs' validity which we deemed acceptable. However, using Malawi as costing template for the entire region introduces a heterogeneity of health systems, cultures, and economies that, arguably cannot be reflected using Malawi's cost – even if adjusted by purchasing power.

Obtaining perfect information on uncertain parameters that compromise the benefit of an intervention is generally desirable. Taking a rational economic perspective, whether the uncertainty around mortality during the postdischarge months when receiving PDMC, and around adherence to PDMC, should be addressed, can be theoretically determined by means of the annual net-monetary benefit that is foregone by the uncertainties' presence. However, this EVPI per country is relatively low. From the perspectives covered by our analyses, the available evidence is thus robust enough to safely recommend PDMC for implementation, while further reducing uncertainties is highly unlikely to change this conclusion. As PDMC is increasingly implemented using nationally adjusted delivery strategies, new uncertainties arise around the optimal delivery of PDMC.

PDMC in the future: reaching past the low hanging fruit?

In global health research, recently more pragmatism has been demanded.[227] Likewise, there is a pragmatic call for a shift in the adherence-discourse, away from the patient-focus towards systems-thinking, finding procedural solutions within the health care system, to address the "pressing rates of poor adherence".[228] Yet, recent implementation designs that followed the adoption of PDMC in the WHO malaria guidelines do not consider any reminder options – in spite of the regimen and its preventive purpose being very prone to forgetting. Some are tackling the problem of caregivers' forgetting by testing weekly rather than monthly courses. However, no further research appears to be done on SMS or any other reminder mechanism that could be implemented alongside PDMC to remind caregivers of either, a due monthly or weekly course.

If such reminders were disregarded due to the conclusions from the delivery trial, a potentially effective reminder that may increase adherence behaviour would be prematurely excluded from further research. The trial design did not allow for any conclusion regarding the contribution of SMS reminders to adherence behaviour, partly justified by relatively low rates of access to phones in the catchment area. This bottleneck widens constantly, as more and more people own or have direct access to mobile communication in the rural population of SSA. The World bank

recorded an increase from 39 to 60 % of the population having a mobile phone subscription between 2018 and 2021. The mobile operator industry predicts that by 2025 86% of the population in SSA will have a SIM connection.[229] In addition, the costs of reminder-SMS systems are relatively small and they underlie economies of scale. Perhaps, a costing study of the providers' per-patient cost of three SMS reminders is useful to quantify the additional cost to PDMC delivery. This way, decision-makers can more confidently include SMS reminders in their considerations as long as we lack evidence on their effect on adherence. Likewise, testing new regimens and drug combinations might merit a factorial addition of digital reminders.

Looking ahead it is, therefore, recommended to update the CEA, presented in Paper 2, including findings from recent publications on mortality, with an adjusted adherence rate, as presented in Paper 3, and with an explicit implementation costing component, i.e. including estimates of the providers' costs to introduce PDMC. This CEA could exclude facility-based delivery and should, in addition, include country-specific per patient costs for sending generic SMS and include these as alternative implementation arms alongside the intervention arm(s) in place. A threshold analysis of the minimum impact of SMS reminders on adherence to reach cost-effectiveness, including the real implementation costs of such a reminder system, would provide important insight for PDMC and other community-delivered interventions. Perhaps the findings of such an updated study are helpful to open our minds for ideas how to maximize the uptake of PDMC in the 21st century.

Conclusion

The postdischarge period is a widely overlooked contributor to child mortality and morbidity in sub-Saharan Africa. Preschool children who were discharged from hospital after they received treatment for severe anaemia are at a particularly high risk of dying or being readmitted to hospital within half a year after discharge. Postdischarge malaria chemoprevention (PDMC) reduces this risk substantially by protecting them from malaria during their period of recovery at home.

This PhD thesis is embedded in the work of a consortium of interdisciplinary researchers who produced the evidence leading to the WHO recommending in 2022 that governments of malaria-endemic sub-Saharan countries better protect this vulnerable population and introduce PDMC. The three studies presented here were designed to inform both the WHO-based process and national decision makers who consider implementing PDMC.

We found that PDMC is more effective and less costly than the standard of care once the costs of health consequences are included. With implementation in mind, the cost-effectiveness analysis (CEA) of PDMC was done for two delivery strategies, and it included differences in adherence. The cost-effective strategy for Malawi, Kenya, and Uganda, is to hand the full course of antimalarials to caregivers at the time of discharge.

However, antimalarials that are not given to a child generate no protective effect. The caregivers must remember to give the medication for three days, interrupted by 28 medication-free days. The children appear healthy and caregivers do not observe a direct curative effect from giving preventive antimalarials. Instead, at times, the drug may cause children to vomit. These complex factors, we suggest, make it hard to predict adherence behaviour to PDMC. In the predictor study, we found that Malawian children at higher risk of malaria during the postdischarge period are less likely to receive to the full PDMC course. Tailoring PDMC delivery in Malawi to the caregivers of these children may, consequently, result in a better postdischarge recovery of the most vulnerable children.

Despite years of research, uncertainties remain in the evidence around PDMC. They may cause insecurity in national deliberations if and how to best implement PDMC. In the value of information study, we quantified the potential benefit to the health systems if the uncertainties identified in the CEA were eliminated. There is only a negligible chance that certainty on these parameters would effect a decision shift from the optimal community-based to facility-based

delivery or a return the former standard of care. Indeed, the cost-effectiveness ranking of these delivery options is robust for Malawi, Kenya, and Uganda, and it is likely true for other malaria-endemic sub-Saharan countries. At this point, resources may therefore be better used for implementation research aiming to improve the effectiveness of PDMC when implemented at scale. Pushing the real effectiveness of PDMC closer to the promised clinical efficacy will directly result in fewer dead and readmitted children. Improving delivery aspects and understanding caregivers' adherence motivations may be good objectives to start with.

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Annex: Scientific papers

Paper 1 with supplementary material

Predicting caregivers' adherence to postdischarge malaria chemoprevention in Malawian pre-school children: a prognostic multivariable analysis

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RESEARCH ARTICLE

Predicting adherence to postdischarge malaria chemoprevention in Malawian pre-school children: A prognostic multivariable analysis

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Abstract

Chemoprevention with antimalarials is a key strategy for malaria control in sub-Saharan Africa. Three months of postdischarge malaria chemoprevention (PDMC) reduces malaria-related mortality and morbidity in pre-school children recently discharged from hospital following recovery from severe anemia. Research on adherence to preventive antimalarials in children is scarce. We aimed to investigate the predictors for caregivers' adherence to three courses of monthly PDMC in Malawi. We used data from a cluster randomized implementation trial of PDMC in Malawi (n = 357). Modified Poisson regression for clustered data was used to obtain relative risks of predictors for full adherence to PDMC. We did not find a conclusive set of predictors for PDMC adherence. The distribution of households across a socio-economic index and caregivers' education showed mixed associations with poor adherence. Caregivers of children with four or more malaria infections in the past year were associated with reduced adherence. With these results, we cannot confirm the associations established in the literature for caregiver adherence to artemisinin-based combination therapies (ACTs). PDMC combines multiple factors that complicate adherence. Our results may indicate that prevention interventions introduce a distinct complexity to ACT adherence behavior. Until we better understand this relationship, PDMC programs should ensure high program fidelity to sustain adherence by caregivers during implementation.

trial results' publication: Nkosi-Gondwe T, Robberstad B, Mukaka MI, R., Opoka R, Banda S, Kühl M-J, et al. Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemisinin-piperaquine for the post-discharge management of severe anemia in Malawian children: A cluster randomized trial. PLOS ONE. 2021;16(9): e0255769. doi: 10.1371/journal.pone.0255769.

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Competing interests: The authors have declared that no competing interests exist.

Introduction

Malaria-related anemia has caused high mortality and morbidity and remains a leading burden of disease in the child population in Malawi, especially in highly endemic areas [1–4]. A recent meta-analysis estimated that for sub-Saharan Africa, the odds of dying among children during the first six months after their treatment for severe anemia are 72% higher than during the treatment phase in hospital, and over two times higher than for those admitted with other conditions [5]. In June 2022, the World Health Organization (WHO) recommended post-discharge malaria chemoprevention ('PDMC', previously called 'PMC' and 'IPTpd') in the updated malaria chemoprevention guidelines for settings with moderate to high malaria transmission [6]. PDMC comprises three months of malaria chemoprevention provided as monthly treatment courses with long-acting antimalarials to preschool children recently discharged from hospital after recovery from severe anemia. A recent multi-center randomized controlled trial (RCT) in Uganda and Kenya provided three months of PDMC with monthly dihydroartemisinin-piperaquine (DP) and found a 70% protective effect against readmission and death during the intervention period [7]. A cluster randomized implementation trial in Malawi assessed adherence to PDMC following different distribution methods of the same PDMC regimen [8]. Full adherence by caregivers who received all three courses of DP at discharge (community-based PDMC) was 44% higher than adherence to a monthly regimen requiring the collection of each course at the hospital (facility-based PDMC). While the main finding of community-based PDMC yielding higher adherence was clear, key underlying determinants influencing adherence to PDMC, beyond the delivery strategy, remain poorly understood.

Evidence suggests relatively poorer overall adherence to antimalarial therapy in infected young children, cared for by their caregivers, than adherence in adults with malaria [9, 10]. Among caregivers, older age, higher education, literacy, and perception of disease severity have been associated with better adherence to their children's therapy [11, 12]. However, predictors for caregiver adherence to malaria treatment in sick children may not apply when using the same drugs for chemoprevention. While chemoprophylactic antimalarial use in infants (perennial malaria chemoprevention (PMC), previously IPTi) and school children (IPTsc) has been more researched, these strategies are delivered in line with established immunization platforms or school schedules [13–15]. Adherence predictors for these interventions are, therefore, not directly applicable to PDMC either. Using data from the implementation trial in Malawi, we thus developed a prognostic multivariable model to investigate potential determinants of PDMC adherence among caregivers from mainly rural communities. We aim to inform national malaria programs in sub-Saharan countries with moderate to high malaria transmission that plan to implement PDMC.

Materials and methods

Design and participants

This study is a secondary analysis of data collected in the PDMC delivery mechanism trial conducted in Malawi, described elsewhere in detail [16]. In short, the cluster-randomized controlled trial assessed two PDMC distribution strategies of the monthly DP regimen in children discharged from hospital after recovery from severe anemia. Children were randomized to receive PDMC using either a community or a facility-based distribution scheme. In addition, two reminder mechanisms (use of short text messages or community health worker reminders) were factorially added to the distribution strategies [8]. However, we disregarded them in this analysis as they did not significantly affect adherence.

We included data from 357 children who were accompanied by their main caregivers and completed the study (Fig 1). Sample size calculations and management of missing data have been published alongside the trial results [8]. Between March 2016 and July 2018, children aged <5 years, living within Zomba District in Southern Malawi whose caregivers gave informed consent were enrolled upon discharge from Zomba Central Hospital. The 3-months follow-up period ended in October 2018. Children not accompanied by their main caregiver were excluded because reliable information on the child and household could not be obtained. The district's 1460 villages (clusters) were randomly allocated to either PDMC delivery arm. Participants from the same village received the same PDMC distribution strategy. Participants in the community-based distribution arm were given the full regimen of 9 tablets upon hospital discharge and instructed to administer it as three monthly courses of a once-daily tablet for three days, starting two weeks after discharge. Participants in the facility-based arm received the same regimen. However, they had to collect the PDMC courses at prescribed monthly intervals from the hospital pharmacy [16]. Both delivery strategies required caregivers to remember to give the medication at the correct intervals or to collect subsequent treatment courses and administer them as instructed.

Ethics statement

This study is part of the PDMC trial in Malawi. It received ethical approval from the research ethics committees of the College of Medicine in Malawi (COMREC, approval number P·02/15/1679) and the Regional Ethics Committee of Western Norway (REK Vest, approval number 2015/537). The trial was registered at ClinicalTrials.gov (identifier: NCT02721420). Before enrolment, written informed consent was obtained from the legal guardians of participating children.

Data collection

All trial participants were followed for the full treatment period (10 weeks). The data for potential predictors were collected by trial personnel during caregiver interviews and medical assessments of participating children following their enrolment at the study hospital. Data were collected in the local language, Chichewa, and recorded in English using Open Data Kit software [16]. To assess adherence, the trial team collected blister packs at the participants' homes and performed tablet counts during unannounced, monthly visits following each course's 3-day administration period. The trial team was not blinded during this primary outcome assessment [16].

Predictors

Potential predictors were considered along the three categories from the UNICEF Extended Model of Care: predictors focused on the child, predictors related to the caregiver and their behavior, and predictors pertaining to their household's resources [17, 18].

Child-related predictors included key demographic details of a child, such as sex and age, anthropometric measures, and hemoglobin level. In addition, a child's malaria-related medical history was considered, including the number of prior malaria infections and malaria-related hospital admissions. Predictors of caregiver behavior and resources included their demographic information, literacy, and educational status, religious affiliation, and tribe, as well as an inquiry on single parenting, number of children, and experience of child death. Some caregiving health behaviors were also included, such as whether a child slept under an insecticide-treated bed net (ITN). Predictive factors related to household resources included a household's socio-economic status (SES, in quintiles) based on an index of various assets, including

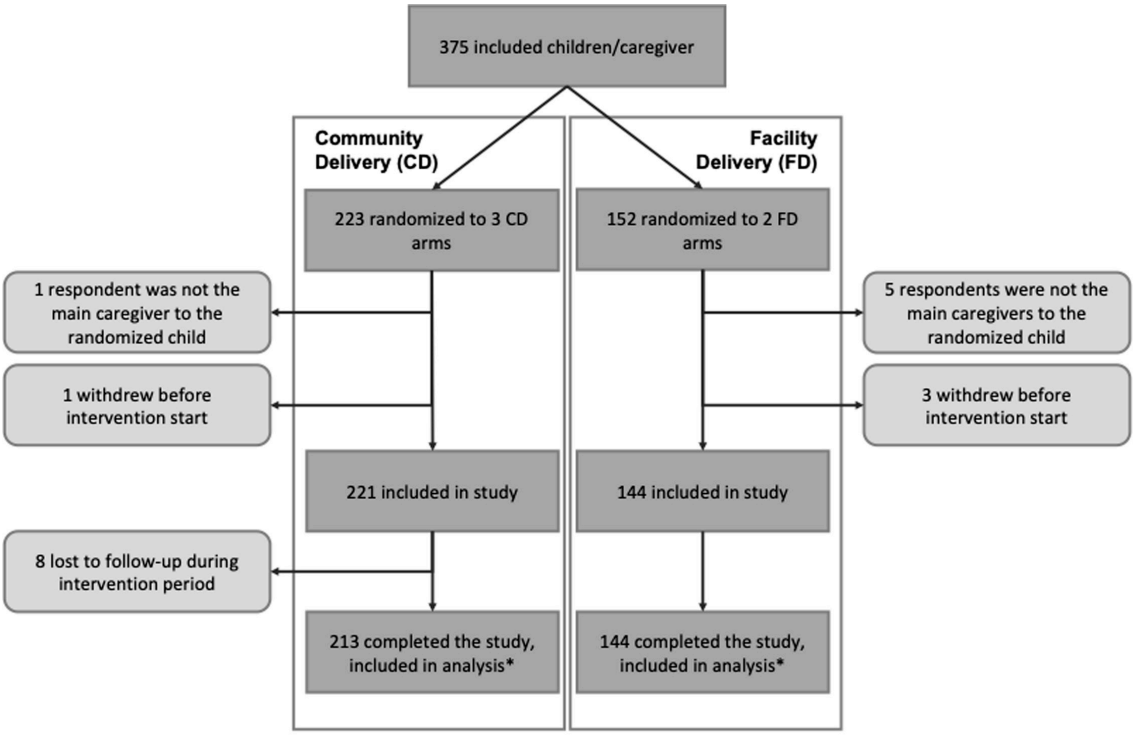

Fig 1. Study profile based on trial data from Gondwe et al, 2021 [8].

