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Should anti-malarial chemoprophylaxis be reimbursed in France? A cost-effectiveness analysis of different reimbursement strategies

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Highlights:

- Medico-economic evaluation of three malaria chemoprophylaxis reimbursement strategies.
- The three strategies decrease the number of imported malaria cases in France.
- The cost per prevented malaria case ranges from €15,000 to €34,000
- Restricting the reimbursement to travelers to West and Central Africa seems the best approach.

ABSTRACT

Objectives: France is the Western country with the highest number of imported malaria cases. This study evaluates the cost and effectiveness of the potential reimbursement of drugs for malaria chemoprophylaxis (CP). It targets travelers with medical insurance in France who are heading to endemic regions in sub-Saharan Africa (SSA), the cost of which is currently fully borne by these travelers.

Patients and methods: A decision-tree model was built to assess the cost-effectiveness of three CP reimbursement strategies compared to the current strategy of non-reimbursement from the French National Health Insurance (NHI) perspective. The three strategies targeted either (1) all travelers to SSA (2) travelers of African origin traveling to visit friends and relatives (VFR) and (3) all travelers to West and Central Africa (WCA). Base-case analysis is complemented with deterministic and probabilistic sensitivity analyses (PSA).

Results: Reimbursement of CP would lead to a decrease in malaria cases. The base-case incremental cost per additional malaria case (ICER) for strategies 1, 2 and 3 is estimated at € 34,623, € 15,136 and € 23,640, respectively. PSA confirms our results, showing that reimbursement has a very high probability of being cost-effective, especially under strategies 2 and 3.

Conclusion: Reimbursement of malaria CP by the French NHI could be cost-effective and have a positive effect on malaria prevention in France. Restricting reimbursement to VFRs allows lower ICERs but does not seem feasible in the current French context, while targeting travelers to WCA, who are at higher risk for malaria, could be a reasonably efficient policy.

Key words: Chemoprophylaxis, Cost-effectiveness, France, Malaria, Reimbursement.

Introduction

France is the country with the highest incidence of imported malaria in the world [1]. In 2018, the total number of imported malaria cases was estimated by the French Malaria National Center (CNRP) at 5550, having increased by 6.3% with respect to 2017 [2]. Nearly all cases (97.8%) originated in Sub-Saharan Africa (SSA), among which an overwhelming majority (95.4%) occurred in West and Central African countries (WCA). According to the CNRP, 85.5% of imported malaria infections occur in patients traveling from Africa, whether they reside in France or are arriving from Africa for the first time [2]. Due to its colonial history, France is the destination of a high number of immigrants coming from WCA [3]. Many of those who reside in France periodically travel back to their country of origin to visit friends and relatives (VFR). They contribute significantly to the annual volume of international journeys from France to malaria endemic regions and, consequently, to the amount of imported malaria cases. The remaining cases (14.5%) are observed in subjects traveling to endemic areas for tourism and occupational or military purposes [2].

The treatment of imported malaria entails significant costs for healthcare systems, including French National Health Insurance (NHI) [4–6]. As imported malaria is a preventable disease, such costs could be partly avoided by improving the use of effective protective measures among travelers to and from endemic areas. These include vector control and personal protection against mosquito bites and the use of antimalarial chemoprophylaxis (CP) when the destination is a high-risk country [7]. However, only 63% to 77% of French travelers [8–11] declare taking malaria CP when travelling to regions of high endemicity, and more than three quarters of imported malaria infections in France occur in patients who did not do so [2]. The reasons for suboptimal use of CP include inadequate knowledge of malaria, fear of adverse events, problematic access to medical consultations as well as the cost of

CP treatments, which are not currently reimbursed by French NHI [8, 9, 12–18]. This might be especially true for African VFR travelers who have, on average, a lower available budget than other categories of travelers and usually travel as families for longer stays [19]. This suggests that a possible solution to improve malaria prevention would be to reduce the cost of CP falling on travelers by allowing reimbursement by NHI. While this would generate additional costs for NHI, it could also be an incentive to medication intake, thereby potentially reducing the number of imported malaria cases and the costs related to their management [20].

Two previous studies have investigated the efficiency of a CP reimbursement strategy compared to no reimbursement, in 2008 in France and in 2010 in Switzerland [5, 21]. They both found that partially reimbursing CP to SSA travelers was a cost-efficient strategy and advocated implementation of this policy in the two contexts. Since then, CP recommendations have changed, costs of medication have decreased due to the advent of generics, and malaria epidemiology has evolved [2, 7].

This work aims to assess the medico-economic consequences of a policy providing partial reimbursement of the three recommended CPs for travels to endemic SSA: Atovaquone-Proguanil (ATVP), Doxycycline (DOXY) and Mefloquine (MFQ).

Materials and methods

The evaluation was made from the perspective of French NHI and consisted of a cost-effectiveness analysis (CEA) of three reimbursement strategies targeting different groups of travelers. In strategy 1, reimbursement is directed to all citizens medically insured in France who travel to endemic areas of SSA. The other two prevention strategies are designed to address the specific needs of two subgroups of travelers at higher risk for malaria: travelers of African origin heading to SSA for VFR (strategy 2) and travelers to WCA exclusively, regardless of travel purposes (strategy 3). In addition,

the outcome of the reimbursement policy was assessed under two alternative scenarios. Under scenario A, reimbursement of CP by NHI would not affect the current proportion of CP drug use in France [5, 21]. Under scenario B, reimbursement would increase the use of ATVP¹, the most expensive but also the most convenient CP drug, which could lead to higher compliance rates compared to the other CP drugs [22]. The rate of reimbursement was set at 65% according to the evaluation of the Haute Autorité de Santé (HAS, French Health Authority) of the three recommended drugs as “medicines with important benefit”.

