Assessing the Impact of Substandard and Falsified Antimalarials in Benin

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Abstract

Substandard and falsified antimalarials contributes to the global malaria burden by increasing the risk of treatment failures, adverse events, unnecessary health expenditures, and avertable deaths. Yet no study has examined this impact in Western Francophone Africa to date. In Benin, where malaria remains endemic and is the leading cause of mortality among children under age five, there is a lack of robust data to combat the issue effectively and inform policy decisions. We adapted the Substandard and Falsified Antimalarial Research Impact (SAFARI) model to assess the health and economic impact of poor-quality antimalarials in this population. The model simulated population characteristics, malaria infection, care-seeking behavior, disease progression, treatment outcomes, and associated costs of malaria. We estimated approximately 1.8 million cases of malaria in Benin among children under age five, which cost $177 million (95% CI: $176 – $178 million) in treatment costs and productivity losses annually. Substandard and falsified antimalarials were responsible for 2.8% (n=165) of deaths and nearly $4.9 million in annual costs. Moreover, we found that replacing all antimalarials with quality-assured artemisinin combination therapies (ACTs) could result in $13.6 million in cost-savings, and increasing pediatric malaria care-seeking by 20% could bring $19.4 million in cost-savings. These results highlight the value of improving access to quality-assured ACTs for malaria treatment and increasing care-seeking in Benin. Policymakers and key stakeholders should use these findings to advocate for increased access to quality-assured antimalarials, inform policies and interventions to improve healthcare access and quality, and reduce the burden of malaria.

Introduction

In a recent meta-analysis, 13.6% of essential medicines were found to be substandard or falsified across low- and middle-income countries.[1] The World Health Organization (WHO) defines substandard medicines as "authorized medical products that fail to meet either their quality standards or specifications or both," while falsified medicines are defined as "medicinal products that deliberately or fraudulently misrepresent their identity, composition, or source."[2] Poor-quality medicines increase the risk of treatment failure, adverse events, and mortality.[3,4] Patients may progress and develop sequelae that require more intensive treatment and admission to healthcare facilities, which takes time away from their ability to work. Substandard and falsified antimalarials come at the expense of increasing economic burden and potentially stunting national economic development as a result of the need for additional healthcare and productivity losses.[3,5]

Antimalarials are the most commonly tested essential medicines found to be substandard or falsified in low-and middle-income countries.[1-3] Regional rates of poor-quality antimalarials as high as 35% have been reported in Africa.[6] Substandard and falsified antimalarials bring to light important health concerns such as drug-resistant infections since antimalarials without appropriate levels of, or even any, active pharmaceutical ingredients (API) could contribute to the development of resistance.[7] Malaria is a preventable, parasitic disease that is commonly treated with artemisinin combination therapies (ACTs). These first-line antimalarials have been integral to the success of global malaria control.[8] Additionally, the implementation of large-scale vector control campaigns and increasing medical access has reduced malaria cases around the world.[9] However, the substantial progress with curbing global malaria has recently stagnated, or started to reverse in many countries, and remains a significant public health threat. Nearly 80% of the global malaria burden remains in Sub-Saharan Africa.[5,9] Moreover, children under age five are the most vulnerable population affected by this disease. Children account for 61% of all malaria deaths worldwide and are at the greatest risk to suffer from consequences of substandard and falsified antimalarials.[5,9]

Recent studies have utilized model simulations to evaluate the health and economic impact of substandard and falsified antimalarials on pediatric malaria.[5,10-12] However, no study have examined this impact in Western Francophone Africa to date. This study focuses on Benin, where malaria is the leading cause of mortality among children under five years of age.[13] The private sector accounts for 70% of antimalarial distribution in Benin and the country relies heavily on imported and poorly-regulated pharmaceuticals from neighboring countries such as Nigeria and Togo.[13] As a result, Benin may be at risk of being impacted by substandard and falsified antimalarials. We applied our agent-based model in Benin to assess the impact of substandard and falsified antimalarials among pediatric patients to provide governments robust data to combat the issue effectively and inform policy decisions.

