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Abstract

Madagascar joined “Roll Back Malaria” in 2002. During the last 15 years, the Malagasy government has received significant external funds to implement malaria operational strategies. Madagascar recorded progress due to scale-up interventions. Nevertheless, the number of malaria cases has increased significantly since 2012. This paper aims to estimate the cost of the national malaria program corresponding to the national strategic plan from 2009 to 2013 and the cost-effectiveness of two malaria control strategies (indoor spraying insecticide -IRS- and insecticide treated nets -ITN), using household survey data from 2014 in two districts in Madagascar. The cost-effectiveness of IRS and ITN was estimated at the district level. For this purpose, the total cost of the national malaria control program (NMCP) and the cost of cases averted were calculated. The NMCP has cost USD 46,588,677 or USD 2.1 per capita per year from 2009 to 2013. The implementation of IRS costs about 4 times more than ITN. The cost effectiveness rate (CER) of IRS per case averted was higher (USD 297.6) than the CER of ITN (USD 56.5 in Ankazobe and USD 31.4 in Brickaville). The CER per Daly averted was USD 531.2 for IRS, USD 53.9 (in Brickaville) and USD 99.6 (in Ankazobe) for ITN. Compared to GDP per capita, ITN strategy appeared highly cost-effective and IRS cost-effective. The cost of IRS being high and less effective in the Malagasy context, a budgetary impact analysis should be relevant before a potential extension of that strategy.

Keywords

Cost-effectiveness, Malaria, ITN & IRS strategies, Madagascar

JEL Codes

D61, I15, I18

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Introduction

Malaria remained the leading cause of worldwide morbidity with 228 million cases and mortality with 405,000 deaths in 2018 (WHO, 2018). Malaria elimination and eradication face significant challenges in terms of technical, operational, and financial resources. The malaria eradication campaign in the world started in 1950 but stopped early, in the 1970s. Malaria burden was heaviest in endemic countries, especially in WHO African regions where 90 % of deaths occurred. In addition to this, malaria was an economic burden for these countries (RBM, 2011). Since 2000, new regional and international strategies have been defined to control, eliminate and eradicate this disease (RBM and point 6 of last MDGs). With the creation of the Global Fund in 2002, the funding for malaria control program has increased significantly from \$ 17 million in 2000 to \$ 2.9 billion in 2015 (WHO, 2016). This international sensitization effort resulted in positive outcomes: between 2000 and 2015, the incidence of malaria in the world had fallen by 46 % and 60% and the number of countries moving towards the elimination of malaria increased (WHO, 2016, 2018).

Madagascar is a very poor country and 80% of the Malagasy people lived in rural area. In 2013, the GDP per capita amounted to constant USD 547 and the poverty incidence equal to 74% (INSTAT, 2013; World Bank, website¹). The first cases of malaria in Madagascar were observed in 1800 and control programs started between 1920-1930 through the introduction of larval control using chemical larvicides and ecological approach using Tilapia. A national malaria eradication program came after, between 1949 and 1962. At the end of this program, the monitoring activities were gradually abandoned, resulting in a resurgence of the disease. Severe and deadly epidemics occurred in 1987 and have been controlled using indoor residual spraying (IRS) of DDT and by allowing large access to chloroquine for the treatment of clinical cases (PNLP, 2011; RBM, 2013). The Malagasy government joined international and regional partners such as Abuja summit declaration in 2000 and RBM in 2002. The current NMCP was created in 1998 and during the last ten years, three national strategic plans for malaria have been elaborated from 2008 to 2012, between 2013 to 2017 (NMCPM, 2015)[8], and finally from 2018 to 2022.

The government introduced malaria control interventions as IRS, intermittent preventive treatment for pregnant women (IPTp) and ITN respectively in 1998, 2000 and 2006. Since

¹ <https://donnees.banquemondiale.org/indicateur/NY.GDP.PCAP.CD?locations=MG>

2005, Madagascar has based its preventive strategies on IRS campaigns in regions on elimination stage, on distribution of ITNs (universal coverage) through mass campaign and routine distribution in regions on control stage, on IPTp for pregnant women and on malaria surveillance systems in all regions. The IEC strategy was mainly done by the government through the NMCP. Although the ministry of health decided to introduce lessons on malaria transmission, prevention and treatment to the fifth and six years pupils of primary school, their impact was limited. And, even the standards for the prevention were officially disseminated by doctors, midwives and community workers, in practice, healthcare staff said that they did not have time to sensitize patients (Pourette et al, 2015). The curative strategy consisted in providing prompt and appropriate treatment of malaria cases by using rapid diagnostic tests (RDTs) and Artemisinin-based Combination Therapy (ACT). The national malaria program guaranteed free access to malaria prevention (ITNs, IRS, IPTp) and free of charge of medical services (PNLP, 2011).

In 2012, the malaria incidence (parasite rate) in the country was 3.11%, spatially heterogeneous and with different seasonal patterns. Madagascar presented four malaria transmission patterns. A high transmission on the equatorial coastal zone (the East), considered as a control zone in scaling phase for universal coverage, with an incidence higher than 10%, but it has decreased since 2011 (14.6% to 12.8% in 2013 and 9% in 2016). A seasonal transmission on the tropical coastal zone (the West), in pre-elimination phase in 2011, the incidence was < 5%, it increased in 2012 (until 10.5%) and then decreased (8.8% in 2016). A low, short and unstable transmission in the sub-desert area (the South), in pre-elimination phase in 2011 (1.5%), but the incidence increased in 2013 (6.4%) and then decreased (5.2% in 2016). An elimination phase in the Central Highlands and its fringe, with an incidence lower than 1.5% (0.8% in 2011, 1.1% in 2013, and 0.9% in 2016) (INSTAT, 2013, 2016).