Model design

A decision-tree model was developed using TreeAge Pro Healthcare and Excel. It compared the status quo, namely non-reimbursement (branch “Reimbursement CP 0%”), versus the alternative strategies of CP reimbursement (branch “Reimbursement CP 65%”). Figure 1 details the non-reimbursement arm of the model. The alternative strategies follow the same decision path. Subjects decide whether or not to begin a treatment with CP prior to their travel, using either ATVP, DOXY or MFQ. For each drug, travelers might be compliant or not with the treatment. It was assumed that non-compliant CP users were not protected from malaria [23]. The effectiveness outcome was measured as the probability of contracting malaria, i.e., 1 in case of malaria occurrence and 0 otherwise. Each terminal node corresponded to a cost outcome taking into account the various expenditures caused by the series of events leading up to that endpoint. Costs and transition probabilities were calculated per travel, with 2018 as the reference year.

Input data

¹ The 65% reimbursement strategy would make ATVP - the most expensive drug among those recommended - much more affordable to travelers, especially VFRs, who are usually not prescribed this drug due to its high price; it could therefore be assumed that, were the reimbursement policy to be approved, general practitioners would prescribe ATVP more often than before, which is the first choice among CP drugs, and that a portion of the DOXY and MFQ users would shift to ATVP.

All data used in the model was obtained through the available literature, or by using expert opinions and making assumptions when data were not available² (Tables 1 and 2). The CEA for the three alternative reimbursement strategies was performed through the same model by changing the inputs in order to characterize each targeted group of travelers. For each input variable, a base-case value was defined as well as a plausible range of values in order to explore uncertainty³.

Study population

The number of travelers departing from France to SSA and WCA countries in 2018 was obtained from the yearly bulletin of commercial air traffic [24]. Because French data were unavailable, the number of VFR travelers annually departing from French airports to SSA was estimated at 27%, which is the proportion of EU residents who travelled outside EU borders for VFR in 2015 [25]. The median length of stay (MLS) in the endemic country was different according to the purpose of the travel. It was set at 15 days for travelers heading to SSA for tourism or business purposes and at 30 days for travelers visiting friends and relatives [5, 12, 15, 21, 26–28]. In this model, a longer stay in the country implied a higher probability of contracting malaria during the journey and a higher cost of reimbursing CP due to the need to purchase a higher quantity of CP to cover a longer period.

Transition probabilities

Estimated transition probabilities are summarized in Table 1. As VFRs usually travel to areas with higher malaria incidence and stay in less protected accommodations [2,3], they are exposed to a greater risk of contracting malaria than the overall population of travelers to SSA. Nevertheless, VFRs are less likely to take malaria CP compared to other travelers [27–29]. In addition, those who opt for CP are more likely to use DOXY, the cheapest malaria CP drug [26]. Since adherence rates for DOXY

² All assumptions have been approved by infectious disease specialists working at Rennes University Hospital.

³ The range of values was obtained by taking into account the min. and max. values found in the existing literature for each variable. When this was not possible, the base-case value was varied in one-way sensitivity analysis by $\pm 25\%$.

are lower than for ATVP and MFQ [22], and since only fully compliant travelers are protected from malaria [23], even VFRs opting for malaria CP may be poorly protected. Studies focusing on travels to WCA also reveal a lower use of CP and higher incidence of malaria compared to the rest of SSA [5, 12, 19, 29, 30].

Cost estimates

Costs were analyzed from the NHI perspective. In the 0% reimbursement arm, we included the cost of a visit to the general practitioner (GP), necessary for obtaining a CP prescription, the cost of the drugs, and the cost of treating severe side effects (SE), weighted by the probability of SE occurrence for each CP treatment. The cost related to malaria treatment was computed as the average cost of malaria-related hospitalization (which takes into account the cost of hospitalization for severe and non-severe forms of malaria according to their frequency in the medico-administrative hospital French database) plus the cost of outpatient care, each weighted by the respective probability of occurrence (see Table 2 for more details). Cost outcomes in the 65% reimbursement arm were computed using the same formulas and adding 65% of the price of CP treatment.

Cost data related to the management of imported malaria were obtained from French government's official databases [31, 32]. The cost of healthcare consumption (medications, medical consultations, and biological assays) was weighted by the reimbursement rates applied by NHI at 65%, 70% and 60%. Respectively. Hospitalization costs were measured by the cost associated with each diagnosis-related group (DRG) weighted by their frequency in French hospitals. Medical cost estimates are summarized in Table 2. The cost falling on NHI per traveler to WCA is assumed to be equal to those calculated per traveler to SSA, while travels for VFR are expected to generate different costs due to longer trip duration and a higher recourse to the less expensive DOXY compared to tourists and business travelers.

Statistical Analysis

The incremental cost-effectiveness ratio (ICER) of “Reimbursement CP 65%” strategy compared to “Reimbursement CP 0%” strategy was computed by dividing the mean cost difference by the mean difference in health outcomes between the two strategies. It was expressed in terms of incremental cost per averted malaria case. The alternative strategy is acceptable if its ICER is lower than the collective Willingness-To-Pay (WTP), i.e. the amount that society is ready to pay for an additional unit of effectiveness. As French health authorities do not provide a value of WTP, efficiency probabilities are displayed over a range of WTP thresholds.

One-way deterministic sensitivity analyses (DSA) were conducted by varying one parameter at a time over a range of values. In addition, overall robustness was tested performing a probabilistic sensitivity analysis (PSA), and 95% confidence intervals (CI) were built using Monte-Carlo simulations with 10,000 iterations, in which inputs were assigned random values according to Beta or Dirichlet distributions for transition probabilities, Gamma distribution for cost parameters and normal distribution for the traveling population. PSA generated incremental cost-effectiveness scatterplots and acceptability curves.