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household items, available resources, livestock possession, dwelling size, building materials, and sanitation facilities. We used principal component analysis to create this wealth index from these variables and multicollinearity analysis to adjust it further (S1 Text; S1 Table; S1 and S2 Figs). Household members owning their dwelling, being connected to the electricity grid, being able to rely on a regular income, and owning a bank account, were factors that we considered potentially important individual predictors for adherence. We therefore removed them from the index and tested them as separate predictors in this category. We also included community-related factors: the kind of drinking water source they used, its distance, and coverage of community-level malaria control efforts, particularly indoor residual spraying. Distance from households to the study hospitals was also considered.

All participants in the PDMC trial received the same preventive treatment either through the community-based or facility-based PDMC delivery mechanism. Adherence to PDMC was the primary outcome [8]. Due to this design, our analysis considered distribution strategy as its own category outside the three UNICEF categories.

Statistical analysis

We expressed 'full adherence' as a binary outcome, defined as administering all nine DP doses over three months (i.e. three monthly DP courses consisting of three tablets each to be given on three consecutive days). Adherence was assessed by presenting three empty blister packs that contained three tablets each. Not returning all three blister packs empty at unannounced visits a few days after each course was termed 'non-adherence', irrespective of whether adherence was self-reported. Adherence data of caregivers whose children died during the trial was censored after the last course when the child was still alive to allow for 'full adherence' if the death occurred before they completed the three-course DP regimen (Fig 1).

Our analysis followed three steps. First, we tabulated each potential predictor by the adherence outcome. We present frequencies and percentages for categorical predictors and mean with standard deviations (SD) for continuous predictors. Thereafter, we conducted predictor analysis and report relative risks (RR) (95% confidence intervals) where adherence was the dependent variable, and each predictor was the independent variable [19]. We used a generalized linear model (GLM) for the Poisson family with a log link and robust variance estimation adjusting for clustering and study arm allocation [20]. The statistical significance of categorical variables was tested per subgroup category and for the entire variable using Wald testing. The Intra-Cluster Correlation coefficient (ICC) in the trial analysis was found to be insignificantly small (0.000008) [8]. This also applies to this secondary analysis, where 357 caregiver-child pairs came from 301 clusters.

Lastly, we included all statistically significant predictors at the $p<0.05$ level in a multivariable model [21, 22]. We tested for interaction with age and sex of both child and caregiver in the initial analysis. We also tested the crude and adjusted analyses for each treatment arm separately in view of the strong treatment effect. All variables included in the final model were tested for multicollinearity. Model performance was assessed by calculating the k-fold cross-validated area under the receiver operating characteristic (ROC)-curve with statistical inference obtained by bootstrapping [23].

Considering the wide distribution within the non-adherent group (zero to eight tablets taken) we created sub-categories, as defined in the previous PDMC trial and the cost-effectiveness analyses: *no or low* (zero to 2 tablets), *medium* (three to less than six tablets), and *high* (six to eight tablets) adherence (Fig 2) [8, 24]. We then conducted ordered logistic regression analysis for this categorical outcome, to test if this resulted in a different predictor selection. Accounting for the smaller sample size, we also inspected each potential predictor's (p-values <0.2) mean prevalence across these groups.

We used the Stata SE statistical analysis software package, version 17. We developed and reported this predictor model according to the EQUATOR TRIPOD-statement [25].

Results

A total of 357 caregiver-child pairs were included in this analysis, of which 213 (60%) had been randomly allocated to community-based PDMC and 144 (40%) to facility-based PDMC (Fig 1). More males than females were enrolled in the trial. The z-scores (mean, SD) were: height-for-age (-1.67, 1.49), weight-for-age (-0.94, 1.06), and weight-for-height (-0.01, 1.17). The corresponding proportions of stunting, underweight, and wasting were 40%, 16% and 4%, respectively. Previous malaria infections were common; 61% had experienced at least one diagnosed malaria infection within the year before their hospital admission, and 9% at least four infections. Approximately four out of five children slept under ITNs. Most caregivers were mothers (94%), and the other caregivers were other family members. Their mean age was 29 years. Approximately one in four was a single parent, and one in five had previously experienced the

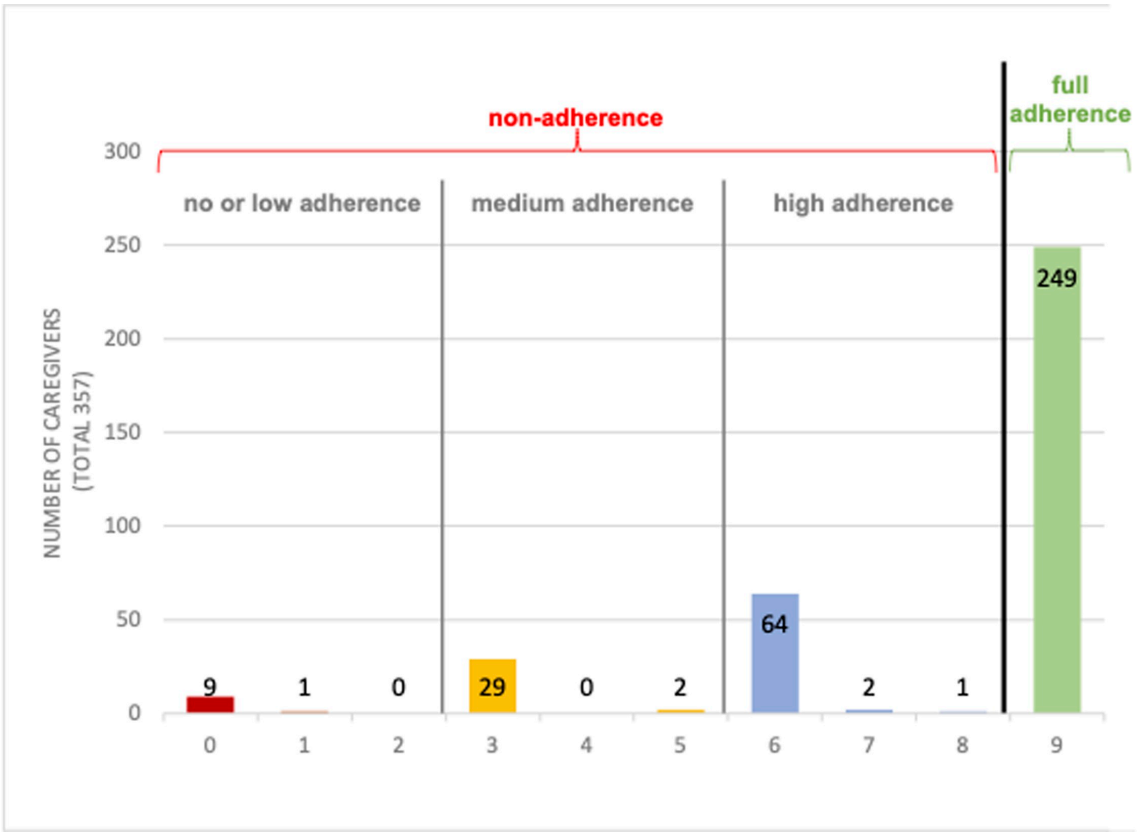

Fig 2. Distribution of adherence behavior: The total number of tablets administered per caregiver.

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death of a child. Almost one in three caregivers was illiterate, and 14% had no education or had not completed primary school. Half of the caregivers had completed upper primary school. 98% of the households had no electricity. Less than 5% used surface water as the main source of drinking water (Table 1).

Out of the included 357 children/caregiver couples, 249 (70%) had full PDMC adherence, and 108 (30%) were categorized as "not adherent" (Table 1). The non-adherent category mostly received either zero, three, or six out of the nine tablets, reflecting that missing doses often involved skipping entire monthly course(s) of three tablets rather than one or two days of a 3-day course (Fig 2) [8]. Four included children died during the study period, all of whom were determined to be fully adherent.

As expected, the allocation to the trial's interventions showed a strong risk of non-adherence associated with facility-based PDMC, compared to community-based PDMC (RR, 95% CI: 0.64, 0.55 to 0.76). None of the potential predictors on child characteristics were associated with adherence except that multiple previous malaria infections (four or more) in the past year were associated with poorer adherence. Among the potential caregiver-related predictors, the

Table 1. Descriptive statistics and regression analysis of potential predictors for adherence to PDMC.

Predictors		Descriptive statistics by outcome frequencies (percentages)—unless row indicated otherwise		Generalized linear model-analysis	
Predictor categories Included potential predictor variables	**Variable categories**	**Non-adherence** n = 108	**Full adherence** n = 249	**Crude relative risk** (95% CI)	**Adjusted relative risk** (95% CI)
Intervention allocation, PMC trial (Gondwe, 2021)					
PMC delivery	community-based	40 (37.0)	173 (69.5)	1	1
	facility-based	68 (63.0)	76 (30.5)	0.65 (0.55, 0.76)**	0.64 (0.55, 0.76)**
Characteristics of child at enrolment					
Sex	male	60 (55.6)	144 (57.8)	1	
	female	48 (44.4)	105 (42.2)	1.00 (0.87, 1.14)	
Child age in months (mean, SD)*		27.35 (13.18)	30.14 (13.63)	1.00 (0.99, 1.00)	
Child was stunted (Z<-2)	yes	52 (48.2)	92 (37.0)	0.88 (0.76, 1.02)	
Child was wasted (Z<-2)	yes	4 (3.7)	11 (4.4)	1.11 (0.85, 1.45)	
	missing	1 (0.9)	0.00		
Child was underweight (Z<-2)	yes	3 (2.8)	10 (4.0)	0.91 (0.71, 1.17)	
	missing	0.00	1 (0.3)		
Height-for-age z-score (mean, SD)*		-1.85 (1.15)	-1.60 (1.60)	1.02 (0.99, 1.06)	
Weight-for-height z-score (mean, SD)*		-0.11 (1.05)	0.04 (1.22)	1.03 (0.98, 1.09)	
Weight-for-age z-score (mean, SD)*		-1.11 (1.07)	-0.87 (1.05)	1.06 (0.99, 1.12)	
Hemoglobin level in g/dl (mean, SD)*		8.11 (1.57)	7.91 (1.41)	0.98 (0.93, 1.02)	
Four or more malaria infections, past year	yes	5 (4.6)	28 (11.2)	0.82 (0.70, 0.96)**	0.83 (0.71, 0.97)**
Hospital admission for malaria, past year	no	100 (92.6)	223 (89.6)	0.84 (0.37, 1.90)	
Child slept under mosquito net during the past night	no	21 (19.4)	58 (23.3)	0.96 (0.80, 1.15)	
Four or more siblings	yes	19 (17.6)	59 (23.7)	0.93 (0.80, 107)	
Characteristics of caregiver and caregiving behavior at enrolment					
Caregiver is the mother	no	7 (6.5)	15 (6.0)	0.92 (0.71, 1.20)	
Caregiver's age in years (mean, SD)*		28.8 (7.79)	29.35 (8.66)	1.01 (0.99, 1.01)	
Caregiver is a single parent	yes	31 (28.7)	63 (25.3)	0.94 (0.80, 1.09)	
Caregiver experienced previous child death	yes	21 (19.4)	46 (18.5)	1.01 (0.85, 1.20)	
Caregiver is illiterate	yes	30 (27.8)	81 (32.5)	0.95 (0.83, 1.09)	
Caregiver's highest completed education level***	none	10 (9.3)	39 (15.7)	1	1
	lower primary	30 (27.8)	55 (22.9)	0.80 (0.66, 0.98)**	0.78 (0.64, 0.95)**
	upper primary	59 (54.6)	120 (48.2)	0.83 (0.70, 0.97)**	0.79 (0.67, 0.92)**
	lower secondary, higher	9 (8.3)	35 (14.1)	1.01 (0.84, 1.22)	0.98 (0.80, 1.21)
Caregiver's religion	Christian	86 (79.6)	187 (75.1)	1	
	other	22 (20.4)	62 (24.9)	0.99 (0.86, 1.15)	
Caregiver's tribe	Chewa	13 (12.0)	40 (16.1)	1	
	Yao	35 (32.4)	77 (30.9)	0.87 (0.73, 1.04)	
	Lomwe	30 (27.8)	80 (32.1)	0.94 (0.79, 1.11)	
	Nyanja	22 (20.4)	35 (14.1)	0.83 (0.64, 1.06)	
	others	8 (7.4)	17 (6.8)	0.91 (0.68, 1.23)	
Caregiver has experience giving medicine to this child	no	12 (11.1)	24 (9.6)	0.97 (0.76, 1.23)	
Household's caregiving resources					

(*Continued*)

Table 1. (Continued)

Predictors		Descriptive statistics by outcome frequencies (percentages)—unless row indicated otherwise		Generalized linear model-analysis	
Number of adults in household (mean, SD)*		2.06 (0.85)	2.21 (0.94)	1.05 (0.98, 1.12)	
Caregiver could report a source of main income	no	34 (31.5)	76 (30.5)	0.98 (0.85, 1.13)	
Distribution by socioeconomic index in quintiles***	poorest quintile	31 (28.7)	59 (23.7)	1	1
	2nd quintile	10 (9.3)	50 (20.1)	1.20 (1.01, 1.42)**	1.23 (1.04, 1.42)**
	3rd quintile	32 (29.6)	42 (16.9)	0.83 (0.66, 1.05)	0.80 (0.64, 1.01)
	4th quintile	18 (16.7)	49 (19.7)	1.06 (0.87, 1.29)	1.04 (0.85, 1.26)
	richest quintile	17 (15.7)	49 (19.7)	1.15 (0.95, 1.39)	1.09 (0.89, 1.32)
Household member owns residential home	no	16 (14.8)	23 (9.2)	0.81 (0.63, 1.05)	
At least one Household member has a bank account	no	102 (94.4)	232 (93.2)	1.06 (0.84, 1.34)	
	do not know	0 (0)	2 (0.8)		
Household has electricity	no	107 (99.1)	243 (97.6)	0.80 (0.54, 1.18)	
Travel distance to clinic, straight line, in km (mean, SD)*		19.83 (8.89)	19.64 (9.10)	0.99 (0.99, 1.01)	
Household has water access within 10 min walk	no	44 (40.7)	113 (45.4)	1.05 (0.92, 1.20)	
Source of drinking water used by the household	piped water (improved)	17 (15.7)	38 (15.3)	1	
	pumped ground water (improved and non-improved)	82 (75.9)	204 (81.9)	1.03 (0.86, 1.24)	
	surface water (non-improved)	9 (8.3)	7 (2.8)	0.66 (0.36, 1.20)	

* Descriptive statistics for continuous variables were calculated using t-test.