ITN and IRS were the most common strategies of vector control and the WHO recommended their implementation. Many studies (Goodman et al., 2001; Guyatt et al., 2002; Kroeger et al., 2002; White et al., 2001; Stelmach et al., 2018; Alonso et al., 2021) analyzed the cost and cost effectiveness of these strategies in endemic countries. However, methods were different (in terms of study design, cost and cost effectiveness analysis) and results difficult to compare. Furthermore, each strategy had its own implementation cost (some interventions were more costly than others were) and would be more or less cost-effective. In fact, in some cases, ITN appeared more efficient and less expensive than IRS while in other cases, IRS, although more

expensive, appeared more efficient than ITN (Goodman et al., 2001). However, some studies concluded that it was not possible to make any generalized assertion on whether ITN or IRS was more cost-effective (White et al., 2011).

The objective of this paper was to estimate the cost-effectiveness of two preventive strategies in Madagascar (ITN and IRS), using a case-control study in two districts. The first one, Brickaville, was located in the Atsinanana region, with a poverty incidence of 66% in 2013. The second, Ankazobe, was located in the fringe of the Analamanga region, with a poverty incidence outside the capital of at least 60% in 2013 (INSTAT, 2013). This study was part of an operational research toolbox named “PALEVALUT” (integrated operational evaluation of malaria control)². It included cost evaluation tools as implementation and consumption costs and epidemiological tools, such as a case-control study, that allowed measuring the protective effectiveness of interventions against the occurrence of acute clinical episode. The contribution of this paper was to estimate the overall cost of the malaria program (by including the cost supported by HF and HH) and the cost and cost-effectiveness of ITN and IRS, two strategies potentially competitive. The Ministry of Public Health of Madagascar (approval n°247/MNSANP/SG of 26/03/2013) and the National Ethic Committee of the Ministry of Public Health of Madagascar (approval n°12/MNSANP/EC of 03/12/2014) approved this study. Participants study gave informed consent.

Methodology

Cost-effectiveness of IRS and ITN was undertaken, first by assessing the cost of the implementation of the malaria control program at national level. Then, at the district level, we estimated the cost of malaria prevention supported by the NMCP, HF and HH, the cost of malaria treatment for HH and HF and the protective effectiveness of the ITN and IRS.

Data collection

Data for the implementation cost of the national malaria control program (government and partners' perspective) were from World Malaria Reports (WMR) from 2009 to 2013, and concerned retrospective expenditures of the government and all the partners (NMCPM, 2014). Although the NMCP published annual reports, data were available only since 2010 and were incomplete, as they did not include malaria activities of all the partners. This period corresponded to the implementation of the two complementary national malaria control

² [http:// www.palevalut.org/](http://www.palevalut.org/)

strategic plans (NMCSP): Round 7 (October 2008 to June 2012) and NSA1 (October 2009 to June 2013), both funded by the Global Fund (PNLP, 2009 to 2013).

Data for the cost of the malaria program burdened by the HH and public HF were from surveys conducted in 2014 in the districts of Brickaville and Ankazobe, respectively located in the eastern transmission pattern (control phase) and in the fringe transmission pattern (elimination phase). The district of Brickaville had a perennial transmission and benefited from several mass campaigns of ITNs distribution with a scaling for universal coverage. The last campaign took place in November 2013. The district of Ankazobe that has benefited from several mass campaigns of pyrethroid-based ITNs (from NMCP) and IRS with Bendiocarb (from USAID) displayed a seasonal transmission. The latest campaign took place in November and December 2013.

The following retrospective data were obtained from surveys:

The cost of malaria prevention and the cost of providing malaria treatment at HF. The survey covered the hospital of the district and four (Ankazobe) and five (Brickaville) public primary health facilities. Private HF at this level were almost nonexistent. There was no private HF in Brickaville, while Akazobe had two. But they were located in town and covered less than 1.5% of the population of the district (MSO, 2019). They were not surveyed as moreover, the cost of their service was borne by households and caught by HH surveys. Collected data related the treatment protocol, direct and indirect cost related to the management of uncomplicated and complicated malaria. The direct cost included personnel cost (based on the time spent by the medical and non-medical staff to manage malaria and the staff monthly salary per socio-professional category), cost of antimalarial medicines, RDT and other malaria consumables. Moreover, other data over the 12 months preceding the survey, such as the number of malaria consultations and hospitalizations, and other HF expenditures, as personnel, equipment and operating expenditures (questionnaire used - in French -) were collected.

The malaria prevention cost and the malaria treatment cost borne by HH. In each district, the survey concerned nine fokontany (basic administrative sub-units at the local level), in two randomly selected communes. In Ankazobe and in Brickaville, respectively, 405 HH with 2,165 individuals and 398 HH with 2,093 individuals were investigated. Collected data concerned spending for malaria prevention (nets, insecticide bomb, etc.), out-of-pocket payments in case of malaria (consultation and/or hospitalization fees, antimalarial medicines, transport cost). HH survey was supplemented by street-vendors and private pharmacies' survey from which households could obtain antimalarial drugs when HF are out-of-stock or for self-medication.