Results

Base-case results

Tables 3.1 and 3.2 show the costs and medical effects of reimbursement strategies 1 and 3, under scenarios A and B. Detailed results of strategy 2 are available on demand⁴.

In all of the strategies and scenarios considered, reimbursing 65% of the cost of malaria CP would lead to lower probability of contracting malaria and higher cost per trip. Strategy 1 requires the

⁴ As positive discrimination based on ethnicity cannot be applied in the French context, we have chosen to present only the main results of this strategy and to focus on the more feasible strategies 1 and 3.

highest investment, while strategy 3 is the least expensive. Scenario B would be expected to have a higher cost compared to scenario A, as it assumes an increased use of the most expensive drug, ATVP. The incremental cost per additional malaria case averted is estimated at € 34,623 for strategy 1, €15,136 for strategy 2 and € 23,640 for strategy 3. In all strategies, scenario B is more cost-effective than scenario A since an increased recourse to ATVP translates into higher protection rates.

Sensitivity analysis

In the DSA analysis for the three strategies, the highest sensitivity of the ICER was observed with respect to changes in the probability of CP use and the probability of contracting malaria without using CP. The ICER is also quite sensitive to changes in adherence rates,, especially for ATVP and DOXY and to the cost of hospitalization for malaria. Tornado diagrams showing the results of the DSA for strategy 1 and 3 are available in the supplementary material.

Figures 2 to 5 display the results of the PSA (incremental cost-effectiveness planes and acceptability curves) for strategies 1 and 3, under scenario A. Graphic results under scenario B can be found in the supplementary material. To sum up the results, for both scenarios, almost all ICER simulations are located in the North-East quadrant, where the reimbursement strategy involves increased effectiveness at a higher cost. The proportion of simulations with positive ICER is higher under scenario B than under scenario A. Acceptability curves indicate that for strategies 1 and 3 to be optimal in 75% of simulations, under scenario A, collective WTP should be around € 55,000 and € 35,000, respectively. Under scenario B, the WTP threshold decreases by around €10,000.

Discussion

Our findings show that the reimbursement of antimalarial CP by French NHI would have a positive effect on malaria prevention in France by reducing imported malaria incidence. However, extending the reimbursement to all travelers from France to SSA countries would be the least cost-effective

strategy under both scenarios of drug distribution. This might be explained by the fact that the target population is heterogeneous, including VFR travelers and people travelling for tourism or occupational or military purposes. Determinants of preventive behavior and the reasons for not using CP are significantly different between different categories of travelers [28]. For example, tourists and business travelers supposedly have fewer budget restrictions and those who do not use CP are more likely to be hindered by socio-psychological barriers rather than financial obstacles [8]. We identified two sub-populations of travelers for whom the reimbursement policy was expected to have a higher impact. First, travelers of African origin who periodically return to SSA for VFR are the most at-risk due to both higher exposure during their travels and lower use of CP [3, 27–29]. CEA confirmed that reimbursing the cost of CP to VFR travelers alone would be much more cost-effective than a global strategy involving all travelers from France to SSA countries. Restriction of the population eligible for reimbursement would decrease the estimated cost per case of malaria avoided by about 50%. However, implementation of a reimbursement strategy using origin as an eligibility criterion for reimbursement would raise practical and ethical issues in France, where positive discrimination has been the subject of intense debates and is not currently allowed. In the third strategy, reimbursement is reserved to travelers heading to endemic countries in WCA, which accounted for 95.4% of infections imported to France in 2018, while only 1.6% originated in East Africa and practically none in South Africa [2]. There is a higher percentage of VFRs traveling to WCA than to the East of the continent [3] and, as almost all malaria cases are imported from WCA, less than 5% of infections would remain excluded from the positive effects of the reimbursement policy. However, while the ICER of the reimbursement strategy restricted to travelers in WCA is much lower than that of the strategy including all travelers to SSA countries, it is still higher than that of the strategy limiting reimbursement to VFR travelers alone. The third reimbursement strategy therefore

appears as a way to reconcile the high degree of efficiency obtained by targeting less heterogeneous groups of subjects with the practicability of discriminating by geographical destination. In fact, the same criterion has already been applied by the French NHI for reimbursing CP in French Guyana; since 2008, CP is reimbursed to French citizens living in the non-endemic part of French Guyana and having to stay for fewer than 3 months in endemic areas of the country (mainly along rivers) [31].

All strategies of reimbursement become more cost-effective when the policy is assumed to increase the percentage of travelers who opt for ATVP (scenario B). This is true to a much lesser extent for the strategy restricted to VFRs because they usually make greater use of DOXY than other categories of travelers.

Two previous studies have shown that CP reimbursement is cost-effective, in some cases even dominant, particularly in a context of full adherence [5, 21]. However, their results are not comparable with ours since the present study is, to our knowledge, the first to consider adherence rates to CP when performing a CEA of a CP reimbursement policy. Moreover, our study is based on updated data for CP recommendations, costs of medication and malaria epidemiology. Nevertheless, our results confirm the conjecture according to which reimbursement of malaria CP could be more efficient when restricted to VFR travelers.

This study presents some limitations, mainly related to the fact that CEA results are highly dependent on the quality of available data for costs, efficacy and transition probabilities, and on various methodological assumptions. First, assuming that travelers not fully compliant with their treatment have a risk similar to those who have not even started CP is inaccurate and leads to underestimation of the actual effects of reimbursement strategies. Second, some assumptions about the expenses incurred by NHI may have led to slight misestimation of the cost outcome; for example, we assumed that the treatment cost is the same whether reimbursement is carried out or not, even if CP limits

the severity of breakthrough malaria, thereby reducing treatment costs. Third, our study did not take into account potential pediatric malaria cases for which both cost and effectiveness data are potentially different. Fourth, our model did not take into account possible additional attacks that may occur with *P. vivax* and *P. ovale*. Finally, a lack of data specific to VFR travelers represented a major limitation in simulating the outcome of reimbursement strategies reserved to VFRs or travelers to WCA.