** Predictors with p-values <0.05.

*** Multilevel variables that were significant as entire variable (p<0.05), calculated using Wald-test.

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caregivers' education showed a significant association with adherence behavior. However, high adherence was correlated with 'no or no completed education'. Compared to this group, having completed lower or upper primary education was associated with higher non-adherence (RR, 95% CI: 0.78, 0.64 to 0.95; and 0.79, 0.67 to 0.92, respectively). At the household level, the socio-economic index showed a mixed picture, where the middle group adhered most poorly.

The model's performance, adjusted for k-fold cross-validation, was acceptable, with the mean area under the ROC-curve estimated to be 0.65 (95%CI: 0.57 to 0.71). The analysis with the non-adherent group separated into non-adherent sub-categories (*high but not full*, *medium*, and *low or no* adherence) did not yield significant predictors, we do not report this analysis. We neither found any important differences comparing the mean occurrence of potential predictors in these sub-groups, each compared among each other and to the fully adherent group.

Discussion

We developed a prognostic multivariable model to analyze determinants of adherence of Malawian caregivers to PDMC, the first predictor analysis for adherence to PDMC. Our results

are mixed, and we cannot explain all findings, although we included key predictors for caregiver adherence as established in the literature in comparable contexts. Some uncertainty remained in measuring the adherence-outcome as a few caregivers were repeatedly not home during control visits, while few others self-reported adherence but having lost or thrown away the empty blister pack. Such problems are recognized in the research on ACT adherence; however, the alternative of self-reporting has been shown to deviate markedly from actual adherence [11, 12].

Two systematic reviews from 2014 of ACT adherence summarized predicting factors for non-adherence to curative malaria treatment with ACTs, i.e., not for prevention. Both reviews reported caregivers' adherence separately from adults' adherence, when minor patients were included [11, 12]. Relatively older caregivers were generally associated with higher adherence levels to ACTs, an association we cannot confirm in our PDMC study. Likewise, higher education levels of caregivers were reported to correlate with improved adherence to ACTs. Our findings suggest an opposite correlation where no completed education, the lowest category, was associated with significantly higher adherence than the next two higher categories (completed lower and upper primary school, respectively). This result may be related to the trial setting where particular attention was given to illiterate caregivers' information and consent procedures, during enrolment, and when instructing them in drug administration. We cannot determine if this has affected our population, but others have demonstrated that a good patient-provider relationship is among the most consistent predictors for improved adherence [26]. Speaking the language of administration instructions, or demonstrably understanding these instructions, was likewise associated with higher adherence in the literature on ACT adherence. The trial offered instructions in Chichewa, the most used language in Southern Malawi, widely spoken in all households.

Relatively low income or socio-economic status has been associated with poor adherence behavior [11, 12]. Contradicting this association, our SES-index indicates mixed directions of adherence behavior across the quintiles. This index, however adjusted, generated a skewed distribution, displaying relatively small differences among the households in the four poorer quintiles. It is possible that our asset-based data included in the index were not sufficiently sensitive to separate this rural population into more substantially different quintiles. Skewedness is a recurrent challenge of asset-based indices in comparable socio-economic settings [27].

Caregivers may well adhere differently to a regimen depending on whether they are treating a notably sick child that shows a positive cause-effect response to their caring, or giving the same regimen as prophylaxis to a seemingly healthy child, without such causal learning [28]. Instead, the direct effect of a preventive regimen may more likely be perceived as "neutral", or even "negative" in case of side-effects like occasional vomiting in case of PDMC-DP [29, 30]. The generally established complexity behind the drivers to adhere to curative treatments may be even greater in case of preventive treatments, especially for caregiver-child relationships. The perceived severity of a child's disease, for example, has been reported as a predictor for increased adherence, specifically for ACT treatment [11, 31]. This determinant cannot be directly translated to PDMC, where a future severity is uncertain and more abstract. Experiencing repeated non-severe malaria infections in a child was associated with poorer caregiver adherence to PDMC.

Prior malaria-related hospital admissions of a child indicate a caregiver's experience of caring for a severely sick child. These experiences from the past may have stimulated caregivers' adherence to PDMC in the same direction as perceived severity increases adherence to curative treatment; however, we did not find this association for PDMC.

Due to the small sample size, we cannot rule out type II errors (not distinguishing a true negative finding from non-identification). In addition, while the data collected was

comprehensive and structured along the framework we used, a more targeted inquiry towards caring attitudes and parenting behavior may have offered a deeper understanding of the decisive actors' motivations and capacities: the caregivers. Understanding their behavior and capacities remains important to tailor implementation mechanisms and patient communication towards improved adherence to PDMC in its given complexity. Future implementation research may thus consider pooling or collecting a larger data sample to better address this. Additionally, qualitative inquiry on regimen experience and adherence motivators may help clarify some of our mixed results. Finally, as we reveal no obvious amendable determinants for poor adherence that can be considered during the roll-out of PDMC programs, implementation efforts need to ensure high general fidelity to programs to achieve high adherence rates among caregivers.

Conclusion

We investigated potential determinants for PDMC adherence of rural caregivers in Malawi and we found no implementation-relevant predictor for their adherence behavior. Our results are mixed and in disagreement with the literature on adherence to ACT treatment in children. It is possible that, compared to malaria treatment, malaria prevention introduces more complexity in caregivers' adherence behavior due to, for example, the absence of an illness to be treated. The analyses reveal no obvious determinants for poor adherence that can be targeted and instead PDMC-programs needs to maximize implementation fidelity to achieve high adherence.

Supporting information

S1 Text. Summary of methods and results behind the index-variable for households' socio-economic status (SES).
(DOCX)

S1 Table. Overview of variables considered in the predictor analysis.
(DOCX)

S1 Fig. The eigenvalues for the 11 principal components included in the adjusted analysis.
(DOCX)

S2 Fig. Households' relative socio-economic status based on adjusted PCA-analysis, separated into quintiles. PCA: Principal Component Analysis.
(DOCX)

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postdischarge antimalarials in Malawian pre-school children

Supplementary Material, S1 Text

S1 Text: Summary of methods and results behind the index-variable for households' socio-economic status (SES)

Using the Stata 17 software package, we developed a socio-economic index for the 357 households from the PDMC trial in Malawi that were included in this predictor analysis [1]. Initially, 88 variables (incl. sub-categories) that included a range of household features and characteristics that potentially reflect a household's economic status were considered (Table S1). Items accessible to or owned by less than 5% or more than 95% of households were excluded in order to strengthen the comparability between relatively wealthy and relatively poor households, leaving 27 variables included. An initial principal component analysis (PCA) was conducted where all households were awarded a relative score summarizing their households' assets. Ordered in ascending order and separated in quintiles, the resulting index showed a skewed shape with the first four quintiles at relatively similar levels and only indicating for the fifth quintile a substantially higher relative socio-economic status. We adjusted the analysis to iteratively reduce multicollinearity: we created a correlation matrix and tested excluding variables with near perfect and very low correlation (>0.9 and <0.1 multiple correlations). The resulting index of 11 variables showed more heterogeneity while remaining skewed This index-value was ranged and divided in quintiles, too, and included in the predictor analysis. (Figures S1, S2).

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Supplementary Material, S1 Table

S1 Table: Overview of variables considered in the Predictor analysis

Variables	Variables included after excluding items available/used by <5% or >95% of households (X: included)	Correlation adjustment (X: included)
The household or one household member has (yes/no):		
- a clock/watch	X	X
- a radio	X	X
- a black and white TV		
- a colour TV		
- a mobile Phone	X	X
- a non-mobile Phone		
- a refrigerator		
- a freezer		
- a generator/inverter		
- a solar panel	X	X
- a washing machine		
- a computer		
- a tractor		
- a digital camera		
- a non-digital camera		
- a video deck		
- a VCR/DVD		
- a sewing machine		
- a bed	X	X
- a table	X	X
- a cabinet/cupboard		
- a fan		
- a cassette player		
- a plow		
- a grain grinder		
- a hammer mill		
- candles	X	

- kerosene	X	
- a bicycle	X	
- a motorcycle/scooter		
- an animal drawn cart		
- a car or truck		
- a boat with motor		
- a boat		
Variables regarding the home build and resources:		
- number of rooms		
- number of household members per sleeping room	X	
- type of toilet used by household 1 "Flush toilet" 2 "Pit latrine" 3 "Dug-out pit with roof" 4 "Dug-out pit without roof" 5 "None" 6 "Does not wish to disclose" 7 "No facility, bush, outdoor"	2 "Pit latrine" 3 "Dug-out pit with roof" 4 "Dug-out pit without roof"	
- toilet is shared with other households (yes/no)	X	
- the type of fuel mainly used for cooking is 1"Electricity" 2"LPG/ natural gas" 3"Biogas" 4"Kerosene" 5"Coal, lignite" 6"Charcoal" 7"Wood/firewood" 8"Straws/Shrubs/grass" 9"Agricultural crop residue" 10"Animal Dung" 11"No food cooked in household"	3"Biogas" 4"Kerosene"	4"Kerosene"

- the main material of your roof is 1"Grass" 2"Iron sheets" 3"Clay" 4"Tiles" 5"Concrete" 6"Plastic Sheeting" 7"Does not wish to disclose" 8"Does not know"	1"Grass" 2"Iron sheets"	1"Grass"
- the main material of your main walls is 1"Grass" 2"Mud (Yomata)" 3"Compacted Earth (Yamdindo)" 4"Mud bricks (unfired)" 5"Burnt bricks" 6"Concrete" 7"Wood" 8"Iron sheets" 9"Does not wish to disclose" 10"Does not know"	2"Mud (Yomata)" 3"Compacted Earth (Yamdindo)" 4"Mud bricks (unfired)"	4"Mud bricks (unfired)"
- the main floor material in your house is 1"Earth/sand" 2"Smoother Mud" 3"Smooth cement" 4"Wood" 5"Tile" 6"Does not wish to disclose" 7"Does not know"	1"Earth/sand" 2"Smoother Mud" 3"Smooth cement"	2"Smoother Mud" 3"Smooth cement"
Variables regarding agricultural land		
- the household owns agricultural land (yes/no)		
- the size of the land in acres (alt. football fields)		
Variables regarding livestock		

- the household owns any livestock (yes/no)	X	
- number of "milk cow/bull		
- number of "sheep"		
- number of "horse/donkey/mule"		
- number of "chicken"	X	
- number of "goats"	X	
- number of "pigs"		

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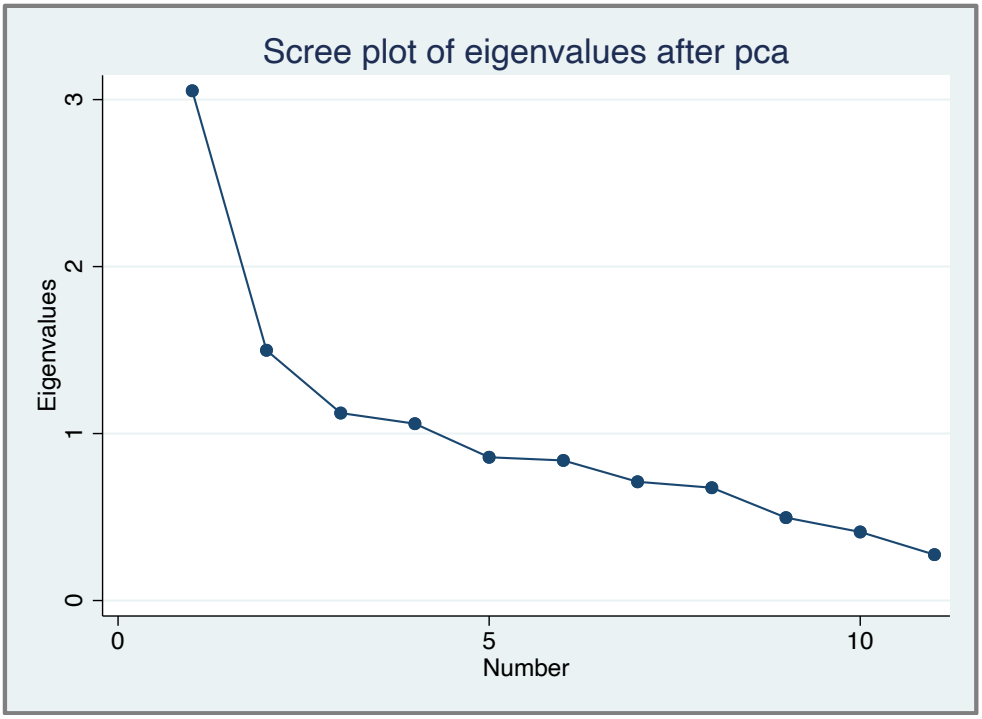
Supplementary Material, S1 Fig

S1 Fig: The eigenvalues for the 11 principal components included in the adjusted analysis



Eigenvalue Principal Component 1 (PC1)	3.05
Proportion of variance explained by PC1	0.27
Scale reliability coefficient (Cronbach's Alpha)	0.71
Kaiser-Meyer-Olkin sampling adecuacy-test	0.72