All costs were collected in Malagasy currency (Ariary) and converted to US dollars at the 2013 exchange rate (Ariary 2008 = USD1).

The protective effectiveness of vector-control interventions (ITNs and IRS) against the occurrence of clinical malaria was determined from case-control studies conducted in HF. Briefly, cases and controls were recruited between May and September 2014 in five HF. Cases were defined as individuals aged ≥ 6 months, residing in the study area, presenting for fever at the HF and testing positive for any Plasmodium species by RDT (CareStart® Malaria), and confirmed by microscopy. Individuals presenting for any other reason than fever at the HF, excepted vaccination or antenatal care, and having neither a recent history of fever nor hyperthermia as measured by axillary temperature, were considered as control individuals. The association between the outcome (case versus control status) and the exposure to control interventions was estimated by multivariate logistic regression model using generalized linear models, and controlling for age, sex, socio-economic status, and commune. The study included 33 clinical malaria cases and 331 controls in Ankazobe, and 180 cases and 601 controls in Brickaville. Separate computations of the protective effectiveness of each malaria control intervention have been conducted for each district.

Cost estimation

Costing of IRS and ITN strategies was undertaken using a three-step procedure. The first step consisted of assessing the total cost of the malaria control program at the national level. The second step was to allocate a part of this total cost to the studied districts according to a distribution-key. The last step was to assess at the district level the total cost of malaria prevention strategies (ITNS and IRS) borne by the NMCP, HF and HH.

The total cost of the national malaria program is borne by the government and its partners. It was computed from WMR reports and was calculated per strategy and per activity over the period 2009 to 2013. The WMR expenditures breakdown included common expenditures (administrative management, planning and overheads, HR and training, supply management, infrastructures and equipment, monitoring and evaluation, other, (A, Table 1), specific expenditures for preventive strategy, nets, insecticides, communication and advocacy (B, Table1) and treatment strategy (RDT, antimalarial medicines (C, Table 1). Using a top-down approach, the common expenditures have been allocated to each strategy (ITN, IRS, IEC, diagnosis and anti-malaria medicines), proportionally to its activity. Once the total cost was estimated for each component of B and C strategies (TCCi), we calculated an average annual

cost $AC_i = TCC_i/5$. Costs were not discounted because they were incurred expenditures and used for the cost-effectiveness analysis whose effectiveness indicator was estimated for one year.

The total cost of the program at the district level (TCDL) included (i) the average annual cost of the NMCP borne by the government and the partners, attributable to the district (TCPDL), (ii) the total cost of malaria prevention borne by HF (TCHF) and (iii) by HH (TCH):

$$TCDL = TCPDL + TCHF + TCH$$

Where:

$$TCPDL = \sum AC_i * \text{district target population} / \text{national target population}$$

$$TCPDL = \sum AC_i * \text{district target population} / \text{national target population}$$

With AC_i , the annual component strategy cost and $i = 1, 2$ (ITN, IRS)

TCHF: included the financial resources spent by public HF to provide malaria prevention strategy (ITN or IRS or ITN+IRS).

TCH: included the financial or non-financial resources (valued in monetary terms) spent by HH to acquire nets or to benefit from IRS. The cost was computed over one year (2014, based on data survey).

$$TCH = (CITN * nITN) * nHous + (CIRS * nIRS)$$

Where:

CITN is the average cost of ITN, **nITN**: the average number of ITN purchased by HH, **nHous**: the number of HH in the district, **CIRS**: the average cost for IRS, **nIRS**: the number of HH who benefited IRS.

Table 1: Cost components decomposition of malaria control program at national and district levels

Items	Components	Sources
I-Total cost of the NMCP from 2009 to 2013		
	Expenditures breakdown	WMR: 2009- 2013
A-Common costs reallocated proportionately to B and C activities	Planning, management, overheads Human resources and training Supply management Infrastructures and equipment Monitoring and evaluation Other	
B- Preventive strategy	ITNs (nets) IRS (insecticides and spray equipment) Communication and advocacy	
C- Treatment strategy	Diagnostic test: RDTs and microscopy Antimalarial medicines	
II- Total cost of malaria prevention program at the district level		
	Average annual cost of ITNs for the NMCP	Authors' estimation: annual cost of ITNs from 2009 to 2013 WMR-2013: Targeted population at the national and the district level
D- ITNs strategy	Total annual cost of ITNs for HF Management and overheads Human resources Supply management Infrastructures and recurrent expenditures Total annual cost of ITNs for HH Cost of nets Other attributable cost to acquire nets	Authors' HF survey 2014: Brickaville: 1 hospital and 5 PHF Ankazobe: 1 hospital and 4 PHF District data: number of HF in the district Authors' HH survey 2014 Brickaville :405 HH (2,165 individuals) Ankazobe: 398 HH (2,093 individuals) District data: number of HF in the district
E- IRS strategy	Average annual cost of IRS for the NMCP Total annual cost of IRS for HF Management and overheads Human resources Supply management Infrastructures and recurrent expenditures Total annual cost of IRS for HH Attributable cost to benefit from IRS	Authors' estimation: annual cost of IRS from 2009 to 2013 WMR-2013: Targeted population at national and district level Authors' HF survey 2014: Brickaville: 1 hospital and 5 PHF Ankazobe: 1 hospital and 4 PHF District data: number of HF in the district Authors' HH survey 2014 Brickaville: 405 HH (2,165 individuals) Ankazobe: 398 HH (2,093 individuals) District-data: number of HH in the district