PSA nevertheless showed that although uncertainty about some inputs may significantly affect the ICER, reimbursement has a high probability of being cost-effective, especially in strategies restricted to VFR and travelers to WCA. In addition, the acceptability curves report that, for WTP only slightly higher than the ICER computed in the base-case analysis, reimbursement is preferred over the current approach in more than 50% of the simulations, thereby confirming supporting the robustness and validity of CEA results. For WTP values from 30% (strategy 2 and 3) to 60% (strategy 1) higher than the base-case ICER, reimbursement would be optimal in 75% of simulations.

Conclusion

Reimbursing the CP costs for travelers heading to endemic regions in SSA would result in a decline in imported malaria infections. To our knowledge, this study was the first to explore the outcomes of three reimbursement strategies. Targeting all citizens who are medically insured in France who travel to endemic areas of SSA is the least cost-effective approach. Restricting reimbursement to VFRs allows lower ICERs but is not feasible. However, as reimbursement for travelers to WCA enables targeting of a significant percentage of cases, as well as a large share of VFRs, the most impacted group, its implementation could be reasonably efficient.

In the context of constrained health budgets, health policies of disease prevention should be assessed within the cost-effectiveness framework, which does not prioritize financial constraints

over health considerations. It rather aims at selecting the best possible health outcome at the lowest possible cost. Our study showed that management of infectious diseases, in our case malaria, is susceptible to cost-effectiveness analysis. It nevertheless remains preliminary in several respects and calls for further research. Moreover, patient-level cost-effectiveness should be complemented with budget impact analysis, which would evaluate the global cost to NHI, as the budget holder, of adding malaria CP to the existing reimbursement package.

Authors' contributions

Emma Bajoux : conceptualization, methodology, investigation, supervision, reviewing

Maud Trépart-Normand : conceptualization, investigation

Jean-Michel Josselin : conceptualization, methodology, supervision, reviewing

Camilla Fiorinia : methodology, investigation , software, formal analysis, writing original draft