Methods

SAFARI Model

We developed SAFARI (Substandard and Falsified Antimalarial Research Impact), an agent-based model, to estimate the health and economic impact of poor-quality antimalarials in children under age five.[5,10] Agent-based models are good at capturing the heterogeneity of complex adaptive systems, such as patient care-seeking behavior and medicine supply chain processes that evolve over time.[14] The SAFARI model has been used to estimate the burden of substandard and falsified antimalarials in the Democratic Republic of the Congo (DRC), Nigeria, Uganda, and Zambia.[5,10-12] In this study, we adapted the SAFARI model to evaluate the burden of poor-quality antimalarials and simulate potential interventions in Benin. The model was developed in Python to simulate population characteristics, malaria infection, care-seeking behavior, disease progression, treatment outcomes, and associated costs of malaria.[11] We simulated 25,000 child-agents over a one-year time horizon, broken into five-day increments. Further details of the methods used by the SAFARI model are described in previous publications.[5,10-12]

Inputs

Model inputs for Benin were gathered through a PubMed literature search alongside a Google search for grey literature including sources such as ACTwatch, the Benin Demographic and Health Survey (DHS), World Malaria Report (WMR), and the Worldwide Antimalarial Resistance Network (WWARN) database.[9,15-19] Data inputs were chosen based on their quality, relevance, and generalizability for the most recent year. Costs in West African Communauté Financière d'Afrique (CFA) franc were converted to 2018 United States Dollars (USD) using local inflation rates and 2018 exchange rates from the World Bank.[20,21] All model inputs, including demographic, epidemiological, care-seeking, and cost data are presented in **Table 1**.

Model Simulation

The flow diagram found in **Figure 1** depicts the movement of child-agents through the adapted SAFARI model.[5] Each child-agent was assigned five demographic characteristics – age, geographic region, socioeconomic status, residence type (urban/rural), and maternal education – based on distributions from the latest Benin DHS.[19] Child-agents moved through the disease simulation according to probabilities calculated from individual characteristics among children under five in Benin.[9,22] Once a child-agent became sick and symptomatic, it could either seek care at one of five locations: public facilities, private facilities, pharmacies, drug stores, or at home (self-treatment). Some child-agents may not seek malaria treatment within a five-day period, where they would face a higher chance of malaria becoming severe.[23] Care-seeking child-agents would receive antimalarial treatment based on reported availability of four treatment options at each facility: ACTs, chloroquine (CQ), quinine, or other antimalarial treatments.[19] Stock-out probabilities, or the probability of a facility running out of antimalarials, were obtained from national stock data.[15]

Some child-agents in the model may receive substandard and falsified antimalarials, based on a study evaluating antimalarial quality in Benin.[24] To account for adverse outcomes caused by substandard and falsified antimalarials, child-agents who received poor-quality antimalarials faced reduced treatment efficacy reflecting antimalarials with subtherapeutic levels of API.[9] As a result of reduced efficacy, child-agents would be at an increased risk for disease progression to severe malaria..[9] Based on medication efficacy, adherence, and quality, child-agents may recover from malaria in the five-day period or remain sick into the following week to return to the start of the model .[25] Some cases of malaria become severe, where a child-agent may be hospitalized and face a probability of death based on case-fatality rates, as well as suffer from malaria-induced neurological complications.[17,18,26]

Outputs

The primary model outputs are estimates of the health impact, direct costs, and productivity losses attributable to substandard and falsified antimalarials taken among children under five in Benin. The health impact is presented as the number of hospitalizations, neurological sequelae, and deaths. Economic outputs assessed direct costs to the patient for medications, testing, and treatment, as well as costs incurred by public facilities for providing treatment at no cost.[15,27-31] Out-of-pocket costs included medical consultation costs from seeking treatment at a health facility, and transportation costs incurred by the caretaker and patient.[27] Productivity losses included short-term lost caretaker time caring for sick children as well as long-term productivity losses from malaria-induced disability or premature death.

Sensitivity and Scenario Analyses

To account for natural variations in model inputs, we conducted sensitivity analyses where key data inputs were ranged probabilistically across 10,000 model runs. Epidemiological data were varied based on beta distributions, while cost data were ranged using gamma distributions.