III-Cost of cases and DALYs averted at the district level

F-Number of cases averted at the district level	NAC through ITNs NAC through IRS	Case control study 2014 Brickaville: 33 cases/331 controls Ankazobe: 180 cases/601 controls
G- Number of malaria cases at the district level	Number of uncomplicated cases Number of complicated cases	[22]
H- DALYs averted	Number of deaths averted Number of mild, moderate and severe malaria cases averted	Case control study 2014 Brickaville: 33 cases/331 controls Ankazobe: 180 cases/601 controls [22, 23]
I-Mean treatment cost of uncomplicated case at HF	Direct cost Healthcare personnel Consumables Medicines Indirect cost: Capital and recurrent expenditures	Authors' HF survey, 2014 Brickaville: 5 PHF Ankazobe: 4 PHF Using ingredients approach with top-down methodology
J- Mean treatment cost of complicated case at HF	Direct cost Healthcare personnel Consumables Medicines Indirect cost Capital and recurrent expenditures	Authors' HF survey, 2014 Brickaville: 1 hospital Ankazobe: 1 hospital Using ingredients approach with top-down methodology
K-Mean treatment cost of uncomplicated case for HH	Direct cost Consultations fees Drugs Indirect cost: Transport, meals, other	Authors' HH survey, 2014 Brickaville : 405 HH (2,165 individuals) Ankazobe: 398 HH (2,093 individuals)
L-Mean treatment cost of complicated case for HH	Direct cost Hospitalization Consumables Drugs Indirect cost Transport, meals, other	Authors' HH survey, 2014 Brickaville : 405 HH (2,165 individuals) Ankazobe: 398 HH (2,093 individuals)

Sources: NMCPM, 2014; PNLP, 2009 to 2013; Kesteman et al. 2016; authors' HF and HH survey; <https://malariaatlas.org/trends/country/MDG>.

The protocol of the Ministry of Health for malaria treatment indicated that complicated cases should be referred and treated at the hospital. All malaria cases where no hospitalization was required corresponded to uncomplicated malaria and were treated at PHF. For the cost analysis, only cases confirmed by RDT test or microscopy were included (non-confirmed cases were excluded). The cost was calculated for complicated cases and for uncomplicated cases over one year (2014). For HF, the cost attributable to malaria treatment included direct cost (as HR, medicines, consumables, etc.) and indirect cost attributed to the management of malaria. The

cost was estimated by applying a standard costing analysis procedure. Capital and recurrent expenditures were estimated using an ingredient approach combined with a top-down methodology (Drummond and McGuire, 2001; Drummond and Sculpher, 2005). For HH, the cost associated with an episode of malaria included medical costs (drugs, TDR, hospitalization, etc.) and non-medical costs (transport, food, or other informal expenses). Individuals concerned are those in the cross-sectional survey who had a fever episode in the three months preceding the survey.

The cost effectiveness rate (CER) of ITN and IRS strategies was computed separately and was performed using cases and Dalys averted. The CER per case averted was calculated based on the annual total net cost (NC) and the number of cases averted (Nca).

$$CER = \frac{NC}{Nca} + \frac{TCDL - TCADL}{Nca}$$

TCDL: annual total cost of the national program at the district level,

TCADL: total cost of cases averted at the district level

$$TCADL = TCAC_{HF} + TCAC_{HH}$$

$$TCAC = Cucc * Naucc + Ccc * Nacc$$

Cucc: average treatment cost of an uncomplicated case, **Naucc**: number of uncomplicated cases averted, **Ccc**: average treatment cost of a complicated case, **Nacc**: number of complicated cases averted.

The estimation of the number of cases averted was based on the case-control study:

$$Nca = EINCM * PAC / (1 - PAC)$$

EINCM: estimated incidence of uncomplicated malaria cases in the general population; **PAC**: Proportion of uncomplicated cases averted in the general population. The proportion of cases averted was obtained as follows:

$$PAC = CMCI * (1 - OR)$$

CMCI: coverage of malaria control intervention, or proportion of the general population exposed to the strategy; odds ratio (OR) of the exposure to the intervention against uncomplicated malaria.

The CER per DALY averted equals to:

$$CER = \frac{NC}{Dalys\ averted}$$

NC= annual total net cost of the national program at the district level

DALYs = sum of the years averted due to disability (YLD) and the years of life averted (YLL)

$$DALYs = YLD + YLL$$

$$YLD = Nad * Le$$

Nad: number of deaths averted: Le=life expectancy at average age of death

$$YLL = NaMild * d1 * coef1 + NaMod * d1 * coef2 + Nacc * d2 * coef3$$

NaMild: number of mild malaria averted; d1: mild malaria average duration; coef1: disability weight for mild malaria;

NaMod: number of moderate malaria averted; coef2: disability weight for moderate malaria

Nacc: number of complicated malaria averted, d2: duration of complicated malaria; coef3: disability weight for complicated malaria

Table 2: Parameters for Dalys estimation

Parameters	Value	Sources
Duration of moderate and mild malaria (days)	7	a
Duration of severe malaria (days)	14	a
Age of death (years)	2	b
Life expectancy at the age of death	62.7	c
Disease weight coefficient ^c		d
MILD malaria	0.006(0.002-0.012)	
Moderate malaria	0.051 (0.032-0.074)	
Complicated malaria	0.133 (0.88-0.19)	
Disease weight proportion		e
MILD malaria	24,8%	
Moderate malaria	66%	
Complicated malaria	9,2%	

^a<https://www.inserm.fr/information-en-sante/dossiers-information/paludisme>;

^b<https://www.who.int/malaria/media/world-malaria-report-2018/fr/>

^c<https://donnees.banquemondiale.org/indicateur/SP.DYN.LE00.IN?locations=MG>

^d<http://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights>

^eHowes, Franchard, Rakotomanga et al., (2018) ; Taylor, Namaste, Lowell J, Useem, Yé, (2020)

Sensitive analyses were conducted using confidence interval (CI) to quantify the uncertainty about effects.