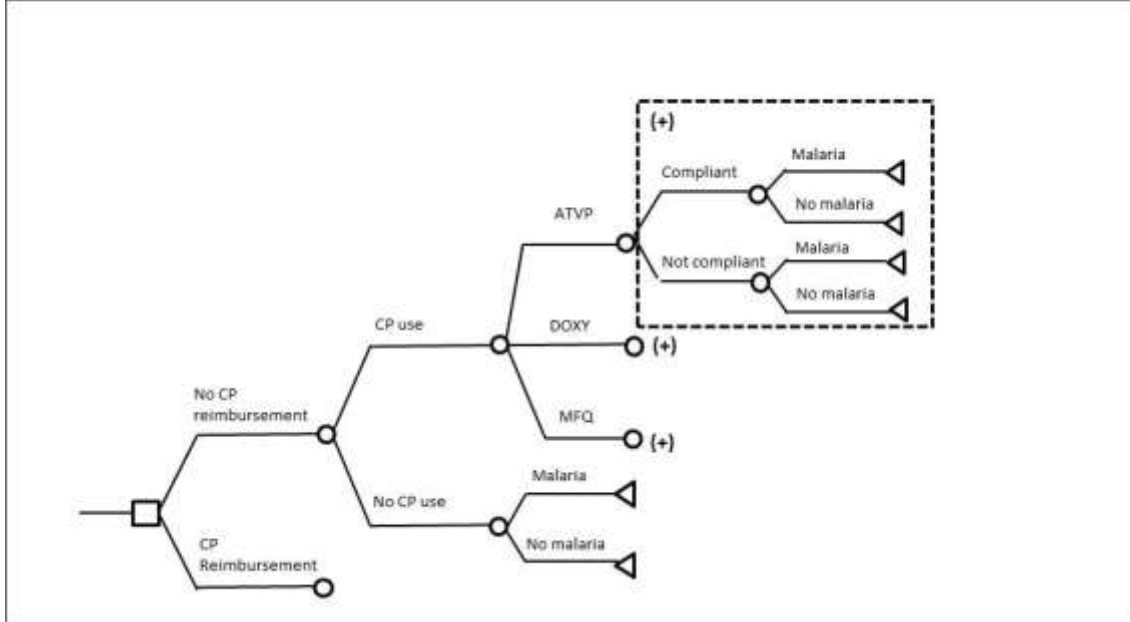
Pierre Tattevin : reviewing

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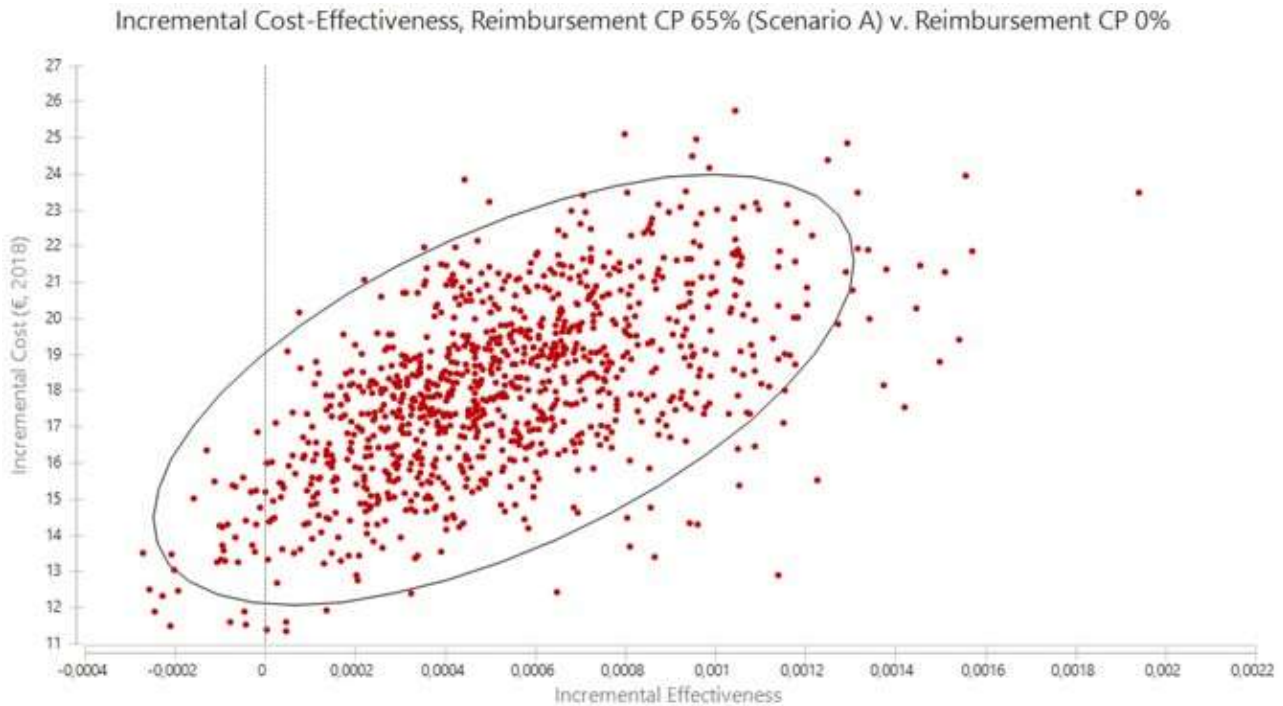
Figure 1. Non-reimbursement arm of the decision tree model. The alternative strategies follow the same decision path.



CP: Chemoprophylaxis. ATVP: Atovaquone-Proguanil. DOXY: Doxycycline. MFQ: Mefloquine

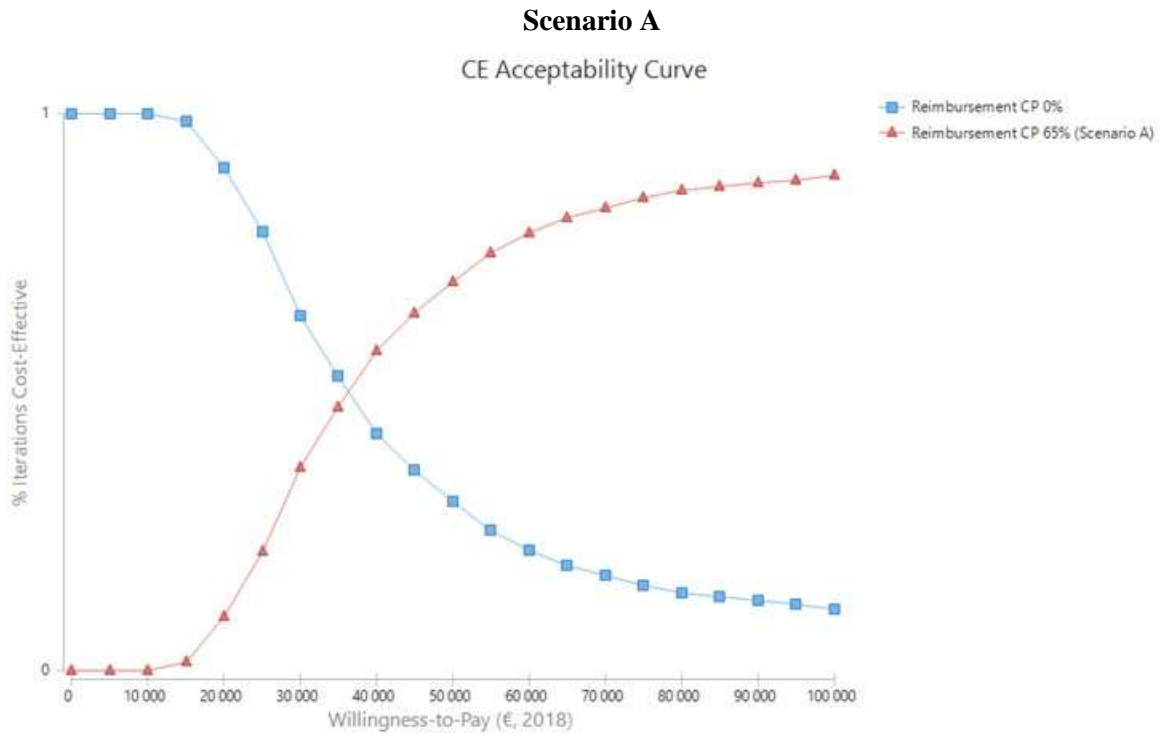
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**Figure 2. Incremental Cost-Effectiveness scatterplot, Strategy 1
Scenario A**



The incremental cost-effectiveness plane plots the difference in effectiveness (on the x axes) against the difference in cost (on the y axes) between the current strategy and reimbursement strategy 1 under scenario A, for 1,000 simulated Incremental Cost-Effectiveness Ratio (Monte-Carlo simulations). Simulations that are located on the right side of the dotted line are cost-effective, meaning that under scenario A, reimbursement strategy 1 most often involves an increase in efficiency (a lower number of yearly imported malaria cases) accompanied by a higher cost compared to the reference strategy.