We ran a variety of scenario analyses. The baseline scenario was run first to estimate the annual health and economic burden of malaria among children in Benin. This baseline scenario was compared with two main scenarios: (1) if all antimalarials were of adequate quality (i.e. absence of substandard and falsified antimalarials); and (2) if all antimalarials were quality-assured ACTs (i.e. replaced CQ, quinine, and other antimalarial treatments with quality ACTs). These scenarios were used to assess the impact of improving the quality of antimalarials, and the additional benefit of increasing access to ACTs along with improved quality. Three additional scenarios were simulated to represent various supply chain, antimalarial treatment policies, and caregiver education interventions. These scenarios included: (1) encouraging 20% more patients to seek care for malaria treatment (i.e. increase in care-seeking habits); (2) having no antimalarial medication stock-outs across all sectors; and (3) replacing all antimalarials with ACTs (i.e. based on current mix of quality-assured and non-quality-assured ACTs).

Results

The SAFARI model simulated nearly 1.8 million cases of malaria among children under the age of five in Benin. Child-agents that progressed to severe malaria resulted in an estimated 14,304 hospitalizations and 6,009 deaths annually. The overall economic impact of malaria was estimated to be $177 million (95% confidence interval (CI): $176,001,833 - $178,039,101) with $169 million (95% CI: $167,879,081 - $169,912,940) in total productivity losses, which included $24.9 million in short-term productivity losses and $143 million in lifetime productivity losses. Total direct costs of seeking malaria treatment amounted to $8.1 million or 4.6% of the total economic impact (95% CI: $8,098,015 - $8,150,898) including $3.6 million in medication costs (95% CI: $3,617,638 - $3,627,735), $3.4 million in costs incurred by public facilities (95% CI: ($3,390,810 - $3,440,376), and $1 million in out-of-pocket costs (95% CI: $1,078,832 - $1,093,522). The health and economic burden of malaria in Benin is summarized in **Table 2**.

Based on our simulation, where the prevalence of substandard and falsified ACTs was estimated at 15%,[24] substandard and falsified antimalarials were responsible for 521 (3.6%) hospitalizations and 165 (2.8%) deaths ($P < 0.001$). The economic impact of poor-quality antimalarials taken by children in Benin was estimated at $4.8 million (95% CI: $4,838,772 - $4,928,657, $P < 0.001$) annually, which included $4.6 million in total productivity losses (95% CI: $4,611,183 - $4,700,923, $P<0.001$). Annual direct costs due to poor-quality antimalarials were estimated at $227,661, which included $102,313 in medication costs, $94,751 in costs incurred by public facilities, and $30,597 in out-of-pocket costs. Short-term productivity losses were estimated at $677,072, while $3,978,982 were attributed to lifetime productivity losses.

It has been reported that only 52.3% of antimalarials that were stocked in public facilities in Benin were ACTs.[19] Availability of ACTs was even lower in other health facilities, where ACTs consisted of 36.0% of antimalarials in private facilities, 26.3% at pharmacies, 29.8% at drug stores, and 33.8% at home.[19] When we simulated replacing all antimalarials with quality-assured ACTs, in which children would have increased access to ACTs and benefited from improved medication quality, this scenario reduced 1,335 (9.3%) hospitalizations and 507 (8.4%) deaths annually compared to the status quo ($P < 0.001$). This resulted in annual cost-savings of $13.6 million (95% CI: $13,591,808 - $13,680,525, $P < 0.001$) including $13 million in total productivity savings (95% CI: $12,972,468 - $13,061,034, $P < 0.001$). Direct costs savings amounted to $619,416 annually, including $447,658 in medication costs, $134,776 in public facility costs, and $36,982 in out-of-pocket costs.

Figure 2 presents the results of five potential scenarios compared to the current malaria landscape in Benin. Results of the model simulation demonstrated that increasing care-seeking habits by 20% across all health facilities had the greatest health and economic impact, as 27.8% of children under 5 with malaria reported not seeking treatment.[19] Increasing care-seeking habits could prevent 824 fewer deaths among children under five annually and $19.4 million in total cost-savings (95% CI: $19,397,012 - $19,481,983). Another scenario we investigated was replacing

the current stock of antimalarials with ACTs. Ensuring access to first-line antimalarials would prevent 311 deaths annually and would result in $8 million in total annual cost-savings (95% CI: $7,957,603 - $8,046,993). The impact of having access to first-line antimalarials were compounded when the ACTs were also quality-assured.