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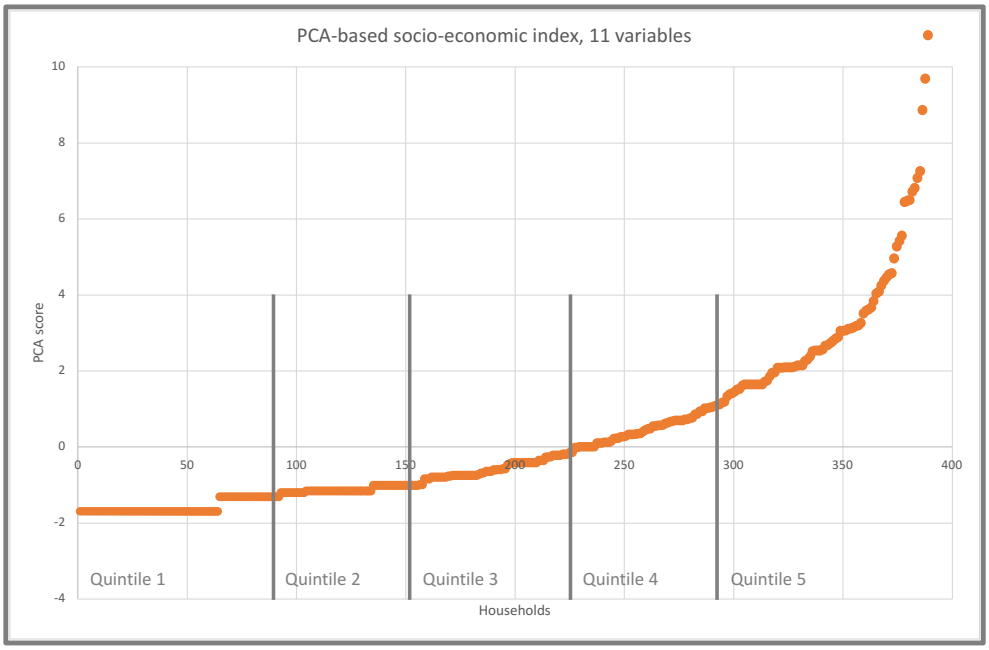
Supplementary Material, S2 Fig

S2 Fig: Households' relative socio-economic status based on adjusted PCA-analysis, separated into quintiles



Legend:

PCA: Principal Component Analysis

Paper 2 with supplementary materials

Economic evaluation of postdischarge malaria chemoprevention in preschool children treated for severe anaemia in Malawi, Kenya, and Uganda: A cost-effectiveness analysis

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Economic evaluation of postdischarge malaria chemoprevention in preschool children treated for severe anaemia in Malawi, Kenya, and Uganda: A cost-effectiveness analysis

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Summary

Background Children hospitalised with severe anaemia in malaria-endemic areas are at a high risk of dying or being readmitted within six months of discharge. A trial in Kenya and Uganda showed that three months of postdischarge malaria chemoprevention (PDMC) with monthly dihydroartemisinin-piperaquine (DP) substantially reduced this risk. The World Health Organization recently included PDMC in its malaria chemoprevention guidelines. We conducted a cost-effectiveness analysis of community-based PDMC delivery (supplying all three PDMC-DP courses to caregivers at discharge to administer at home), facility-based PDMC delivery (monthly dispensing of PDMC-DP at the hospital), and the standard of care (no PDMC).

Methods We combined data from two recently completed trials; one placebo-controlled trial in Kenya and Uganda collecting efficacy data (May 6, 2016 until November 15, 2018; n=1049), and one delivery mechanism trial from Malawi collecting adherence data (March 24, 2016 until October 3, 2018; n=375). Cost data were collected alongside both trials. Three Markov decision models, one each for Malawi, Kenya, and Uganda, were used to compute incremental cost-effectiveness ratios expressed as costs per quality-adjusted life-year (QALY) gained. Deterministic and probabilistic sensitivity analyses were performed to account for uncertainty.

Findings Both PDMC strategies were cost-saving in each country, meaning less costly and more effective in increasing health-adjusted life expectancy than the standard of care. The estimated incremental cost savings for community-based PDMC compared to the standard of care were US$ 22·10 (Malawi), 38·52 (Kenya), and 26·23 (Uganda) per child treated. The incremental effectiveness gain using either PDMC strategy varied between 0·3 and 0·4 QALYs. Community-based PDMC was less costly and more effective than facility-based PDMC. These results remained robust in sensitivity analyses.

Interpretation PDMC under implementation conditions is cost-saving. Caregivers receiving PDMC at discharge is a cost-effective delivery strategy for implementation in malaria-endemic southeastern African settings.

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Keywords: Economic evaluation; Cost-effectiveness analysis; Intermittent preventive therapy; IPTpd; Postdischarge; Post-discharge; malaria chemoprevention; PDMC; PMC; Malaria prophylaxis; malaria prevention; Dihydroartemisinin-piperaquine; DP; Adherence; Sub-Saharan Africa; Malawi; Kenya; Uganda; Preschool children; Children under five years of age; Severe anaemia

Research in context

Evidence before this study

In malaria-endemic areas of sub-Saharan Africa preschool children treated for severe anaemia are 72% more likely to die within six months of discharge than during the in-hospital period. Three months post-discharge malaria chemoprevention (PDMC) reduces post-discharge mortality and hospital readmissions by 70%. In 20 high-burden African countries, one hospital readmission could be prevented for every two to five children receiving PDMC, amounting to an estimated 36 000 annual hospital readmissions averted under full PDMC coverage. Using the search terms "cost-effective*", "cost-benefit", or "economic evaluation" paired with "malaria", "anaemia", or "anemia", with "post-discharge", "post-discharge", or "post-discharge" with "prophyla*" or "prevent*", and with "child*", we searched without language restriction for publications published between Jan 1, 2000, and Aug 25, 2022, in the databases of PubMed (seven results) and Web of Science (five results). We conducted the searches on Aug 26, 2022, and found no previous economic evaluations of post-discharge use of malaria chemoprevention in children.

Added value of this study

This study offers a methodological approach to combining cost information with adherence and efficacy data in country-specific Markov models. We show that implementing PDMC would be cost-saving and likely cost-effective in Kenya, Uganda, and Malawi. We identify a cost-effective delivery strategy: providing all PDMC courses to the caregiver at discharge to administer monthly at home.

Implications of all the available evidence

Countries in sub-Saharan Africa with moderate to high malaria transmission should consider making PDMC accessible to all children with severe anaemia surviving the acute in-hospital phase.

Introduction

Despite large-scale control efforts, malaria burden reductions have stagnated in parts of sub-Saharan Africa.[1] Severe anaemia remains a leading cause of mortality and morbidity in children under five years of age, and malaria is one of the main causes. In highly malaria-endemic areas, severe anaemia may be found in approximately one-third of hospitalised children and contribute to 50% of deaths attributed to malaria.[2-6]

Young children discharged from hospital after treatment for severe anaemia are at high risk of dying or being readmitted for at least six months postdischarge,[7-9] this risk is 2·7 times higher than children admitted for other reasons and 1·7 times higher than during hospitalisation.[10] In June 2022, postdischarge malaria chemoprevention ('PDMC', previously called 'PMC' and 'IPTpd') was included in the updated malaria chemoprevention guidelines from the World Health Organisation (WHO) for settings with moderate to high malaria transmission.[12] This was based in part on the results of a multi-country trial in Kenya and Uganda that showed that in preschool children with severe anaemia, three months of monthly PDMC with the long-acting antimalarial dihydroartemisinin-piperaquine (DP) reduced the risk of malaria-associated re-admission or death by 70% during the three months intervention period.[8] This suggests that malaria is a major cause of morbidity and mortality after discharge in these areas. An implementation trial in Malawi compared the effects of community-based versus facility-based delivery strategies for PDMC on adherence to all three courses of PDMC.[11] The highest adherence was achieved with community-based delivery, where caregivers were provided at discharge with all courses to administer PDMC monthly at home. Both trials were performed simultaneously between 2016 and 2018.

Based on the WHO guidelines, countries in sub-Saharan Africa with moderate to high malaria transmission should consider making PDMC accessible to all children with severe anaemia surviving the acute in-hospital phase. Here we combined data from these two trials to establish the cost-effectiveness of PDMC under implementation conditions and inform national guideline development in malaria-endemic areas in sub-Saharan Africa.

Methods

Study design

Three novel decision-analytical discrete-time models (Markov), one each for Malawi, Kenya, and Uganda,

were developed to assess the cost-effectiveness per country of the two PDMC delivery strategies against the standard of care using TreeAge Pro 2022. Results were reported according to the Consolidated Health Economic Evaluation Reporting Standards-statement.[13] We combined data from the efficacy trial in Kenya and Uganda, data from the implementation trial in Malawi, data from interviews and process observations in Malawi, and data from the literature. Each country model used the same three health states: *healthy*, *severely sick*, and *dead*, with severe sickness defined as any hospital admission within six months of discharge. The modelled cohorts entered the model upon the first PDMC course, which was given approximately 14 days after discharge from the hospital. We assumed the cohort to start in the *healthy* state and then move within the model in six cycles of one month each. At the end of each cycle, children in the cohort could change between the *healthy* and *severely sick* states. The absorbing *dead* state could be reached from either the *healthy* or the *severely sick* state. Additionally, non-severe health events, mostly clinic visits for uncomplicated clinical malaria, were modelled as occurring during a cycle within the *healthy* state (Figure S1). We conducted deterministic and probabilistic sensitivity analyses for each country and reported the results as incremental cost-effectiveness ratios (ICERs) expressed as costs per quality-adjusted life-year (QALY) gained. We used 3% global discounting for all costs and utilities.

Efficacy and adherence data

The efficacy estimates were obtained from the trial in Kenya and Uganda.[8] This two-arm placebo-controlled trial used three courses of monthly PDMC regimen with DP administered at the ends of the 2nd, 6th, and 10th week postdischarge. Each course comprised three doses of DP given once daily. Adherence to the first dose of each monthly course was assessed during home visits as directly observed therapy. In addition, daily telephone contact with caregivers and random home visits were used to verify the adherence to each course's second and third dose. Mortality and readmission rates were assessed for six months postdischarge.

The adherence data were obtained from the trial in Malawi that assessed adherence to the same PDMC regimen and compared community-based with facility-based delivery strategies.[11] Community-based PDMC consisted of providing all three PDMC courses to the caregivers at the time of hospital discharge combined with instructions how to administer the tablets at home. Facility-based PDMC consisted of instructions to the caregivers to collect each monthly DP course from the hospital's outpatient department. After each course, adherence was determined by inspection of blister packs collected during unannounced home visits. Community-based PDMC resulted in higher adherence than facility-based (71% vs 52% adherence to the full three courses, Table S1). We categorised adherence into *high* (all nine tablets taken, three per course), *medium* (six to eight tablets), *low* (three to five tablets), and *very low or no* adherence (zero to two tablets). We used these adherence rates to project the efficacy of PDMC under implementation conditions (Figure S2).

All study hospitals in Malawi and Uganda (public hospitals) and Kenya (public and private hospitals) were in high malaria transmission areas. Both trials included children aged younger than five years admitted for all-cause severe anaemia, excluding severe anaemia due to genetic factors, trauma, or malignancies. Hospitalised children received the standard of care for severe anaemia, including blood transfusions, parenteral antimalarials (in case of severe malarial anaemia), and antibiotics when indicated. At discharge, all children received the standard of care consisting of 3-day antimalarial treatment with oral artemether-lumefantrine, which provides an average of about 13 days of post-treatment prophylaxis against malaria, regardless of the presence of malaria parasites at the time of treatment.[14]

Effects and rewards

Lacking quality of life weights, we used inverted annual disability weights from the 2019 Global Burden of Disease study to approximate QALYs for severe sickness and non-severe events.[15,16] Within the first six months, completing a month in the *healthy* state was rewarded with the monthly equivalent of one full QALY. During this period, any hospital readmission (*severely sick*) translated to a one-month-long QALY reduction by the weighted average disability weight for the causes of readmission recorded in the efficacy trial (0·158 QALY/12). Based on the same data, any disutility from a non-severe health event within the healthy state was equated to two weeks of the average annual disability weight of these events (0·046 QALY/26). For children who died, no further QALYs were accounted. Based on our assumption of complete recovery by six months, surviving children were awarded their 2018 national average health-adjusted life expectancy subtracted by their average age at study completion (Malawi: 54·7 years; Kenya: 56·0 years; Uganda: 56·0 years).[17] The rewards were not half-cycle-corrected because of the relatively short cycle length.

The monthly transitions between the three health states were controlled by transition probabilities extracted from the efficacy trial's health outcomes (Table S2).[8] We assumed that the trial's outcomes for the PDMC-arm and for the placebo-arm corresponded to the efficacy of 100% and 0% adherence to PDMC, respectively. We further assumed a linear dose-response and matched the mean number of administered tablets per adherence category with the corresponding efficacy estimate. For example, *high adherence* (nine out of nine

tablets taken) corresponded to 100% of the established efficacy, whereas for *medium adherence* (mean of 6·04 of nine tables given), we adjusted the efficacy by 67%. In this category, the modelled death or readmission probabilities were adjusted to combine 67% transition probabilities corresponding to the trial's PDMC arm with 33% of probabilities corresponding to the placebo arm. We repeated this process by linear interpolation for the other two adherence categories (Figure S2). We disregarded information about the order of courses in case of non-adherence, for example, whether the 1st, 2nd, or 3rd course of PDMC was skipped in a child who received six out of nine tablets because no evidence existed how this impacted PDMC efficacy.

Intervention costs

We combined the healthcare provider perspective with the patients' household perspective to estimate the societal cost of PDMC implementation. We included both intervention-related costs and the costs of adverse health events during the discharge period. We employed a pragmatic ingredients approach, based on a mixed-methods inquiry, to determine directly and indirectly incurred costs related to PDMC and health outcomes postdischarge.[18]

We collected provider intervention cost data at Zomba Central Hospital in Malawi in 2018. For Kenya and Uganda, personnel salaries were based on local rates. We adopted providers' cost of DP from the national procurement systems (Malawi) and the literature (Kenya, Uganda), with a 30% surcharge for handling and wastage as it is standard practise in Malawi (Tables 1 and S5). Pharmacies' additional costs to disseminate and orient patients on PDMC in Malawi, according to the two PDMC strategies, were determined by time and motion observations and the average salaries of the involved personnel (Table S4). The intervention costs to households, i.e. the cost of receiving and administering DP, were prospectively collected alongside both trials and in the analysis adjusted to delivery strategy and strategy-dependent adherence rates (Table S7).