Results

Organization of the NMCP in Madagascar

The NMCP was composed of one direction, one project department, one finance and administration division and five technical divisions related to the strategies implemented: vector control, case management, epidemiological surveillance, monitoring and evaluation and malaria information, education and communication (IEC). The national malaria program implementation was coordinated by the Ministry of Health through the NMCP and financed by donors and technical partners as Global Fund, PMI, UNICEF, WHO. During the period 2009 to 2013, the Global Fund financed 55.9% and PMI 41.7% of the budget. The other funds came from the Malagasy Government (less than 1%), UNICEF, WHO and the Principality of Monaco. However, as the result of the political crisis in 2009, PMI did not work in collaboration with the Malagasy government. PMI, directly supported activities at the community level and operated independently. Consequently, the NMCP external core funding was withdrawn and the implementation of the program was insufficiently coordinated over this period. Since 2002, Madagascar had benefited from eight malaria grants from the Global Fund. Funding was allocated to entities named principal recipients (PR). Each PR was working with organizations, known as sub-recipient (SR), which realized the program activities (Figure 1).

The NMCP defined every year a malaria action plan with input needs (for instance the quantity of ACT, ITN, etc.) that the Global Fund ordered from the PRs. Once the inputs were available, the NMCP with the SRs implemented the activities: training, distribution, supervision, etc. In some cases, the NMCP became a SR and managed a few parts of the Global Fund funding allocated to malaria.

Malaria morbidity, and mortality and universal coverage

From 2003 to 2011, the country registered progress in the fight against malaria. According to the Ministry of health, malaria morbidity decreased from 13% to 1% and from 22% to 5% among children under five. During the same period, the malaria mortality rate fell from 26% to 8 % among children under five and from 13% to 2% for those over five years [6]. However, this decreasing trend has been reversed since 2012. Compared to 2011, the number of confirmed cases increased about 51% in 2012, 69.3% in 2014 and threefold in 2015 (Table 3).

Table 3: Evolution of confirmed malaria cases between 2007 and 2015

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Confirmed cases	736,194	352,520	299,094	293,910	255,814	395,149	387,045	433,101	752,176

Source: NMCPM, 2014.

The national survey on malaria indicators 2013 (INSTAT, 2016) indicated that households obtained their ITNs mainly from mass-campaigns (77% in rural areas and 63% in urban areas). The ITN universal coverage of HH owned at least on ITN was 79% and the coverage of at least one ITN to three people was 57%. In highlands (where malaria incidence is low), the night before the survey, 16% of individuals slept under ITN, whereas the proportion was 71% in the equatorial zone (where malaria incidence was high). Between 2010 and 2013, IRS strategy was generalized in 21 districts, and targeted in 32. In areas where it was generalized (like in the highlands and its fringe where Ankazobe was located), the IRS coverage was 80% in 2011 and 61% in 2013 (INSTAT, 2016).

Cost estimation

The total cost of the NMCP over the period 2009 to 2013 was estimated to USD 232,943,385 with preventive inputs representing 43.3% (ITNS and IRS) and support inputs (ACTs, RDTs, and microscope) 8.9%. The program management represented 9.8 % and the monitoring & evaluation 5.7%. The remaining 32.4% of the total cost was shared between human resources and training 18.2%, communication and advocacy 3.2%, supply, infrastructure and equipment 8.3% and other 2.8% (Table 4). On average, the NMCP spent over this period USD 46,588,677 per year.

Table 4: Cost the NMCP per activity in Madagascar over the 2009 to 2013 period

Expenditures breakdown	Amount in USD (%)
Expenditure-to allocate per activity	
Planning, management, overheads	22,745,931 (9.8%)
Human resources	18,518,363 (7.9%)
Training	23,667,298 (10.2%)
Monitoring and evaluation	13,218,294 (5.7%)
Supply management	8,082,821 (3.5%)
Infrastructure and equipment	11,220,417 (4.8%)
Other	6,643,229 (2.9%)
Total of common costs	104,096,353 (44.7 %)
Preventive strategies	
ITNs (nets)	62,603,037 (26.9%)
IRS (insecticides and spray equipment)	38,111,964 (16.4%)
Communication and advocacy	7,492,650 (3.2%)
Total	108,207,651 (46.5%)
Treatment strategy	
Diagnostic test: RDTs, microscopy	10,726,918 (4.6%)
Antimalarial medicines	9,912,463 (4.3%)
Total	20,639,381 (8.9%)
Total cost	232,943,385 (100%)

Source: NMCPM, 2014

Cost of the malaria prevention program at the district level

According to the results presented in Table 5, the implementation of IRS costs about four times higher than the ITN strategy in Ankazobe (fringe zone).