While the probability of encountering a stock-out was high for those who sought care at a private facility (52.5%) or a drug store (61.5%), only 8.4% of pediatric malaria patients sought care at private facilities and 11.1% at drug stores.[19] Therefore, having no stock-outs had a lower impact compared to other scenarios by preventing 165 fewer deaths annually and amounted to $5.3 million in total annual cost-savings (95% CI: $5,263,853 - $5,353,637).

Discussion

This is a novel study evaluating the health and economic impact of substandard and falsified antimalarials on the pediatric population in Benin. We simulated that improving the quality of antimalarials can reduce 3.6% of malaria deaths and save a total of $4.8 million annually, including nearly $95,000 in facility costs and $100,000 in medication costs. The results of this study is not only important to demonstrate the reduction of unnecessary costs for the healthcare system and the population, but to also ensure that antimalarials are safe, efficacious, and trustworthy.

We demonstrated that access to ACTs – especially quality-assured ACTs – contributes significantly to reducing the malaria burden. Replacing all antimalarials with ACTs can result in $8.0 million in annual cost-savings, while an additional $5.6 million in cost-savings could be achieved if all ACTs were quality-assured. This was primarily due to lack of availability of ACTs, which constituted 34-52% of antimalarials at various health facilities.[19] Efforts in providing quality-assured ACTs could benefit Benin significantly, especially in the private sector where the probability of experiencing a stock-out is as high as 61.5% at these healthcare facilities.[15]

Among the potential scenarios we simulated, increasing care-seeking behavior by 20% demonstrated the largest health and economic impact. If more children are able to seek care for malaria, the likelihood of obtaining effective treatment increases, which could prevent at least 824 deaths or save $19.4 million a year. In Benin, 27.8% of children with malaria did not seek medical treatment.[19] This could prolong treatment duration, increase the risk of disease progression, and lead to preventable deaths and disabilities. While we acknowledge that conducting interventions to increase care-seeking by 20% may be a challenge, our scenarios demonstrate the comparative impact of improving different aspects of access to malaria care for children in Benin.

It is important to acknowledge how far Benin has come in reducing the burden of malaria. In 1982, Benin created the National Malaria Control Program (NMCP) which has been responsible for monitoring and evaluating all activities deemed to control the disease.[32] The NMCP aimed to reduce the burden of malaria in Benin with help provided by key stakeholders such as the United States Agency for International Development (USAID) and the United States President's Malaria Initiative (PMI).[32] The NMCP has provided free access to ACTs and testing for children under five years of age at the community level and health facilities.[33] Additionally, they have contributed to the destruction of 118 tons of counterfeit medicines (including ACTs) in 2019 alone.[33] Despite these efforts, malaria remains to be endemic in Benin and only 28% of children under age five received first-line treatment for uncomplicated malaria according to ACTwatch.[13]

While ACTs are largely available through public facilities, over 70% of antimalarials are distributed through the private sector in Benin.[13] In addition, the private sector is rarely present in NMCP activities and the country's surveillance system does not cover drug stores.[32] Efforts in providing access to ACTs could be directed towards the private sector through regulation and increased surveillance of private facilities including drug stores.[22] In 2019, the NMCP, in collaboration with PMI, have partnered with the Private Sector Health Platform (PSHP) to manage and monitor the performance of the antimalarial supply chain through the presence of Young Professional Logisticians (YPLs) in private sector facilities.[33] Continued engagement with the

private sector would be critical to reduce substandard and falsified medicines, and also to increase access to first-line antimalarial medications.