Both delivery strategies of PDMC started two weeks postdischarge. The baseline cost for the standard of care was incurred before starting the first postdischarge course of PDMC and was therefore assumed to be zero for all three arms. The intervention cost to the providers was estimated to be between 2·48 and 4·41 United States Dollars (USD) for either PDMC delivery strategy in any country (Table 1). In contrast, the baseline intervention costs to households differed substantially between the delivery arms and countries. Community-based delivery, i.e., receiving all three PDMC courses upon discharge with instructions on administering them, was estimated to cost caregivers an average of 0·26 USD in Malawi, and 0·09 and 0·07 USD in Kenya and Uganda, respectively. Facility-based delivery resulted in substantially higher costs incurred by households (7·43 USD in Malawi, 10·09 USD in Kenya, 10·16 USD in Uganda) due to the required travel to the hospital (Table 1, S7). The households' costs to administer a PDMC course were assumed to be the same in both arms. The households' lost productivity due to administering PDMC was estimated as the value of time spent providing the care. We valued the time using the minimum national salary rates of 2018. Direct and indirect costs were allowed to vary by country (Tables 1 and S7–8).

Costs of adverse health events

We assumed the cost per hospital readmission after discharge to be generally the same in all arms and that they only differed by country. As a proxy for the provider and household costs for any "all-cause" readmission, we used the average costs incurred for treating severe anaemia at Zomba Central Hospital, Malawi. Patient and clinical pathways were recorded by following clinical practice and interviewing hospital staff. The costs of involved personnel were calculated based on hospitals' average salaries for these positions and the reported time spent per patient (Table S7). Fifty random treatment records of children enrolled in the implementation trial in Malawi were reviewed for readmission duration, medication and procedures provided. The costs of medicines and equipment were itemised, valued, and costed based on Malawi's central health equipment procurement database.[23] Extra costs for handling and wastage were also added (Table S6). These costs were adopted for the Kenyan and Ugandan models. We excluded all costs related to a child's death, such as funeral costs.

Blood transfusion costs were estimated separately due to their significant contribution to the total costs (Figure 1). Laboratory staff estimated that 70% of the blood available at Zomba Central Hospital originated from the central blood bank and 30% from local donations. We used this ratio to estimate blood transfusion costs for Malawi based on the literature on transfusion costs.[22] For Kenya and Uganda, we relied on WHO cost estimates and the literature.[5,24] Approximately 42% of readmissions in the control arm of the efficacy trial required blood transfusions, compared to 29% in the intervention arm (Table S5).[8] We estimated the average transfusions needed for the different adherence categories using linear interpolation.

Non-severe health events comprised outpatient visits at health centres and hospital outpatient departments. We established the average costs for a non-severe illness by employing the same process as for readmission costs. In the absence of access to patient files, we approximated the average medication costs based on the standard of care for the most frequent diagnosis:

PERSPECTIVE: Cost component	Base Case			Range (CI*; point estimates: +/- 50%)				Distribution	Source
				low		high			
	Standard of care	PDMC Community delivery	PDMC Facility delivery	PDMC Community delivery	PDMC Facility delivery	PDMC Community delivery	PDMC Facility delivery		
Intervention costs									
PROVIDER: Dihydroartemisinin−piperaquine (DP) price per treatment, USD*									
Kenya	0·00	2·97	2·97	1·48		4·45		Point estimate	MSH Price Guide (2015)[19]
Malawi	0·00	2·36	2·36	1·18		3·54		Point estimate	Fernandes (2020)[20]
Uganda	0·00	2·30	2·30	1·15		3·45		Point estimate	GF Price Reference Report (2015)[21]
PROVIDER: Pharmacist time cost, USD									
Kenya	0·00	0·72	1·44	0·36	0·72	1·08	2·16	Point estimate	PDMC Malawi cost study
Malawi	0·00	0·12	0·24	0·06	0·12	0·18	0·36	Point estimate	(unpublished, Tables S3-9)
Uganda	0·00	0·29	0·58	0·15	0·29	0·44	0·87	Point estimate	
HOUSEHOLD: Total household drug collection cost, USD									
Kenya	0·00	0·09	10·09	0·05	5·05	0·14	15·13	Gamma	PDMC Malawi cost study
Malawi	0·00	0·26	7·43	0·13	3·72	0·39	11·15	Gamma	(unpublished, Tables S3-9)
Uganda	0·00	0·07	10·16	0·04	5·08	0·11	15·24	Gamma	
HOUSEHOLD: total household drug administration cost, USD									
Kenya	0·00	1·94		0·97		2·91		Gamma	Kwambai (2020)[8]
Malawi	0·00	1·07		0·54		1·61		Gamma	PDMC Malawi cost study (unpublished, Tables S3-9)
Uganda	0·00	3·31		1·66		4·97		Gamma	Kwambai (2020)[8]
Costs of adverse health events									
PROVIDER: total health personnel cost per inpatient treatment, USD									
Kenya		15·74		7·87		23·61		Point estimate	PDMC Malawi cost study
Malawi		10·56		5·28		15·84		Point estimate	(unpublished, Tables S3-9)
Uganda		11·45		5·73		17·18		Point estimate	
PROVIDER: cost per blood transfusions per inpatient treatment incl.· laboratory costs, transportation and wastage, USD									
Kenya		73·10		36·55		109·65		Point estimate	PDMC Malawi cost study (unpub-
Malawi		65·93		32·97		98·60		Point estimate	lished) combined with adjusted
Uganda		82·24		41·12		123·36		Point estimate	costs from Medina-Lara (2007)[22]
PROVIDER: sum of medicines, equipment, and other material costs per inpatient treatment, including SOC at discharge, USD									
Kenya		18·67		9·34		28·01		Point estimate	PDMC Malawi cost study
Malawi		18·67		9·34		28·01		Point estimate	(unpublished, Tables S3-9)
Uganda		18·67		9·34		28·01		Point estimate	

Table 1 *(Continued)*

PERSPECTIVE: Cost component	Base Case			Range (CI*; point estimates: +/- 50%)				Distribution	Source
				low		high			
	Standard of care	PDMC Community delivery	PDMC Facility delivery	PDMC Community delivery	PDMC Facility delivery	PDMC Community delivery	PDMC Facility delivery		
PROVIDER: sum of hospital administration and support services per inpatient treatment, USD									
Kenya		12·37		6·19		18·56		Point estimate	PDMC Malawi cost study (unpublished, Tables S3—9)
Malawi		3·04		1·52		4·56		Point estimate	
Uganda		5·17		2·59		7·76		Point estimate	
PROVIDER: total cost per outpatient treatment, USD									
Kenya		3·39		1·77		5·01		Point estimate	PDMC Malawi cost study (unpublished, Tables S3—9)
Malawi		2·40		1·22		3·58		Point estimate	
Uganda		2·53		1·31		3·75		Point estimate	
HOUSEHOLD: total cost per inpatient stay incl.· transport and lost productivity, and patient transfusion cost (only applicable for Kenya), USD									
Kenya		55·26		40·09		70·43		Gamma	Kwambai (2020)[8]
Malawi		12·94		11·35		14·54		Gamma	PDMC Malawi cost study (unpublished, Tables S3—9)
Uganda		20·04		18·10		21·98		Gamma	Kwambai (2020)[8]
HOUSEHOLD: total household cost per outpatient visit incl.· transport and lost productivity, USD									
Kenya		11·92		9·34		14·49		Gamma	Kwambai (2020)[8]
Malawi		5·34		4·31		6·70		Gamma	PDMC Malawi cost study (unpublished, Tables S3—9)
Uganda		9·60		8·45		10·75		Gamma	Kwambai (2020)[8]

***Table 1*: Component costs and estimated distributions for postdischarge malaria chemoprevention (PDMC) interventions and adverse health events from provider and household perspectives for each country.**

The detailed items summarised in the component costs can be found in the supplementary materials (*Tables S5, S10*).

*CI— Confidence interval (95%).

**USD— United States Dollar.

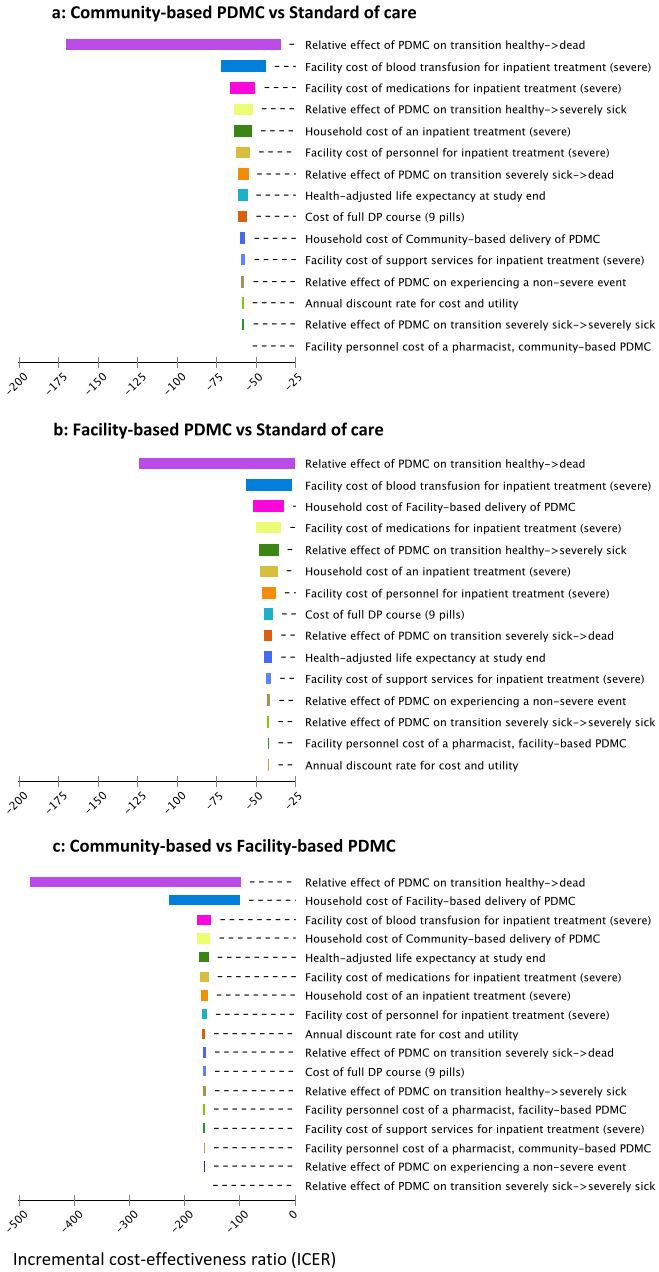

Figure 1. a-c: Deterministic sensitivity analysis for Malawi; tornado diagram of community-delivered PDMC and facility-delivered PDMC versus standard of care (1a, 1b), and a comparison of both PDMC strategies (1c).

uncomplicated clinical malaria (85%).[8] Support services costs, including information technology, laundry and cleaning, were allocated using the annual share of malaria-related admissions among the paediatrics patients as the allocation key. Maintenance costs were allocated using the surface share of the paediatric inpatient ward and outpatient department as the allocation key (Table S8). Both costs were adopted for Kenya and Uganda. Hospital capital costs were disregarded as all relevant facilities in Malawi were publicly owned and over 30 years old.

Direct household costs and time used for adverse health events were collected from the caregivers of children partaking in the trials. We estimated indirect household costs as productive time lost for the emergency-related time, valued by minimum national salary rates (Table S8). All cost data collected during the trials were converted into USD, using the exchange rates of June 2018. All others were inflation-adjusted to 2018.

Analysis and uncertainty

Univariate deterministic sensitivity analyses of key input variables were performed using +/- one standard deviation of their mean values. We used +/-50% ranges for point estimates of costs, which typically have larger variation than other data, and +/-25% for other variables where we lacked inference data (Table 1). We also report one-way sensitivity analyses as Tornado diagrams with pairwise comparisons of two strategies.

As explained above, we assumed a linear dose-effect relationship of DP in the base-case analysis, thus a proportionally reduced effect with lower adherence. We conducted scenario analyses for a concave and convex dose-effect curve leading to higher or lower efficacy for the *medium* and *low* adherence categories (Figure S2). We performed probabilistic sensitivity analyses for each country using Monte Carlo simulation with 10 000 iterations. The distribution shapes and confidence intervals determined the analysis parameters where they were available. In their absence, the ranges from the deterministic sensitivity analysis were adopted with standard distributions for costs (gamma) and probabilities (beta).

Ethics Statement

The data we used was collected as part of two clinical trials with ethical approval, documented elsewhere in detail. The responsible review committees in Kenya, Uganda, the United Kingdom, and Norway approved the efficacy trial.[8] The implementation trial was approved by review committees in Malawi and Norway.[11] All approved our use of the trial data for this study.

Role of the funding source

The funder had no role in study design, collection, analysis, and interpretation of data, or in the writing and submission of this study. MJK and BR had full access to the data and took the decision to submit the results for publication.

Results

Cost-effectiveness

From a societal perspective, combining both health care provider and household perspectives, the average expected cost of community-based PDMC per child treated in Malawi, Kenya, and Uganda was 22·74, 37·87, and 29·78 USD, respectively, which represents an average reduction of costs by 49%, 50% and 47% compared to the estimated average cost of the standard of care. Facility-delivered PDMC incurred a smaller reduction of cost by an average of 31%, 35%, and 27%, respectively (Table 2). In both PDMC strategies, the intervention costs of PDMC were more than outweighed by saved costs for readmission.

Compared to the standard of care, both community-based and facility-based PDMC resulted in net cost savings for health care providers from the reduced readmissions. These savings were most influenced

The three Figure 1a-c combine data from Kwambai (2020), Gondwe (2021), as well as unpublished costing data from Malawi (Tables S4–9).[8,11] The baseline strategy is named second in each graph. The variables are sorted according to decreasing sensitivity on the ICER. The ICER is expressed in terms of USD per QALY gained. A willingness to pay-threshold of one gross domestic product (GDP) per capita was included (535 USD in Malawi, 2017). The ICERs shown here are negative as result of the negative cost and positive incremental effects of PDMC. The figures show the potential changes in the overall incremental cost-effectiveness ratio (ICER) that can be achieved when varying single parameters between lower and higher value estimates. No modification in a single variable was influential enough to result in a positive ICER for any of the three two-strategy comparisons. This means that within its parameters, no variable could impact the model to the degree that the respective baseline strategy would become cost-effective. In all comparisons, the probability of dying was the variable with the highest single potential to influence the ICER value. This is explained by the reward used in the model: health-adjusted life expectancy. Any child death results in a complete loss of the life expectancy rewarded to surviving children. This life expectancy, however, decreases only by a relatively small amount when children transition to non-healthy states within the six-months follow-up period. In the comparisons with the standard of care, the cost of blood transfusion is the second most influential parameter. Blood transfusions are less frequent with PDMC-treatment because of the reduction in readmissions compared to standard of care. In addition, a readmitted child with PDMC treatment was less likely to need a blood transfusion than a readmitted child receiving standard of care. Figure 1a and b indicate that community-based PDMC is the better strategy based on the overall ICER, which is partly explained by the higher sensitivity of household costs under facility-based delivery (Figure 1b). PDMC=postdischarge malaria chemoprevention. DP=dihydroartemisinin−piperaquine. ICER= incremental cost-effectiveness ratio. USD=United States Dollars.