Figure 3. Acceptability Curve, Strategy 1



Acceptability curves determine, for a range of willingness-to-pay values (the amount of money that society is willing to pay for an additional unit of effectiveness with a new strategy compared to the current strategy), the probability that the reimbursement strategy 1 is cost-effective compared to no reimbursement. Acceptability curves quantify the uncertainty around the ICER estimation. The crossing point of the two lines identifies the willingness-to-pay threshold for which reimbursement strategy 1 becomes cost-effective in 50% of the simulations under scenario A. For a given willingness-to-pay, the higher the curve, the higher the probability of cost-effectiveness confidence in the results. For example, for willingness to pay of € 55,000 per additional malaria case prevented, the probability of strategy 1 cost-effectiveness is estimated at 75%.

Figure 4. Incremental Cost-Effectiveness scatterplot, Strategy 3

Scenario A

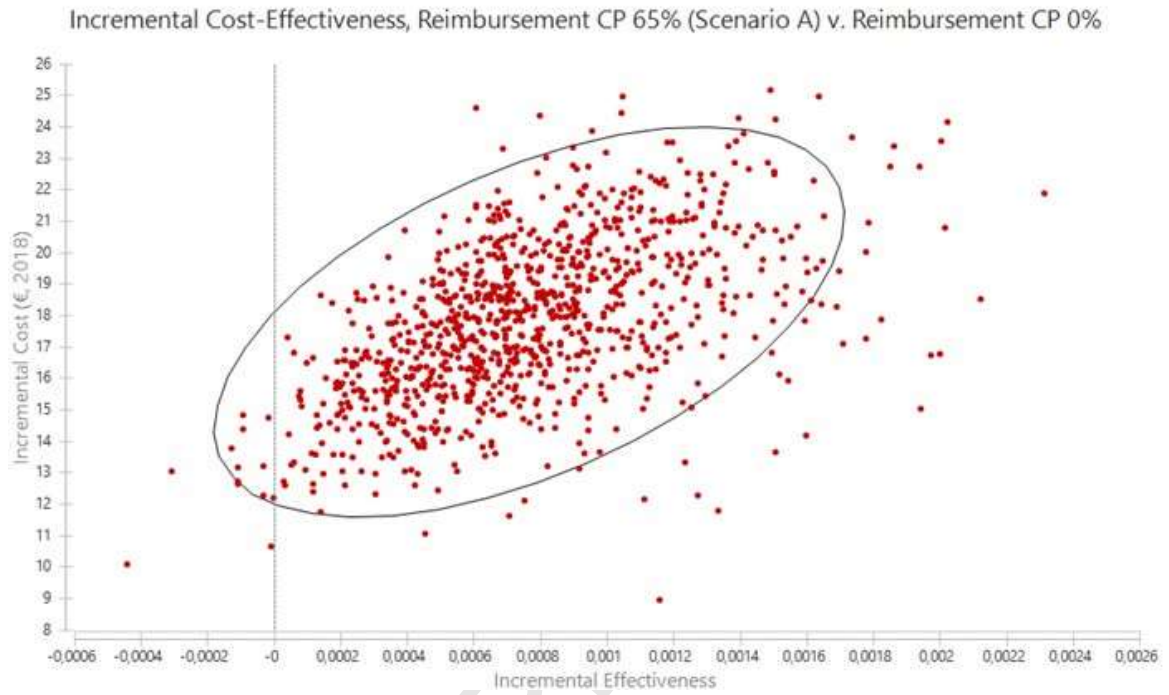


Figure 5. Acceptability Curve, Strategy 3

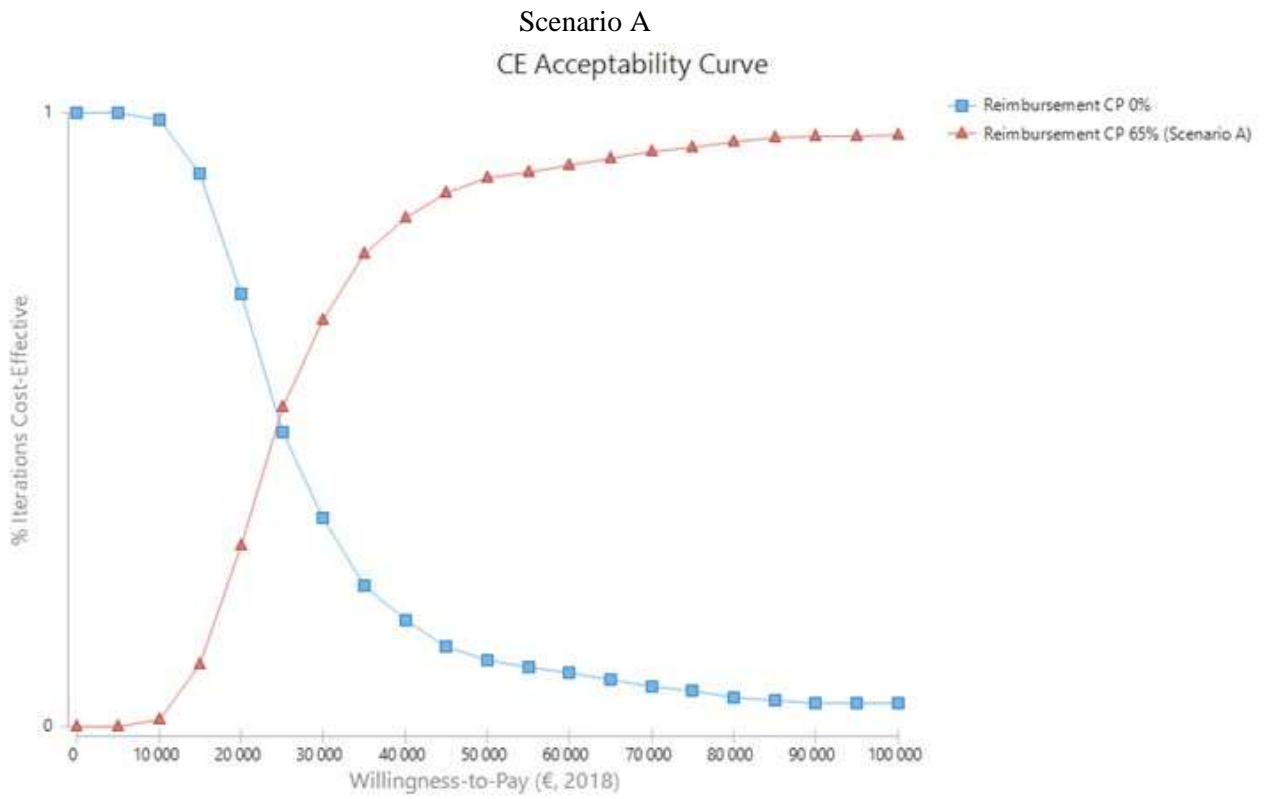


Table 1. Transition probability used in the decision-tree model

Definition of transition probabilities (a)	Estimates (likeliest)			Min-max (b)			References (c)
	Strategy 1	Strategy 2	Strategy 3	Strategy 1	Strategy 2	Strategy 3	
Adherence rates to ATVP	0.70	0.70	0.70	0.64 - 0.92	0.64 - 0.93	0.64 - 0.94	(8,18,22)
Adherence rates to DOXY	0.44	0.44	0.44	0.42 - 0.79	0.42 - 0.79	0.42 - 0.79	(18,22)
Adherence rates to MFQ	0.72	0.72	0.72	0.56 - 0.89	0.56 - 0.90	0.56 - 0.91	(8,18,22)
Prophylactic effectiveness of ATVP	0.96	0.96	0.96	0.91 - 0.98	0.91 - 0.98	0.91 - 0.98	(33)
Prophylactic effectiveness of DOXY	0.93	0.93	0.93	0.80 - 0.97	0.80 - 0.98	0.80 - 0.98	(34)
Prophylactic effectiveness of MFQ	0.91	0.91	0.91	0.81 - 0.96	0.81 - 0.97	0.81 - 0.98	(35)
Probability of hospitalization	0.74	0.74	0.74	0.59 - 0.87	0.59 - 0.87	0.59 - 0.87	(36)
Probability of contracting malaria with ATVP	2.22 10 ⁻⁴	4.43 10 ⁻⁴	2.73 10 ⁻⁴	0.67 10 ⁻⁴ – 10.40 10 ⁻⁴	1.18 10 ⁻⁴ – 27.60 10 ⁻⁴	0.67 10 ⁻⁴ - 10.40 10 ⁻⁴	-