Our results are in line with the existing literature. Model estimates of malaria cases and deaths are comparable to current epidemiological data projecting 1.7 million child malaria cases and around 4,900 deaths annually in Benin.[9,22] Our Benin SAFARI model results were similar to the DRC SAFARI model, in which the "increasing care-seeking" scenario had the greatest impact on reducing the malaria burden, due to current low levels of care-seeking rates.[10] Yet the results of this study were distinct from findings from the Nigeria SAFARI model, where stock-outs and quality of antimalarials were noted as a bigger problem.[11] Differences between Nigeria and Benin can be attributed to the overall lower ACT prevalence in Benin's market share.[11,15]

There are several limitations to note. When compiling data inputs for the model, there was a noticeable lack of data especially on the quality and efficacy of antimalarials in Benin, as well as country-specific cost data. This made it difficult to capture the true heterogeneity within the country. While we conducted an extensive literature search to utilize the best and most recent data available, the model utilized some estimates from neighboring countries and previous SAFARI models. We have conducted rigorous probabilistic sensitivity analyses to capture the uncertainty around our main estimates. We believe the gaps in data demonstrates an opportunity for further research to generate more accurate information to combat the malaria burden in Benin. Lastly, this study focused on the benefits of various scenarios rather than the costs of interventions to implement these scenarios. Future studies to estimate the costs alongside benefits could be helpful for decision makers in estimating the returns on their investments. Despite these limitations, we believe our analysis is important in demonstrating the impact of and raising awareness of substandard and falsified antimalarials in Benin.

Conclusion

To our knowledge, this study is the first to assess the impact of substandard and falsified antimalarials in the pediatric population of Benin. Access to quality-assured, first-line ACTs is still a predominate challenge in Benin. Results of this study can be used to inform policymakers and key stakeholders of the impact of poor-quality antimalarials and advocate for increased access to quality-assured ACTs. For example, this study could be utilized to advocate for better medication access to achieve Benin's National Strategic Plan (NSP) to reduce the number of annual malaria cases and the national mortality rate, and strengthen the management and coordination of the malaria program.[22] Implementation of policies and programs that aim to improve medicinal quality and access of ACTs can reduce the burden of malaria and may mitigate the development of antimalarial resistance not only in Benin, but also beyond. These efforts may set the precedent for other African nations where malaria remains endemic.

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None.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Tables and Figures

Table 1. Data inputs for the adapted SAFARI model

Model Inputs	Estimate	SD (Range)	Source
Demographic and Epidemiological Data			
Malaria cases of children <5 years old	1,774,127		WMR 2019 [9] and PMI [22]
Case fatality rate for severe malaria in the community (do not go to hospital)	0.150	0.05	Camponovo 2017 [25]
Case-fatality rate inpatient care	0.097	0.01	Camponovo 2017 [25]
Neurological sequelae rate (care sought)	0.031	(0.028 – 0.035)	Dondorp 2010 [34]
Neurological sequelae rate (care not sought)	0.194	0.028	Dondorp 2010 [34]
Probability of Testing			DHS 2017-2018[19]
Public facility	0.519		
Private facility	0.296		
Pharmacy	0.085		
Drug store	0.073		
Cure Rates			Abdulla 2008 [17] and Faucher 2009 [18]
ACT	0.973	0.020	
CQ	0.444	0.112	
Quinine	0.710	0.087	
Other	0.819	0.100	
No treatment	0.000		
Caregiver length of care, days	5		Assumption
Length of illness, days	5		Assumption
Medication Taken by Facility			
Public Facilities			DHS 2017-2018[19]
% ACT	52.3%		
% CQ	15.8%		
% Quinine	20.4%		
% Other treatment	11.6%		
Private Facilities			

% ACT	36.0%		
% CQ	2.9%		
% Quinine	30.9%		
% Other treatment	30.3%		
Pharmacies			
% ACT	26.3%		
% CQ	36.9%		
% Quinine	24.0%		
% Other treatment	12.8%		
Drug Stores			
% ACT	29.8%		
% CQ	24.0%		
% Quinine	35.2%		
% Other treatment	11.0%		
Self-Treatment			
% ACT	33.8%		
% CQ	33.2%		
% Quinine	18.6%		
% Other treatment	14.2%		
Care-Seeking			
Care-Seeking Behavior			
Public facility	20.7%	23%	
Private facility	8.4%	15%	
Pharmacy	9.2%	10%	DHS 2017-2018[19]
Drug store	11.1%	14%	
Self-treatment	22.8%	18%	
No treatment	27.8%	19%	
SF and Treatment Adherence Proportions			
ACT SF Proportions			
Not SF: API > 85%	85.0%		Baba-Moussa 2015 [24]
Category 1: API = 75-85%	53.9%		