Country	Strategy	Cost (USD[a])				Effectiveness (QALY[b])		Cost-effectiveness
		Health care provider cost	Household cost	Total cost	Incremental cost	HALE[c]	Incremental QALY	ICER[d]
Malawi	Standard of care	36·00	8·91	44·84		52·65		negative
	PDMC Facility-delivered	19·50	11·65	31·11	−13·72	52·98	0·33	negative
	PDMC Community-delivered	16·95	5·83	22·74	−8·37	53·03	0·05	dominant
Kenya	Standard of care	46·63	29·98	76·40		53·86		negative
	PDMC Facility-delivered	26·27	23·47	51·49	−24·91	54·20	0·34	negative
	PDMC Community-delivered	22·54	15·72	37·87	−13·61	54·25	0·05	dominant
Uganda	Standard of care	41·95	14·16	56·00		53·84		negative
	PDMC Facility-delivered	22·46	18·44	40·84	−15·16	54·18	0·34	negative
	PDMC Community-delivered	19·33	10·50	29·78	−11·07	54·23	0·05	dominant

***Table 2*: Incremental cost-effectiveness ratios per country, comparing community-based postdischarge malaria chemoprevention (PDMC) with facility-based PDMC, and with the national standard of care.**

Incremental cost-effectiveness rankings per country. This table reports mean values from Monte-Carlo simulations of 10·000 iterations per country. Confidence intervals are shown as 95% confidence interval ellipsoids in Figures 3a-c; an extended version of this table with confidence intervals of the mean values is shown in the supplementary materials, Table S9. When comparing the three strategies, Community-delivered PDMC was the absolute dominant strategy: it was at the same time the least costly over the expected lifetime of a child (lowest cost per QALY gained) and yielded the most health-adjusted life-years. The incremental quality-adjusted life years (QALY) specify each strategy's expected impact on mortality and morbidity. The incremental values indicate that the facility-based distribution also absolutely dominates the standard of care. However, it is less cost-saving and less effective than community-based distribution when compared to standard of care.

[a] USD− United States Dollar.
[b] QALY− Quality-adjusted life years.
[c] HALE− Health-adjusted life expectancy.
[d] ICER− Incremental cost-effectiveness ratio.

by the reduced need for blood transfusions and the proportionate reduction in blood transfusions per readmission when using PDMC (Figure S2). Due to its increased adherence, community-based delivery was the least costly delivery strategy for providers. From a household perspective, community-based PDMC compared to the average standard of care costs per child treated resulted in net savings of approximately one-third, one-half, and one-quarter in Malawi, Kenya, and Uganda, respectively. However, facility-based delivery was, on average, more costly to households in Malawi and Uganda than the standard of care, with the monthly drug collection costs outweighing the costs of an increased readmission risk (Table 2).

The differences in effects were relatively less pronounced. PDMC primarily reduces readmissions, and each readmission translated into a reduction of a child's quality of life, lasting one month, in the models. In all three countries, the combination of reduced mortality and morbidity resulted in an expected gain of 0·4 QALY to a child's health-adjusted life expectancy when comparing community-based PDMC to the standard of care. This was 0·3 QALY for facility-based PDMC (Table 2).

Both PDMC strategies were cost-saving as they were less costly and more effective than the standard of care over the lifetime of a child eligible for PDMC. These results were largely driven by cost savings from fewer non-severe and severe adverse events relative to the standard of care. In each country, community-based delivery was the cost-effective strategy. Compared to community-based PDMC, the higher household costs of obtaining PDMC at the hospitals, and the associated lower adherence, made facility-based delivery sub-optimal for PDMC delivery (Table 2).

Sensitivity Analyses

One-way deterministic sensitivity analyses showed that the effect of PDMC on the probability of dying was the most influential individual determinant on the ICERs for both strategies, explained by the heavy impact of mortality on children's health-adjusted life expectancy, compared to the impact of short-term disability weights for readmissions and non-severe health events (Figure 1). No single parameter was sufficiently influential for facility-based PDMC or the standard of care to become the optimal strategy. Only unrealistically large changes to any single parameter could lead to a conclusion-changing base-case ICER. Univariate sensitivity analysis of the Malawi data showed that community-based delivery was consistently more cost-effective than facility-based delivery. Deterministic sensitivity analysis for Uganda and Kenya showed similar results. Changing the linear dose-effect assumption to convex or concave scenarios did not change the ranking in any of the three countries.

The probabilistic sensitivity analyses based on Monte Carlo simulations suggested that community-based PDMC is highly likely to be superior to standard care and facility-based PDMC in Malawi (Figure 2). The

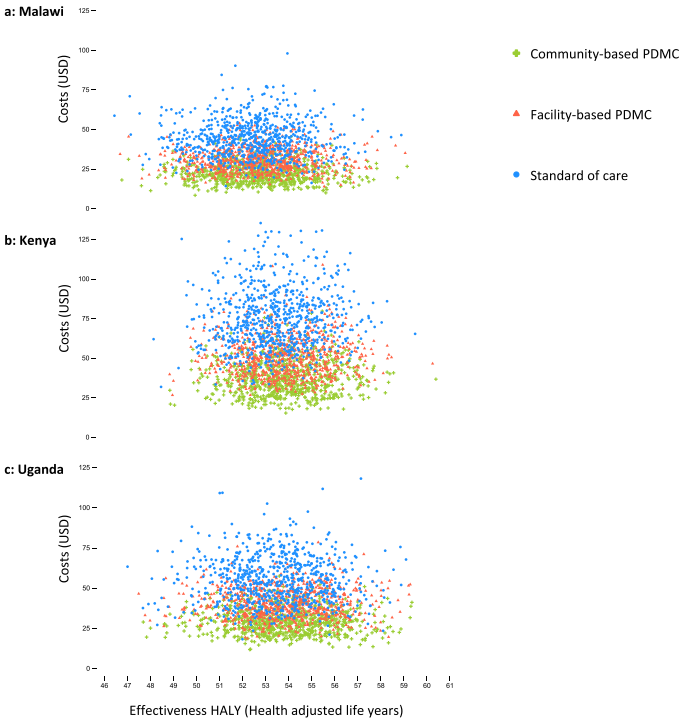

Figure 2. a-c: Monte Carlo simulation of 750 iterations for cost-effectiveness analysis of the two PDMC strategies and the standard of care in Malawi, Kenya, and Uganda.

We used 10,000 iterations per country model for the general cost-effectiveness and probabilistic sensitivity analyses (Tables 2 and S10). For visualization purposes, we reduced the number of iterations in the above scatterplots. The 750 iterations display 750 independent cost-effectiveness analyses per country, each conducted with probabilistic sampling from the distributions provided (Table 1). The plots thus display 750 times three interrelated cost-effectiveness values, one per strategy. In each country, there is relatively little difference between the three differently coloured intervention "clouds" on the x-axis, "Effectiveness HALY (Health adjusted life years)". This indicates a relatively small difference in effectiveness between the strategies; however, a weak accumulation of relatively higher effectiveness values can be observed in favour of community-based PDMC delivery (green crosses) over facility-based PDMC delivery (red triangles), over the standard of care (blue dots). The difference in costs between the strategies is more clearly illustrated, shown as the horizontal layering of the clouds along the y-axis ("Costs (USD)"), with community-based PDMC being predominantly less costly than facility-based PDMC than the standard of care. PDMC=postdischarge malaria chemoprevention. DP=dihydroartemisinin−piperaquine. USD=United States Dollars.

differences between the strategies' cost-effectiveness rankings were largely driven by costs, as suggested by the horizontal layering of the strategies' iteration clusters on the y-axes (Figure 2). Changes in effectiveness were less influential, which is shown in the relatively small differences between clusters on the x-axes (Figure 2). Pairwise comparisons of the strategies' incremental costs and effectiveness in Malawi were assessed against a willingness-to-pay threshold (WTP) set at one gross domestic product per capita in 2017, i.e. 535 USD (Figure 3). These analyses show that community-based delivery of PDMC with the estimated WTP was cost-effective in 95·3% of our iterations, with 93·6% being superior, i.e. resulting in lower cost and higher effectiveness, compared to the standard of care (Figure 3a, Table S10). In Kenya, at a WTP of 1708 USD, community- and facility-based PDMC were cost-effective compared to standard of care in 94·4% and 94·1% of the iterations. The corresponding figures in Uganda were 94·9% and 94·4% (WTP of 770 USD). Community-

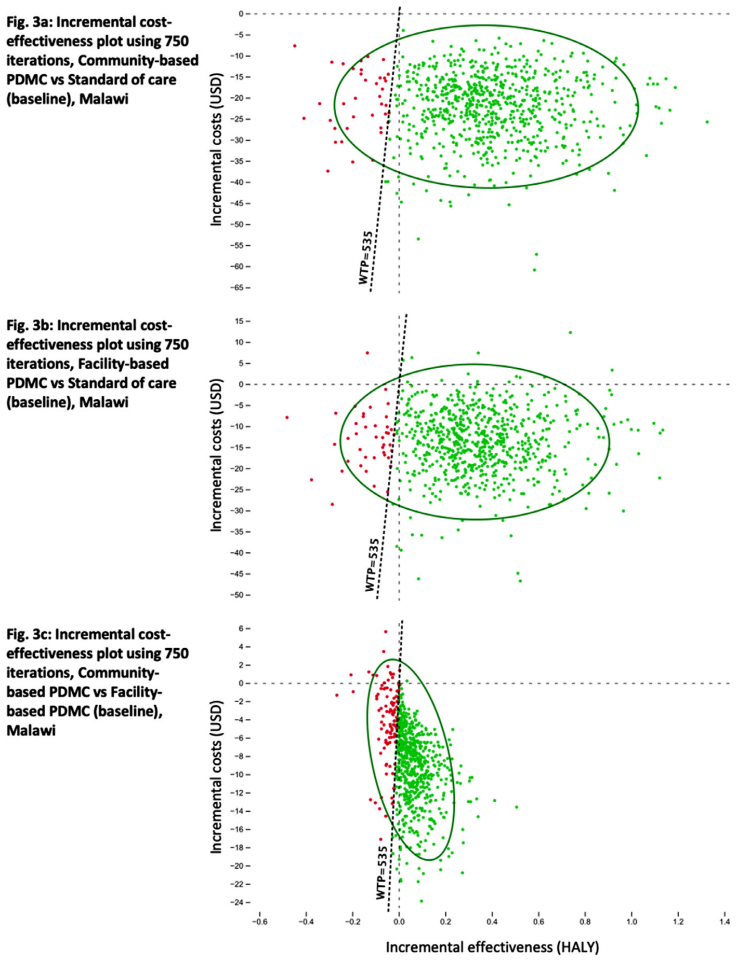

Figure 3. a-c: Simulation of incremental cost-effectiveness calculations for PDMC in Malawi (750 iterations) with pairwise comparisons of the three strategies, each with a 95% confidence ellipse, and a willingness to pay-line of one GDP per capita in USD (WTP, 535 USD for Malawi, 2017): a) community-based PDMC versus standard of care; b) facility-based PDMC versus standard of care; c) community- versus facility-based PDMC.

In each of the three scatterplots, the expected average cost and effectiveness of the baseline strategy are set as zero USD and zero HALY, respectively, at the intersection of the dotted lines. Each of the 750 dots (red and green) represents the cost and effectiveness of the comparator strategy in 750 iterations. Green dots indicate that the comparator strategy was cost-effective compared to the baseline (East of the WTP) in that particular iteration. Red dots represent iterations where the baseline strategy was found cost-effective (West of the WTP). The green ellipses show the 95% confidence interval. The frequency and proportion of iterations (10·000) per quadrant and category are shown for all countries in the supplementary material (Table S10). PDMC=postdischarge malaria chemoprevention. DP=dihydroartemisinin−piperaquine. USD=United States Dollars.

based PDMC was the cost-effective PDMC-strategy in 84·9% (Malawi), 82·6% (Kenya) and 85·0% (Uganda) of 10 000 model iterations per country (Table S10).

Discussion

This cost-effectiveness analysis showed that both PDMC strategies were cost-effective and cost-saving compared

to standard of care. They were less costly and more effective in terms of quality-adjusted life-years than the standard of care from a facility and household perspective in all three countries. The main driver of the PDMC dominance is the reduced cost resulting from fewer readmissions in the PDMC arms relative to the standard of care.

Community-delivered PDMC was the most cost-saving of the two strategies because the repeated multiple hour-travels for drug collection in the facility-based strategy presented the caregivers with higher costs and a disincentive to adhere. These results remained robust in the deterministic and probabilistic sensitivity analyses and were consistent across all three countries. The results were also robust to changes in the assumptions about the relationship between adherence and effectiveness. We assumed a linear dose-response because there were no real-life dose-response data about this relationship. We adjusted for this uncertainty through scenario analyses and the probabilistic sensitivity of the models, neither of which changed the cost-effectiveness ranking. Our finding that community-based delivery of PDMC is cost-effective is consistent with healthcare providers' and caregivers' preferences as reported in previous qualitative studies from Malawi.[25,26]

We expect our results to be useful for policy considerations. Establishing the cost-effectiveness of an intervention is essential for informed priority setting and developing benefit packages in a health system. One strength of our analysis is the high internal validity for southeastern Africa by combining the context-specific efficacy estimates from a large placebo-controlled efficacy trial in Uganda and Kenya with strategy-specific adherence data from a delivery mechanism trial in Malawi. By adjusting PDMC's proven efficacy with robust adherence data, we offer a modelling method to tailor cost-effectiveness analyses for greater external validity and policy relevance more broadly.