Table 5: Average annual cost (USD) of ITNS and IRS strategies at the district level over the period 2009-2013

	National Target population (1)	District Target population (2)	Annual cost of the strategy at national level (TC) (3) USD	Annual cost of the strategy at the district level (TCPDL) (2)*(3)/ (1) USD
District of Ankazobe				
ITNs	13,218,942	138,272	22,636,087.3	236,776.7
IRS	2,038,005	138,272	13,780,573.4	934,967.0
District of Brickaville				
ITNs	13,218,942	187,629	22,636,087.3	321,295.5

Source: Authors' calculation from NMCPM, 2014.

Malaria prevention costs for HF and for HH

According to the HF survey, activities for malaria prevention delivered by HF were free of charge. Indeed, the district health office implemented the IRS activities. PHF distributed nets during the antenatal visits but this activity did not generate any management additional cost.

Concerning HH, in the two districts, 97% of HH had nets with 97% of which were endowments. In Ankazobe, the HH coverage rate for IRS was 80 %. The absence of IRS for the remaining 20% was due to the absence of HH members during the period of IRS campaign. Concerning the cost, 99% of HH did not spend any financial resources in order to benefit from it. Therefore, the malaria prevention cost could be considered almost null for HF and for HH.

Malaria treatment cost for HF

The average cost of malaria treatment is relatively comparable in the two districts (Table 6)

Table 6: Cost of malaria treatment for HF in 2014 (USD)

	Total cost for HF surveyed (1)	Number of cases for HF surveyed (2)	Mean cost (Cpc) (1)/(2)
Ankazobe			
Uncomplicated case	3,326.3	1,007	3.3
Complicated case	4,139.5	32	129.4
Brickaville			
Uncomplicated case	4,027.,8	968	4.2
Complicated case	5,206.3	46	113.2

Source: Authors' calculation from HF survey 2014

Malaria treatment cost for HH

Ankazobe and Brickaville counted four and three medicine-depots respectively, all of them located in the district capital. Although antimalarial medicines are sold there, HH surveys showed that HH used these depots or, failing that and turned to street-vendors, when antimalarials are out-of-stock in public HF (Pourette et al., 2015; IPM, 2015). In Brickaville and Ankazobe, 35% and 17% of the HH respectively reported that they had at least one member presenting malaria sign during the three last months preceding the survey. The average cost for an uncomplicated case was two times higher in Brickaville than in Ankazobe (Table 7).

Table 7: Malaria treatment cost for HH at the district level (USD), 2013

	Total cost across all HH surveyed (1)	Number of cases across all HH surveyed (2)	Mean cost per case (1)/ (2)
Ankazobe			
Uncomplicated case	224	112	2.0
Complicated case	0	0	11.4*
Brickaville			
Uncomplicated case	1,558	380	4.1
Complicated case	57	5	11.4

* As no member of HH surveyed in Ankazobe presented a complicated case, the average cost of complicated malaria treatment was considered as the same as Brickaville. Source: Authors' calculation from HH survey 2014
Source: Authors' calculation from HF survey 2014.

Effectiveness of IRS and ITN strategies

The case-control study showed that the OR of ITN use, in association with the occurrence of uncomplicated malaria, was lower than one (thus protective), low (<0.50) and statistically significant in both Ankazobe and Brickaville districts (Table 8), demonstrating thus that ITN was an effective intervention in preventing uncomplicated malaria. The protective effectiveness of ITN was lower in Brickaville than in Ankazobe, but this difference was not statistically

significant. Nevertheless, the central value (77% in Ankazobe and 57% in Brickaville) was used for subsequent calculations. Regarding IRS, the OR was lower than one, relatively low, but not statistically significant (the 95% confidence interval includes one, Table 8). Therefore, the protective effectiveness of IRS could not be demonstrated in this study, but the central value (0.50) was kept for further calculations as it was coherent with previous findings [34]. The study also tested the possibility that IRS and ITN would work in synergy. This hypothesis was discarded as the OR of the exposure to ITN only was inferior (OR 0.14, 95% CI [0.01- 0.98]), although not significantly, to the exposure to both ITN and IRS (OR 0.26, 95% CI [0.08- 0.87]). Therefore, the study, in the calculation, considered that the two strategies worked independently to prevent malaria.

Table 8: Protective effectiveness, and number of malaria cases averted per year, 2013

Strategy	Population of district	EINCM	OR intervention	Protective effectiveness	Coverage (CMCI)	PAC	Nca
Ankazobe							
ITN	138,272	3,742	0.23 [0.08- 0.68]	77%	65%	50%	3,725
IRS	138,272	3,742	0.50 [0.13- 2.03]	50%	90%	45%	3,070
Brickaville							
ITN	187,629	7,006	0.43 [0.20- 0.86]	57%	92%	53%	7,785

NB: EINCM: estimated incidence of uncomplicated malaria cases; OR of the exposure to the intervention against uncomplicated malaria [95% confidence intervals]; CMCI: coverage of malaria control intervention; PAC: proportion of uncomplicated malaria cases averted in the general population; Nca: total number of cases averted. Source: Ravolanjarasoa et al. Case-control studies for the evaluation of the protective effectiveness of malaria control interventions: how are they influenced by definitions of cases or controls? (Unpublished observations) Source: Authors' calculation from survey 2014

Table 9: Estimated cases averted (mild/moderate/complicated) and deaths averted

	Nca	Nmildca	Nmodca	Ncca	Nda
ITN					
Ankazobe					
Number	3725	924	2459	343	9
95% CI (lb)	2384	591	1573	219	5
95%-CI (u)	4694	1164	3098	432	14
Brickaville					
Number	7785	1931	5138	716	21
95% CI (lb)	5141	1275	3393	473	10
95% CI (ub)	9695	2404	6398	892	34
IRS					
Ankazobe					
Number	3070	761	2026	282	7
95% CI (lb)	819	203	540	75	4
95% CI (ub)	3820	947	2521	351	12

Nac: number of cases averted, Namild: number of mild malaria cases averted, Nmodca: number of moderate malaria cases averted, Ncca: Number of complicated malaria cases averted, Nda: number of deaths averted.