Category 2: API = 50-75%	23.2%		
Category 3: API < 50%	22.9%		
Treatment Adherence Proportions			Bruxvoort 2015 [35]
Good: Completes 5-6 Doses	74.7%		
Okay: Completes 4 Doses	10.9%		
Bad: Completes 3 Doses	7.3%		
Very Bad: Completes 2 Doses	3.1%		
Does Not Adhere: Completes 0-1 Dose	3.9%		
Patient Costs			
Cost for Care-Seeking Base			Rashed 2000 [27]
Public, Private	$0.73		
Public, Private (Rural)	$0.57		
Pharmacy, Drug store	$0.37		
Pharmacy, Drug store (Rural)	$0.28		
Cost of special foods	$1.00		Hansen 2017 [28]
Cost of supplemental medicines	$1.00		Batwala 2011 [29]
Average testing cost	$1.79		ACTwatch 2016 [15]
Average testing cost (Public)	$0.00		
Additional cost for care-seeking (Private)	$16.28		Jimoh 2007 [30], Salawu 2016 [31]
Cost of hospitalization	$1.17		Rashed 2000 [27]
Productivity loss per sick day	$2.55		World Bank 2018 [36]
Productivity losses from death	$23,281.21		Assumption
Neurological sequelae disability productivity losses	$9,731.74		
Neurological sequelae disability productivity losses (Severe)	$3,015.91		
Patient Drug Costs			
Public Facilities			ACTwatch 2016 [15]
Average cost of ACTs	$0.00		
Average cost of quinine	$0.00		
Private Facilities			
Average cost of ACTs	$1.82	($1.36 - $3.41)	

Average cost of CQ	$0.42	($0.41 - $1.06)	
Average cost of quinine	$4.30	($3.58 - $5.37)	
Pharmacies			
Average cost of ACTs	$4.97	($3.97 - $6.56)	
Average cost of CQ, assumption same as private	$0.42	($0.41 - $1.06)	
Average cost of quinine	$19.31	($5.89 - $26.06)	
Drug Stores			
Average cost of ACTs	$1.36	($1.02 - $1.70)	
Average cost of CQ	$0.41	($0.41 - $0.42)	
Average cost of quinine	$3.58	($2.86 - $4.30)	
Self-Treatment			
Average cost of ACTs	$0.00		
Average cost of Quinine	$0.00		
Facility Costs			
Facility cost per test (adj)	$1.27	$0.29	Uzochukwu 2009 [37], Onwujekwe 2013 [38]
Facility cost of supplemental drugs (antibiotics, analgesics, etc.)	$1.90	$0.36	Management Sciences for Health [39], WHO 2015 [26]
Facility cost per ACT	$1.28	$0.05	
Facility cost per CQ	$0.05	$0.01	
Facility cost per other drug	$0.05	$0.03	
Public facility cost per case (w/o testing or drugs)	$2.96	$2.19	WHO 2010 [40]
Facility cost per pediatric malaria hospitalization (Public)	$69.30	$31.70	
Stockout Probabilities of any ACT, %			
Public facility	5.0%		ACTwatch 2016 [15]
Private facility	52.5%		
Pharmacy	0.0%		
Drug stores	61.5%		
Self-treatment	0.0%		

ACT=artemisinin-based combination therapy, API=active pharmaceutical ingredient, CQ=chloroquine DHS=Demographic Health Survey, PMI=President's Malaria Initiative, SD = standard deviation, SF=substandard or falsified, WHO=World Health Organization, WMR=World Malaria Report

Table 2. Potential impact of simulated scenarios compared to the current burden of malaria in Benin