Limitations include using facility costing data for Kenya and Uganda partly based on data obtained in Malawi. Although we used country-specific unit estimates for personnel costs and the costs of blood transfusions to control for the largest share of between-country differences, some directly adopted costs may result in inaccurate estimates. Furthermore, we used standardised ranges for sensitivity analysis of the cost components for which inference data were lacking. Lastly, our analysis does not consider the health systems' costs at the regional and national levels of introducing PDMC. PDMC, unlike intermittent preventive treatment in infants or pregnancy, does not have an existing platform through which it can be delivered, and new delivery strategies and country-specific implementation modes must be considered. Future research comparing the country-specific implementation cost and exploring the underlying structural factors may provide additional support to national health systems' implementation efforts.

PDMC is a relatively simple intervention with a high potential of being cost-saving because it is less costly and more effective in increasing health-adjusted life expectancy than the current standard of care in Kenya, Uganda, and Malawi. In addition, providing all PDMC courses to the caregiver at discharge, combined with instructions on administering them, is less costly for providers and households and more effective than a facility-based delivery that requires the caregiver to collect each monthly dose of PDMC.

Contributors

MJK was responsible for the conceptualisation and methodology, data curation and verification, software use, formal analysis, the writing of the original draft, visualisation of results, and the editing of the manuscript. BR was responsible for the conceptualisation and methodology, he verified and validated the data, contributed to software use and formal analysis, as well as the writing of the original draft, results visualisation, and manuscript editing. KSP has verified the underlying data, was responsible for validation and investigation, and contributed to the review and editing of the manuscript. BR and KSP together supervised and administrated the project behind this study and aquired the funding for it. FTK was responsible for the conceptualisation, the data verification, investigation, the review and editing of the manuscript, and aquired the project funding. RO is responsible for data curation, validation, investigation, review and editing of the manuscript, as well as funding acquisition. TNG, AD, TKK, ATM, CCJ, RI contributed in the data curation, the validation and investigation, and in the editing and review of this manuscript. In addition, TNG, AD, and TKK also verified the underlying data. MJK and BR had full access to the dataset and accept the responsibility to submit this study for publication.

Data sharing statement

This study did not use individual participant data. We used summarised data from two trials that shared data according to the requirements of the International Committee of Medical Journal Editors.[8,11,27,28]

Declaration of interests

There are no conflicts of interest to declare.

Acknowledgements

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part of the European and Developing Countries Clinical Trials Partnership (EDCTP2), supported by the European Union.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101669.

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Annex: Supplementary materials

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Economic evaluation of postdischarge malaria chemoprevention in preschool children treated for severe anaemia: cost-effectiveness analyses for Malawi, Kenya, and Uganda.

Table of Contents

Supplementary Figures

Figure S1: Overview of our decision model, exemplary for Malawi, with a decision tree to control adherence and a Markov model to control health outcomes over the follow-up period of six months.

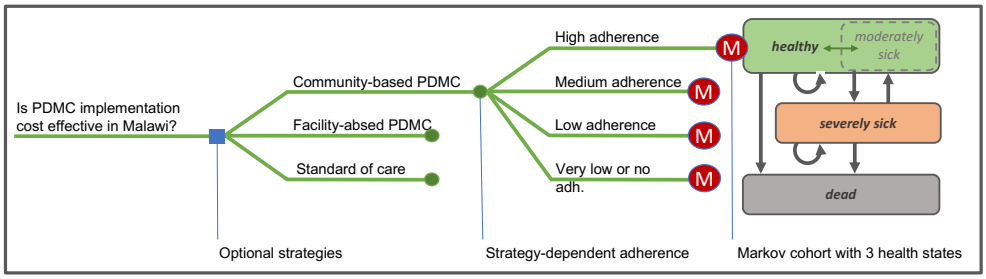
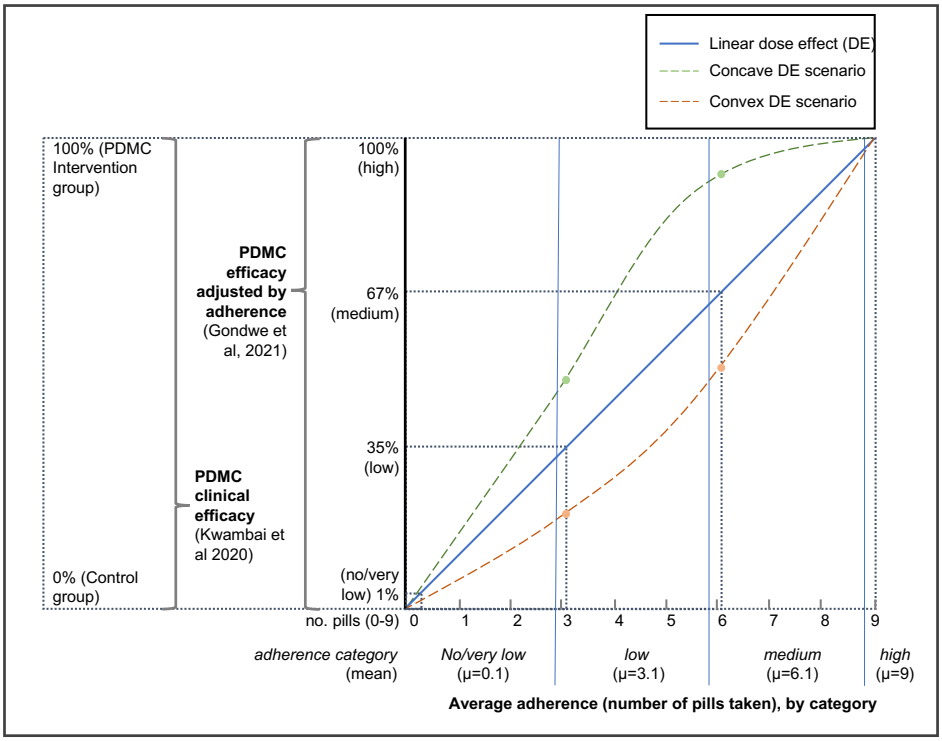


Figure S2: Linear extrapolation of dose-effect (DE) estimates of PDMC by adherence category, including scenario analyses for a convex and a concave dose-effect curve between zero (standard of care) and full efficacy of PDMC.



On the left of the graph, the efficacy range for PDMC-adherence is defined by the protective effect of PDMC on child mortality and readmission rate (100%) compared to the placebo/standard of care efficacy (0%).[1] Based on the mean values for pills given per adherence category, we extrapolated the efficacy of the categories *no or very low*, *low*, and *medium* adherence.[2] High adherence is equated to the full intervention effect of the efficacy trial (100%). Further, we assumed a concavely-shaped (+20%, green) and convexly-shaped (-20%, orange) dose-effect within the same range, thus not changing the efficacy of full adherence.

Abbreviations: PDMC=postdischarge malaria chemoprevention.

Supplementary Tables

Table S1: The five arms used in the implementation trial (Gondwe et al., 2021) were pooled in two arms: community- and facility-based PDMC delivery.[2] The factorial allocation in the trial added reminder options combining SMS-reminder with in-person-reminders by village-based Health Surveillance Assistants (HSA).

Category of adherence	Community-based delivery of PDMC					Facility-based delivery of PDMC			
	3 arms in Gondwe (2021)					2 arms in Gondwe (2021)			
	Com-SMS	Com+SMS	Com+HSA	pooled total	(%)	Fac-SMS	Fac+SMS	pooled total	percent
No or very low	1	2	2	5	2·3	4	2	6	4·0
Low	8	4	6	18	8·1	12	14	26	17·3
Medium	16	9	17	42	19·0	21	19	40	26·7
High	43	59	54	156	70·6	39	39	78	52·0
Total	68 (100)	74 (100)	79 (100)	221	100·0	76 (100)	74 (100)	150·0	100·0

Abbreviations: PDMC=postdischarge malaria chemoprevention. Com=community-based delivery of PDMC. Fac=facility-based delivery of PDMC. +SMS/-SMS=with/without SMS reminder.

Table S2: Transition probabilities between the health states *healthy*, *severely sick,* and *dead* for the standard of care arm and the relative risk of transitions with PDMC treatment, derived from the PDMC efficacy trial (Kwambai et al., 2020).[1]

Starting state	Trial arm allocation	Transition state		
		healthy	*severely sick*	*dead*
healthy	Standard of Care (base case)	0·8710	0·1238	0·0051
	Relative risk with PDMC	1·0954	0·3391	0·7490
severely sick	Standard of Care (base case)	0·9043	0·0891	0·0066
	Relative risk with PDMC	1·0121	0·8738	1·0472
dead	Standard of Care (base case)	-	-	1
	Probability PDMC	-	-	1

Abbreviations: PDMC=postdischarge malaria chemoprevention.

Table S3: Medication and medical equipment costs for intervention, readmission, and non-severe treatment (Clinic/OPD) in Malawi, Kenya, and Uganda. This data was collected alongside the implementation trial (Gondwe, 2021) and has not been separately published.[2]

			Malawi (USD)				Kenya (USD)				Uganda (USD)			
	Medication and medical equipment components	**average units needed for standard treatment, based on Malawi data**	**cost per unit**	**mean cost per child**	**lower limit**	**upper limit**	**cost per unit**	**mean cost per child**	**lower limit**	**upper limit**	**cost per unit**	**mean cost per child**	**lower limit**	**upper limit**
PDMC Intervention	dihydroartemisinin-piperaquine	9	0·33	2·97	1·48	4·45	0·25	2·25	1·13	3·38	0·26	2·30	1·15	3·45
Readmission	average sum medication for SA treatment: see Table S6	n/a; see Table S6	n/a	15·03	7·52	22·55	see Malawi				see Malawi			
	blood transfusion, placebo-arm, efficacy trial (Kwambai 2020))	0·42	65·93	27·69	13·85	41·54	73·10	30·70	15·35	46·05	82·40	34·61	17·72	51·91
	blood transfusion, PMC-arm, efficacy trial (Kwambai 2020))	0·29	65·93	19·38	9·69	29·08	73·10	21·49	10·75	32·24	82·40	24·23	12·41	36·34
Clinic/OPD	standard of care medication, clinical malaria: artemether/lumefanterine	6	0·14	0·85	0·43	1·28	see Malawi				see Malawi			

Abbreviations: PDMC=postdischarge malaria chemoprevention. USD=United States Dollars. Clinic/OPD=Summary category for visits to local clinics and health centres as well as the outpatient department of the hospital (OPD).

Table S4: Facility personnel costs for intervention, readmission, and non-severe treatment (Clinic/OPD), based on hospital practice in Malawi. This data was collected alongside the implementation trial (Gondwe, 2021) and has not been separately published.[2]

			Malawi (USD)		Kenya (USD)		Uganda (USD)	
	Hospital employee position	Average time spent per child based on observations in Zomba Central Hospital, Malawi (hours)	Hourly personnel cost	Personnel cost per child treated with PDMC	Hourly personnel cost	Personnel cost per child treated with PDMC	Hourly personnel cost	Personnel cost per child treated with PDMC*
PDMC Intervention	Pharmacist, community-based PDMC	0·08	1·43	0·12	5·75	0·48	4·61	0·38
	Pharmacist, facility-based PDMC	0·17	1·43	0·24	5·75	0·96	4·61	0·77
Readmisson	Clinician	0·87	3·25	2·81	7·10	6·15	6·60	5·72
	Nurse	1·83	2·85	5·23	3·46	6·34	1·46	2·67
	Pharmacist	0·17	1·43	0·24	5·75	0·96	4·61	0·77
	patient attendant	0·42	0·97	0·41	2·43	1·01	0·02	0·01
	clerk	0·18	1·03	0·19	2·57	0·47	1·54	0·28
	average total personnel cost per child treated			**8·87**		**14·94**		**9·46**
Clinic/OPD	Clinician	0·08	3·25	0·27	7·10	0·59	6·60	0·55
	Nurse	0·33	2·85	0·95	3·46	1·15	1·46	0·49
	Pharmacist	0·08	1·43	0·12	5·75	0·48	4·61	0·38
	patient attendant	0·08	0·97	0·08	2·43	0·20	0·02	0·00
	clerk	0·17	1·03	0·17	2·57	0·43	1·54	0·26
	average total personnel cost per child treated			**1·59**		**2·85**		**1·68**

Abbreviations: PDMC=postdischarge malaria chemoprevention. USD=United States Dollars. Clinic/OPD=Summary category for visits to local clinics and health centres and the outpatient department of the hospital (OPD).

Table S5: Medication overview used for severe anaemia (SA) treatment in Malawi in preschool children, derived from a sample of 50 children. Cost shown in Malawi Kwacha (MKW) and total in US Dollars (USD). This data was collected alongside the implementation trial (Gondwe, 2021) and has not been separately published.[2]

Medication for inpatient treatment	Unit price (MKW)	Average units needed per child if indicated	Cost if indicated (MKW)	Costs with additional wastage and freight (30%)	Proportion of children with indication	Average total per SA treatment (MKW)	Average total per SA treatment (USD)
Medication SA treatment							
Albendazole, 200 milligrams (mg)	6·42	2·00	12·84	16·98	0·30	5·09	0·01
Amoxycillin, 125mg/5milliliters (ml) suspension	676·40	1·00	676·40	894·54	0·05	44·73	0·06
Artesunate, 60mg with diluent	1472·00	3·00	4416·00	5840·16	1·03	5986·16	8·20
Benzylpenicillin, 3 grams (g)	149·00	13·00	1937·00	2561·68	0·48	1216·80	1·67
Ceftriaxone, 1g	178·00	5·00	890·00	1177·03	0·13	153·01	0·21
Dextrose 50%, 50ml	457·00	1·00	457·00	604·38	0·08	48·35	0·07
Diazepam 5mg/ml, 2ml	121·00	1·00	121·00	160·02	0·03	4·00	0·01
Furosemide (Frusemide) 10mg/ml, 2ml	40·00	1·00	40·00	52·90	0·05	2·65	0·00
Gentamycin Sulphate 40mg/ml, 2ml	43·00	5·00	215·00	284·34	0·33	92·41	0·13
Ferrous sulphate 200mg/folic acid 250 micrograms, coated tablets	2·25	30·00	67·56	89·35	0·08	6·70	0·01
Artemether-lumefantrine, 20mg-120mg	37·76	6·00	226·56	299·63	0·53	157·30	0·22
Nystatin oral suspension 100,000 IU/ml, 20ml	399·00	1·00	399·00	527·68	0·13	65·96	0·09
Paracetamol syrup 120mg/5ml, 100ml	313·00	9·00	2817·00	3725·48	0·85	3166·66	4·34
Phenobarbitone sodium 200mg/ml, 1ml	637·00	1·00	637·00	842·43	0·03	21·06	0·03
Zinc sulphate 20mg, tablets	4·50	10·00	45·00	59·51	0·03	1·49	0·00
Average total medication cost for SA treatment per child						**10972·37**	**15·03**
Medication at discharge							
Albendazole, 200mg	6·42	2·00	12·84	16·98	0·70	11·88	0·02
Artemether-lumefantrine, 20mg-120mg	37·76	6·00	226·56	299·63	0·48	142·32	0·19
Ferrous sulphate 200mg/folic acid 250 micrograms, coated tablets	2·25	30·00	67·56	89·35	0·93	82·65	0·11
Average discharge cost for SA treatment per child						**236·85**	**0·32**