Cost-effectiveness of IRS and ITN strategies

The CER per case averted of ITN strategy was similar although somehow higher in Ankazobe than in Brickaville (Table 10), consistently with the difference in incidence between the two districts. More importantly, the CER of IRS strategy was higher (USD 297.6) than the CER of ITN strategy in the two districts (USD 56.7 in Ankazobe and USD 31.6 in Brickaville).

Table 10: Cost-effectiveness ratio per case averted (USD)

	Nucca (1)	Nacc (2)	Nca (3)	Cucc		Ccc		TCAC		TCADL	TCPDL	NC	CER /Nca
				HH (4)	HF (5)	HH (6)	HF (7)	HH (8)	HH (9)	(10)=(8)+ (9)	(11)	(12)=(11)- (10)	(12)/(3)
ITN													
Ankazobe													
Value	3382	343	3725	2	3.3	11.4	129.4	10671.4	15068.4	25739.8	236776.7	211037.0	56.7
95% CI (lb)	2165	219	2384	2	3.3	11.4	129.4	6829.7	9643.8	16473.4	236776.7	220303.3	92.4
95% CI (ub)	4262	432	4694	2	3.3	11.4	129.4	13445.9	18986.1	32432.1	236776.7	204344.6	43.5
Brickaville													
Value	7069	716	7785	4.1	4.2	11.4	113.2	37146.9	37853.8	75000.7	321295.5	246294.8	31.6
95% CI (lb)	4668	473	5141	4.1	4.2	11.4	113.2	24531.0	24997.8	49528.8	321295.5	271766.7	52.9
95% CI (ub)	8803	892	9695	4.1	4.2	11.4	113.2	46258.4	47138.7	93397.1	321295.5	227898.4	23.5
IRS (Ankazobe)													
Value	2788	282	3070	2	3.3	11.4	129.4	8794.9	12418.8	21213.7	934967.0	913753.3	297.6
95% CI (lb)	743	75	819	2	3.3	11.4	129.4	2345.3	3311.7	5657.0	934967.0	929310.0	1135.2
95% CI (ub)	3469	351	3820	2	3.3	11.4	129.4	10944.8	15454.5	26399.3	934967.0	908567.7	237.8

Nucca: number of uncomplicated cases averted, Nacc: number of complicated cases averted, Nca: total number of cases averted, HH: households, HF: health facilities;

Cucc: average cost of uncomplicated cases, Ccc: average cost of complicated case, TCAC: weighted average cost of averted cases, TCPDL: total cost of the program at district level, TCADL: total cost of cases averted at district level, NC: annual total net cost of the national program at the district level, CER: cost effectiveness ratio. CI for uncertainty about effects, lb: lower bound, ul: upper bound.

Source: Authors' calculation from surveys

The CER per DALY averted was USD 531.2 for IRS and USD 53.9 (in Brickaville) and USD 99.6 (in Ankazobe) for ITN. Based on the WHO cost-effectiveness threshold (based upon a country's per-capita gross domestic product (Marseille et al., 2015), both strategies would be considered as cost-effective as Madagascar's GDP was USD 541 in 2013. IRS was less cost-effective than ITN, which is considered as highly cost-effective (the CER per DALY was much lower than three times Madagascar GDP per-capita).

Table 11: Cost-effectiveness ratio per DALY averted in 2013 (USD)

	YLLmild	YLLmod	YLLcc	YLL	YLD	DALYs	NC	CER/Daly averted
ITN Ankazobe								
Value	38.8	877.7	638.1	1554.6	564.3	2118.9	211037.0	99.6
95% CI lb	8.3	352.5	270.2	630.9	313.5	944.4	220303.3	233.3
95% CI ul	97.8	1604.6	1148.6	2851.0	877.8	3728.8	204344.6	54.8
Brickaville								
Value	81.1	1834.3	1333.6	3249.0	1316.7	4565.7	246294.8	53.9
95% CI lb	17.8	760.1	582.7	1360.6	627	1987.6	271766.7	136.7
95% CI ul	202.0	3314.4	2372.4	5888.8	2131.8	8020.6	227898.4	28.4
IRS (Ankazobe)								
Value	32.0	723.4	525.9	1281.2	438.9	1720.1	913753.3	531.2
95% CI lb	2.8	121.0	92.8	216.7	250.8	467.5	929310.0	1988.0
95% CI ul	79.6	1306.1	934.9	2320.7	752.4	3073.1	908567.7	295.7

YLLmild: Years of life averted due to mild malaria averted, YLLmod: Years of life averted due to moderate malaria averted YLLcc: Years of life averted due to complicated malaria averted., YLL: years of life averted of cases averted (YLLmild+YLLmod+Yllcc), YLL: Years averted to disability, NC: annual total net cost of the national program at the district level

Discussion

The objective of this study was to evaluate the cost and cost-effectiveness of malaria control strategies. The average annual cost of the NMCP was USD 2.1 per capita and it represented 13.5% of the total health expenditure per capita. Malaria remained an important public health concern, all the more so due to the increasing number of cases since 2012. The study showed that the cost of implementing malaria control at the district level remained largely supported by the NMCP and its partners. Indeed, the amount spent on malaria in terms of prevention was insignificant for HH and HF who supported only the malaria treatment cost.