	Burden of Malaria		No SF ACTs			All ACTs + No SF ACTs		
	Baseline	95%CI	Potential Impact	% Diff	P-value	Potential Impact	% Diff	P-value
Health Impact								
Average number of malaria cases	1,774,114	(1,773,887 - 1,774,341)						
Average number of hospitalizations	14,304	(14,242 - 14,366)	-521	-3.6%	<0.001***	-1335	-9.3%	<0.001***
Average number of deaths	6,009	(5,966 - 6,052)	-165	-2.8%	<0.001***	-507	-8.4%	<0.001***
Economic Impact								
Medication costs	$3,622,687	($3,617,638 - $3,627,735)	-$102,313	-2.8%	<0.001***	-$447,658	-12.4%	<0.001***
Out-of-pocket costs	$1,086,177	($1,078,832 - $1,093,522)	-$30,597	-2.8%	<0.001***	-$36,982	-3.4%	<0.001***
Facility costs	$3,415,593	($3,390,810 - $3,440,376)	-$94,751	-2.8%	<0.001***	-$134,776	-3.9%	<0.001***
Total direct costs	$8,124,457	($8,098,015 - $8,150,898)	-$227,661	-2.8%	<0.001***	-$171,758	-3.8%	<0.001***
Short-term productivity losses	$24,987,698	($24,984,181 - $24,991,214)	-$677,072	-2.7%	<0.001***	-$821,227	-3.3%	<0.001***
Lifetime productivity losses	$143,908,313	($142,891,311 - $144,925,314)	-$3,978,982	-2.8%	<0.001***	-$12,195,524	-8.5%	<0.001***
Total productivity losses	$168,896,010	($167,879,081 - $169,912,940)	-$4,656,053	-2.8%	<0.001***	-$13,016,751	-7.7%	<0.001***
Total economic impact	$177,020,467	($176,001,833 - $178,039,101)	-$4,883,715	-2.8%	<0.001***	-$13,636,167	-7.7%	<0.001***

ACTs = artemisinin-based combination therapies; CI = confidence interval; % Diff = percent difference of the scenario compared to baseline SF = substandard or falsified; ***P < 0.05

Figure 1. Substandard and Falsified Antimalarial Research Impact (SAFARI) Model Flow Diagram[5]