Probability of contracting malaria with DOXY	3.91 10 ⁻⁴	7.80 10 ⁻⁴	4.81 10 ⁻⁴	0.80 10 ⁻⁴ – 24.50 10 ⁻⁴	1.41 10 ⁻⁴ - 65.30 10 ⁻⁴	0.80 10 ⁻⁴ – 24.50 10 ⁻⁴	-
Probability of contracting malaria with MFQ	4.75 10 ⁻⁴	9.49 10 ⁻⁴	5.85 10 ⁻⁴	1.28 10 ⁻⁴ – 23.10 10 ⁻⁴	2.25 10 ⁻⁴ – 61.75 10 ⁻⁴	1.28 10 ⁻⁴ – 23.10 10 ⁻⁴	-
Probability of contracting malaria without CP	52.8 10 ⁻⁴	105.4 10 ⁻⁴	65.00 10 ⁻⁴	32.00 10 ⁻⁴ – 122.00 10 ⁻⁴	56.35 10 ⁻⁴ - 325.00 10 ⁻⁴	32.00 10 ⁻⁴ - 122.00 10 ⁻⁴	(2,10,16,37–39)
Probability of recourse to CP in the 0% strategy	0.71	0.54	0.65	0.52 - 0.84	0.31 - 0.82	0.50 - 0.82	(5,8,10,12,27–30,39)
Probability of recourse to ATVP in the 0% strategy	0.54	0.23	0.54	-	-	-	(26)
Probability of recourse to DOXY in the 0% strategy	0.39	0.56	0.39	-	-	-	(26)
Probability of recourse to MFQ in the 0% strategy	0.07	0.21	0.07	-	-	-	(26)
Probability of recourse to CP in the 65% strategy	0.88	0.83	0.86	0.76 - 0.95	0.70 - 0.96	0.80 - 0.93	-
Probability of recourse to ATVP in the 65% strategy	0.81	0.72	0.81	-	-	-	-
Probability of recourse to DOXY in the 65% strategy	0.16	0.21	0.16	-	-	-	-
Probability of recourse to MFQ in the 65% strategy	0.03	0.08	0.03	-	-	-	-
Probability of severe side effects due to ATVP	0.07	0.07	0.07	0.02 - 0.11	0.02 - 0.11	0.02 - 0.11	(40)

Probability of severe side effects due to DOXY	0.0	0.0	0.06	0.02 - 0.10	0.02 - 0.10	0.02 - 0.10	(40)
Probability of severe side effects due to MFQ	0.10	0.10	0.10	0.06 - 0.15	0.06 - 0.16	0.06 - 0.17	(40)

(a) Calculated for MLS of 15 days in SSA and WCA for strategies 1 and 3, respectively, and 30-day MLS in SSA for strategy 2

(b) Possible range of values identified in the literature; (c) “-” indicates that the estimate of transition probability stems from a calculation and is not directly extracted from the literature

CP: Chemoprophylaxis. ATVP: Atovaquone-Proguanil. DOXY: Doxycycline. MFQ: Mefloquine

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Table 2. Medical cost estimates (€, 2018).