The malaria control national program was not uniform over the country; it was adapted to the epidemiological context that counted four transmission patterns. In Brickaville, where the transmission was high, besides case management and the TPI for pregnant women, ITNs was the only prevention strategy. In Ankazobe where the transmission is low, generalized IRS was added. In the two study sites, the most cost-effective strategy was ITN. In the district of Ankazobe, the cost-effectiveness ratio of IRS was five times higher than the ITN one. The IRS strategy turned out to be more costly overall. The fact that the IRS was adopted in the pre-elimination zones (where the incidence is low) explained in part that this strategy turned out to be less cost-effective than the ITN strategy. In Ankazobe, ITN showed a higher protective

effectiveness than IRS (77 vs 55%) but was also cheaper (237 vs 935 K\$), hence the cost-effectiveness ratio was almost six times smaller even if the coverage was lower (65 vs 92%). The impact of a possible emerging resistance to pyrethroids contained in ITN and to bendiocarb used in IRS in Madagascar (Rakotondranaivo et al., 2018; Rakotoson,) may have played a role in decreasing the protective effectiveness of interventions, as evaluated by the case-control studies. However, this effect was taken into account in the present study. Otherwise, in endemic areas, IRS was recommended as a powerful vector control for reducing malaria transmission, but in Madagascar, the NMPC chose to implement IRS in pre-elimination malaria phase areas as in Ankazobe. That might explain why the IRS was less efficient than ITNs. But, the same result was found in India where IRS was implemented in a low transmission area (Bhatia, Fox-Rushby, Mills 2004). In Thailand and Benin where IRS was on the contrary implemented in high endemic areas, it turned out less efficient than ITNs (Kamolratanakul et al., 2001) or it was only efficient in urban areas (Makoutoude et al., 2014°).

Although the study showed that IRS was less cost-efficient than ITN, this intervention should not be completely discarded, as it still prevented thousands of cases each year. Indeed, in the district of Ankazobe, IRS prevented 3000 cases of uncomplicated malaria cases each year, just after ITN, prevented 3700 cases each year. The IRS performance is to be related to its large coverage (92%), compared with ITNs (65%). The WMR suggested that the resurgence of malaria observed in recent years might be associated with the excessive withdrawal of IRS (RMB, 2013). The WHO latest guidelines for malaria control (WHO, 2019) indicated that using both IRS and ITN was not always more effective than, either ITN or IRS used alone, as we found in our study. Therefore, the WHO was not recommending choosing one strategy over another and considered that local evidence such as the financial aspect, malaria endemicity and cost-effectiveness were major factors in decision making in certain countries (WHO, 2019). A recent literature discusses the opportunity of taking decisions only upon a national-income-based approach. Authors argue that CER should be placed in the context of other local policy (such as equity, ethics), program options, or budgetary impact (Bertram et al., 2016). For Madagascar, we found that the IRS strategy was costly and less effective, while a combined IRS-ITN strategy did not appear more effective than ITN alone. It seems then more reasonable to expand ITN coverage to accelerate progress towards malaria elimination.

This study encountered several difficulties including the data collection. Existing data were scattered among different technical and financial partners who have implemented malaria

control activities. Moreover, without technical and financial reporting of all activities carried out by partners, the NMCP cannot establish the details of financial reports of the program per strategy implemented. The study also presented some limitations. The first was that it was performed in two districts only, out of 114 in Madagascar. Nevertheless, because the protective effectiveness of malaria control interventions was there highly consistent with that of national studies (Kesteman et al., 2017), and because the cost of these strategies was relatively uniform throughout the country, these results could be extrapolated to the areas in Madagascar with similar malaria endemicity (fringe and equatorial transmission patterns), at least. The second limitation was the absence of data from private HF and self-medication from HH. According to the Ministry of Health, there was no system to capture the number of consultations and cases managed by private HF. However, that limitation had a low impact on cost estimation as the use of private HF in malaria cases was low and nevertheless caught by HH surveys. Finally, the evaluation of the effectiveness relies on field epidemiological surveys, which are subject to biases and uncertainty. Nevertheless, the evaluations of the effectiveness of each intervention resulting from the case-control study here were reliable, as they were consistent with previous large-scale studies in Madagascar (Kesteman et al., 2016) and elsewhere (Kesteman et al., 2017).

Conclusion

The study confirmed that ITN strategy is less costly than IRS. In areas with a low malaria transmission, IRS appeared less cost-effective than ITN. This suggested that the NMCP who began to reduce IRS implementation, should tend toward a targeted IRS in endemic areas and to remove IRS in low transmission areas. Compared to GDP per capita, ITN strategy appeared highly cost-effective and IRS cost-effective. The cost of IRS being high and less effective in the Malagasy context, a budgetary impact analysis should be relevant before a potential extension of that strategy.

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