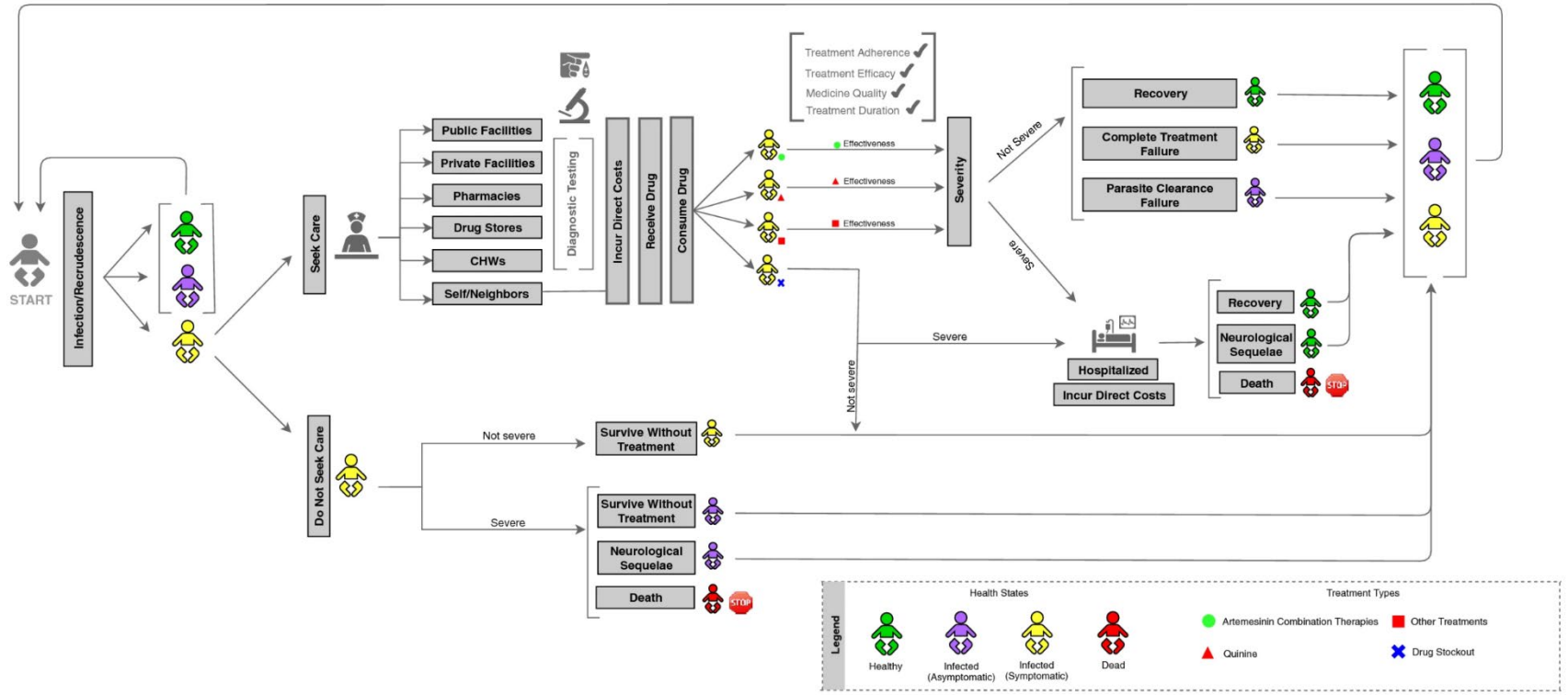
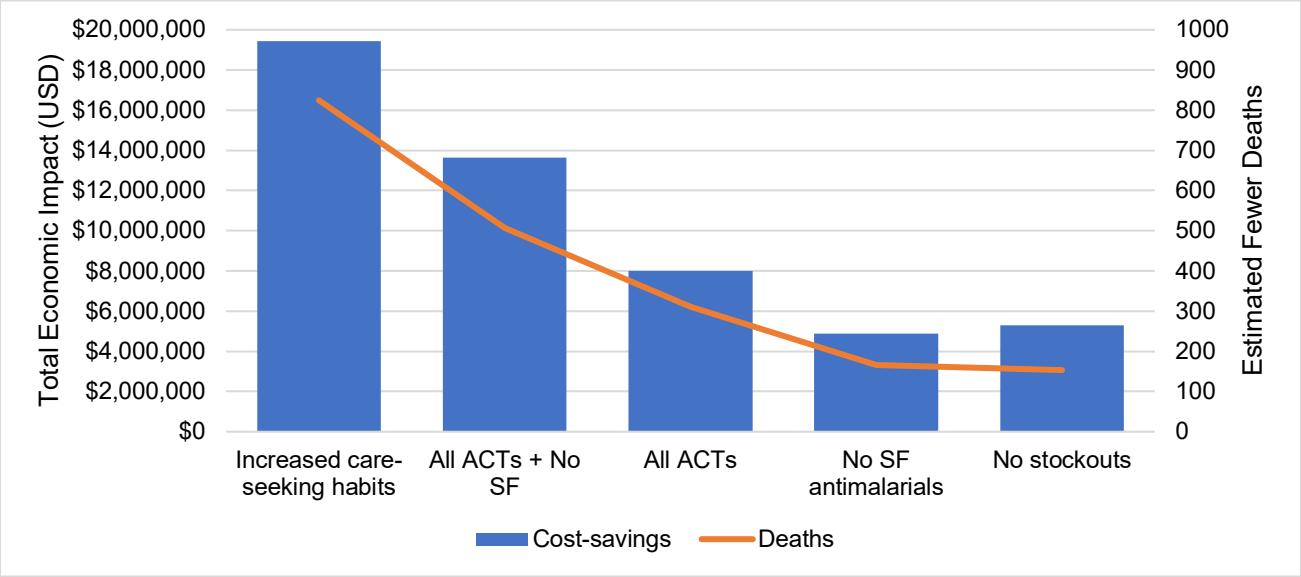


Figure 2. Estimated cost-savings and prevented deaths of simulated scenarios compared to baseline malaria burden in Benin



ACTs = artemisinin-based combination therapies; SF = substandard or falsified

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