Table S6: Support service costs based on annual expenses of Zomba Central Hospital, Malawi, separated in inpatient paediatric department cost (severe health event) and outpatient department or clinic visits for non-severe events. This data was collected alongside the implementation trial (Gondwe 2021) and has not been separately published.[2] It was adopted for Kenya and Uganda, and adjusted for average hospital days of children readmitted in the efficacy trial (Kwambai, 2020).[1]

Facility running cost and support services	Total expenses 2017-18 (MKW)	Proportion of the inpatient paediatric ward (IPD) of the entire hospital*	Proportion of outpatient paediatric department (OPD) of the entire hospital*	Estimated annual cost, IPD (MKW)	Estimated annual cost, OPD (MKW)	IPD daily patient cost (6076 patients/year)	Patient cost for full SA treatment (Malawi: 4·66 days)	OPD per patient-cost (9114 patients/year, MKW)
Medical Equipment	5000000·00	0·18	0·04	900000·00	180000·00	148·12	690·26	44·44
Building rehabilitation	5500000·00	0·18	0·04	990000·00	198000·00	162·94	759·28	48·88
Maintenance	12000000·00	0·18	0·04	2160000·00	432000·00	355·50	1656·62	106·65
Internet	7200000·00	0·18	0·04	1296000·00	259200·00	213·30	993·97	63·99
Water	43000000·00	0·18	0·04	7740000·00	1548000·00	1273·86	5936·21	382·16
Landscaping	12000000·00	0·18	0·04	2160000·00	432000·00	355·50	1656·62	106·65
Security service	15000000·00	0·18	0·04	2700000·00	540000·00	444·37	2070·77	133·31
Total cost per patient (MKW)						2953·59	13763·72	590·72
Total cost per patient (USD)						4·05	18·85	0·81
Total cost per patient, Kenya (average inpatient duration: 5·54 days, USD)							22·41	0·96
Total cost per patient, Uganda (average inpatient duration: 3·86 days, USD)							15·62	0·67

*The proportion was determined as the departments' respective share of the hospitals overall surface area (buildings only).

Abbreviations: SA=Severe anaemia. PDMC=postdischarge malaria chemoprevention. MKW=Malawi Kwacha. USD=United States Dollars.

Table S7: Household costs for PDMC intervention. The data on households' economic costs from Malawi was collected alongside the implementation trial (Gondwe 2021) and has not been separately published.[2] Data for Kenya and Uganda was collected alongside the efficacy trial and has neither been published (Kwambai, 2020).[1]

Household Cost: PDMC Intervention									
	Uganda			**Kenya**			**Malawi**		
	mean	*CI*		*mean*	*CI*		*mean*	*CI*	
		lower	*upper*		*lower*	*upper*		*lower*	*upper*
Financial cost due to administering PDMC at home (UGX, KES, MKW)	10820·48	8516·66	13124·29	6·46	1·24	11·68	94·26	41·21	147·31
Time spent administering full treatment, 9 tablets (Minutes)	138·70	127·69	127·69	178·57	159·42	197·72	258·00	85·36	430·64
Equivalent minimum salary, 8·5 hrs/day (UGX, KES, MKW)	1414·21	1301·89	1301·89	190·09	169·70	210·47	680·92	225·29	1136·54
Total cost intervention (UGX, KES, MKW)	12234·69	9818·56	14426·19	196·55	170·94	222·15	775·18	266·50	1283·86
Total cost intervention (USD)	**3·31**	**2·65**	**3·90**	**1·94**	**1·68**	**2·19**	**1·07**	**0·37**	**1·78**
Household Cost of DHP collection at hospital (facility-based delivery)									
Money spent on transport (UGX, KES, MKW)	16146·13	15564·72	16727·53	362·30	332·31	392·29	1818·06	1557·95	2078·18
Duration of transportation and hospital visit (hours)	4·20	4·04	4·36	2·22	2·11	2·32	5·34	4·94	5·75
Equivalent minimum salary, 8·5 hrs/day (UGX, KES, MKW)	21841·49	21027·12	22655·86	1203·72	1147·04	1260·40	7193·85	6650·37	7737·34
Total costs for collection (UGX, KES, MKW)	37987·62	36591·84	39383·39	1566·02	1479·35	1652·69	9011·92	8208·32	9815·51
Total costs for collection (USD)	**10·27**	**9·89**	**10·64**	**15·43**	**14·57**	**16·28**	**12·46**	**11·35**	**13·58**

Abbreviations: PDMC=postdischarge malaria chemoprevention. UGX=Ugandan Shilling. KES=Kenyan Shilling. MKW=Malawi Kwacha. USD=United States Dollars. CI=Confidence interval.

Table S8: Household costs for hospital readmission and treatment of non-severe cases. The data on households' economic costs from Malawi was collected alongside the implementation trial (Gondwe 2021) and has not been separately published.[2] Data for Kenya and Uganda was collected alongside the efficacy trial and has neither been published (Kwambai, 2020).[1]

Household costs: Hospital readmission									
	Uganda			**Kenya**			**Malawi**		
	mean	*CI*		*mean*	*CI*		*mean*	*CI*	
		lower	*upper*		*lower*	*upper*		*lower*	*upper*
Time spent in the hospital (days)	5·80	5·31	6·29	6·32	4·86	7·78	5·05	4·64	5·46
Equivalent minimum salary, 8·5 hrs/day (UGX, KES, MKW)	30162·35	27636·81	32683·80	3430·97	2638·34	4223·59	6803·34	6251·38	7355·29
Money spent at the hospital (UGX, KES, MKW)	24381·88	21204·01	27559·74	446·54	223·27	669·81	99·32	37·94	160·71
Money spent on transport (UGX, KES, MKW)	15947·08	14752·78	17141·37	602·50	384·37	820·63	1818·06	1557·95	2078·18
Total costs of readmission (UGX, KES, MKW)	70491·31	63593·60	77384·91	4480·01	3245·98	5714·03	8720·73	7847·28	9594·18
Total costs of readmission (USD)	**19·05**	**17·19**	**20·91**	**44·14**	**31·98**	**56·30**	**12·06**	**10·85**	**13·27**
Household costs: Outpatient department or clinic visit for a non-severe event									
	Uganda			**Kenya**			**Malawi**		
	mean	*CI*		*mean*	*CI*		*mean*	*CI*	
		lower	*upper*		*lower*	*upper*		*lower*	*upper*
Time spent by caregiver and partner for caring at home, transport to the clinic, time at the clinic (hours)	29·42	27·17	31·68	26·63	24·42	28·84	26·48	22·51	30·46
Equivalent min· salary, 8·5 hrs/day (UGX, KES, MKW)	8516·94	7136·45	9896·06	710·89	569·53	851·88	1739·10	1346·00	2368·25
Money spent at the hospital (UGX, KES, MKW)	7149·06	4982·98	9315·13	98·21	49·11	147·32	21·31	8·14	34·49
Money spent on transport (UGX, KES, MKW)	19859·74	15564·72	16727·53	362·30	332·31	392·29	1818·06	1557·95	2078·18
Total costs of clinic visit (UGX, KES, MKW)	35525·73	27684·15	35938·73	1171·40	950·94	1391·48	3578·47	2912·09	4480·91
Total costs of clinic visit (USD)	**9·60**	**7·48**	**9·71**	**11·54**	**9·37**	**13·71**	**4·95**	**4·03**	**6·20**

Abbreviations: PDMC=postdischarge malaria chemoprevention. UGX=Ugandan Shilling. KES=Kenyan Shilling. MKW=Malawi Kwacha. USD=United States Dollars. CI=Confidence interval.

Table S9 Incremental cost-effectiveness ratios per country, comparing community-based postdischarge malaria chemoprevention (PDMC) with facility-based PDMC, and with the national standard of care.

Country	Strategy	Cost (USD)				Effectiveness (QALY)		Cost-effectiveness
		Health care provider cost (mean, 95% CI)	Household cost (mean, 95% CI)	Total cost (mean, 95% CI)	Incremental cost (mean values)	HALE (mean, 95% CI)	Incremental QALY (mean values)	ICER
Malawi	Standard of care	36·00 (35·78 - 36·21)	8·91 (8·83 - 8·99)	44·84 (44·61 - 45·07)		52·65 (52·61 - 52·69)		negative
	PDMC Facility-delivered	19·50 (19·38 - 19·62)	11·65 (11·57 - 11·73)	31·11 (30·97 - 31·26)	-13·72	52·98 (52·94 - 53·02)	0·33	negative
	PDMC Community-delivered	16·95 (16·84 - 17·06)	5·83 (5·78 - 5·87)	22·74 (22·62 - 22·87)	-8·37	53·03 (53·00 - 53·07)	0·05	dominant
Kenya	Standard of care	46·63 (46·38 - 46·87)	29·98 (29·71 - 30·26)	76·40 (76·02 - 76·77)		53·86 (53·83 - 53·89)		negative
	PDMC Facility-delivered	26·27 (26·13 - 26·41)	23·47 (23·30 - 23·63)	51·49 (51·25 - 51·73)	-24·91	54·20 (54·17 - 54·23)	0·34	negative
	PDMC Community-delivered	22·54 (22·42 - 22·67)	15·72 (15·57 - 15·85)	37·87 (37·66 - 38·08)	-13·61	54·25 (54·22 - 54·28)	0·05	dominant
Uganda	Standard of care	41·95 (41·70 - 42·20)	14·16 (14·03 - 14·28)	56·00 (55·71 - 56·29)		53·84 (53·81 - 53·88)		negative
	PDMC Facility-delivered	22·46 (22·33 - 22·60)	18·44 (18·32 - 18·56)	40·84 (40·66 - 41·03)	-15·16	54·18 (54·14 - 54·22)	0·34	negative
	PDMC Community-delivered	19·33 (19·21 - 19·46)	10·50 (10·43 - 10·57)	29·78 (29·62 - 29·93)	-11·07	54·23 (54·20 - 54·27)	0·05	dominant

Abbreviations: PDMC=postdischarge malaria chemoprevention. USD=United States Dollar. QALY=Quality-adjusted life years. 95% CI=95% confidence interval with upper and lower limits in brackets. HALE=Health-adjusted life expectancy. ICER=Incremental cost-effectiveness ratio.

Table S10 Probabilistic sensitivity analysis: Incremental cost-effectiveness report of in pairwise comparison of the two PMDC strategies and standard of care for each country-model, using 10.000 iterations. (see Figure 3a-c for a scatterplot Figure using the Malawi model and 750 iterations).

				Malawi			Kenya			Uganda		
Component	**Quadrant**	**Incremental effectiveness (IE)**	**Incremental cost (IC)**	**Incremental cost-effectiveness**	**Frequency**	**Proportion**	**Incremental cost-effectiveness**	**Frequency**	**Proportion**	**Incremental cost-effectiveness**	**Frequency**	**Proportion**
Community- based PDMC vs. Standard of Care (baseline)												
C1	IV	IE>0	IC<0	Superior	9365	0.9365	Superior	9337	0.9337	Superior	9353	0.9353
C2	I	IE>0	IC>0	ICER<535·0	0	0	ICER<1708·0	0	0	ICER<770·0	0	0
C3	III	IE<0	IC<0	ICER>535·0	166	0·0166	ICER>1708·0	103	0·0103	ICER>770·0	139	0·0139
C4	I	IE>0	IC>0	ICER>535·0	0	0	ICER>1708·0	0	0	ICER>770·0	0	0
C5	III	IE<0	IC<0	ICER<535·0	469	0·0469	ICER<1708·0	560	0·056	ICER<770·0	508	0·0508
C6	II	IE<0	IC>0	Inferior	0	0	Inferior	0	0	Inferior	0	0
Facility-based PDMC vs· Standard of Care (baseline)												
C1	IV	IE>0	IC<0	Superior	9169	0·9169	Superior	9244	0·9244	Superior	8868	0·8868
C2	I	IE>0	IC>0	ICER<535·0	192	0·0192	ICER<1708·0	89	0·0089	ICER<770·0	478	0·0478
C3	III	IE<0	IC<0	ICER>535·0	135	0·0135	ICER>1708·0	75	0·0075	ICER>770·0	93	0·0093
C4	I	IE>0	IC>0	ICER>535·0	0	0	ICER>1708·0	0	0	ICER>770·0	1	0·0001
C5	III	IE<0	IC<0	ICER<535·0	496	0·0496	ICER<1708·0	586	0·0586	ICER<770·0	520	0·052
C6	II	IE<0	IC>0	Inferior	8	0·0008	Inferior	6	0·0006	Inferior	40	0·004
Community-based PDMC vs· Facility-based PDMC (baseline)												
C1	IV	IE>0	IC<0	Superior	7737	0·7737	Superior	7766	0·7766	Superior	7754	0·7754
C2	I	IE>0	IC>0	ICER<535·0	13	0·0013	ICER<1708·0	22	0·0022	ICER<770·0	41	0·0041
C3	III	IE<0	IC<0	ICER>535·0	737	0·0737	ICER>1708·0	476	0·0476	ICER>770·0	704	0·0704
C4	I	IE>0	IC>0	ICER>535·0	1	0·0001	ICER>1708·0	2	0·0002	ICER>770·0	4	0·0004
C5	III	IE<0	IC<0	ICER<535·0	1303	0·1303	ICER<1708·0	1516	0·1516	ICER<770·0	1280	0·128
C6	II	IE<0	IC>0	Inferior	209	0.0209	Inferior	218	0.0218	Inferior	217	0.0217

The quadrants are populated according to comparator strategies' cost and effectiveness relative to the average values of the respective baseline-strategy. The categories are defined by these quadrants and additionally limited, where there is no absolute superiority or inferiority, by the willingness to pay threshold. The number of iterations per quadrant and category is listed under "frequency".

Abbreviations: PDMC=postdischarge malaria chemoprevention. ICER=Incremental cost-effectiveness ratio.

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Paper 3

Do we need to know more? An analysis of the value of further research on postdischarge malaria chemoprevention in preschool children in sub-Saharan Africa

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