Definition of medical cost estimates	Estimates (likeliest)		Distribution (min - max)		References
	Strategies 1 and 3	Strategy 2	Strategies 1 and 3	Strategy 2	
Direct cost of ATVP	25.58	51.17	42.08 - 47.78	51.17 - 62.56	(31)
Direct cost of DOXY	7.31	10.87	23.81 - 30.059	10.87 - 31.29	(31)
Direct cost of MFQ	18.16	36.32	34.66 - 35.56	36.32 - 38.13	(31)
Direct cost of one GP consultation	16.50		-		
Direct average cost of outpatient care for malaria	181.83		-		(31,32)
Direct average cost of hospital care for malaria	1,807.36		714.45 - 6,678.47		(32)
Direct cost of treating severe side effects	17.50		16.50 - 21.88		(31)

GP: General Practitioner. ATVP: Atovaquone-Proguanil. DOXY: Doxycycline. MFQ: Mefloquine

Data for calculating costs are extracted from French medico-administrative databases. Costs of chemoprophylaxis (CP) treatment are calculated as the price set by French health authorities for each CP drug multiplied by the quantity needed to cover the entire stay in the country according to French recommendations. For example, a tourist heading to SSA for 15 days will need 22 tablets of ATVP (1 tablet the day before departure plus 1 tablet per day after departure until 1 week after return), that is to say two boxes of ATVP. Cost of hospitalizations was calculated as the average of the tariffs corresponding to the five Diagnosis-Related Groups (DRG) for malaria, weighted by each DRG frequency in the French administrative database (32). Cost of follow-up, including three infectious disease specialist consultations and biological assays after discharge, were accounted for in the total cost of malaria-related hospitalizations. Concerning cost of outpatient care, it included consultations with GP and infectious disease specialists, biological assays, and antimalarial medications, as recommended by French guidelines. Cost of treating side effects was calculated as the cost of one GP consultation and that of antinausea treatment. Data on all costs are freely available online. More details on costs calculation are available on demand.

Table 3.1 Cost-effectiveness analysis results for strategy 1

CEA for strategy 1 (65% reimbursement of malaria CP to all travelers to SSA)	0% reimbursement	65% reimbursement (scenario A) ^a	65% reimbursement (scenario B) ^b
Study population ^c	1,711,680	1,711,680	1,711,680
Cost per journey (€) (95% CI) ^d	16.88 € (11.09 – 29.34)	35.02 € (28.57 – 45.68)	38.71 € (32.04 – 48.50)
Cost per year (€) (95% CI) ^d	28,896,835 € (18,998,086 – 50,223,585)	59,955,132 € (48,872,317 – 78,235,280)	66,265,920 € (54,854,380 – 83,055,699)
Effect per journey Probability of contracting malaria (95% CI) ^d	0.003166 (0.0018 – 0.0048)	0.002642 (0.0015 – 0.0040)	0.002349 (0.0014 – 0.0037)
Effect per year Number of malaria cases (95% CI) ^d	5,419 (3,162 – 8,346)	4,522 (2,665 – 6,937)	4,020 (2,331 – 6,304)
Incremental effectiveness			
Number of malaria cases prevented	Reference strategy	897	1,398
Incremental cost			
Per journey	Reference strategy	18.14 €	21.83 €
Total	Reference strategy	31,058,297 €	37,369,084 €
ICER ^e			
Per additional malaria cases prevented	Reference strategy	34,623.19 €	26,721.56 €

^a assuming a constant distribution of recourse to CP in the 0% and 65% reimbursement strategy

^b assuming an increased recourse to ATVP in the 65% reimbursement strategy

^c number of departing passenger from France to endemic countries of SSA in 2018

^d 95% CI of 10,000 Monte Carlo simulations with a Beta, Dirichlet and Gamma distributions

^e Results of the CEA using the likeliest estimates

CEA: Cost-Effectiveness Analysis. ICER: Incremental Cost-Effectiveness Ratio. CI: Confidence Interval. CP: Chemoprophylaxis. SSA: Sub-Saharan Africa

This table shows estimates of the effectiveness (i.e., number of malaria cases prevented) of partial reimbursement of CP (65% of the price) by French National Health Insurance, as well as the related costs, per trip and per year. Results are presented under scenarios A and B compared to no reimbursement. The annual costs and effectiveness are calculated with respect to the population targeted by the reimbursement strategy 1, i.e., the estimated number of travelers who visited SSA in 2018. Values in brackets represent the 95% CI calculated in the probabilistic sensitivity analysis. The second part of the table presents the estimates of incremental effectiveness and costs, i.e. the difference in effectiveness and cost between the reimbursement strategy and no reimbursement, under scenario A and B. Under scenario A, reimbursement of 65% of the cost of CP to SSA travelers could prevent 897 malaria cases per year, creating an additional cost of approximately € 31 million to the National Health Insurance, compared to the non-reimbursement strategy. The ICER synthesizes this information by providing the cost per additional malaria case prevented; it is calculated as the cost difference between strategy 1 and the current strategy divided by the difference in effectiveness ($ICER_{S_0 \rightarrow S_1} = \frac{\Delta C_{0 \rightarrow 1}}{\Delta E_{0 \rightarrow 1}} = \frac{C_0 - C_1}{E_0 - E_1}$). Thus, under scenario A, each additional malaria case prevented would cost around € 34,000 to the French National Health Insurance.

Table 3.2 Cost-effectiveness analysis results for strategy 3

CEA for strategy 3 (65% reimbursement of malaria CP to all travelers to WAC)	0% reimbursement	65% reimbursement (scenario A) ^a	65% reimbursement (scenario B) ^b
Study population ^c	1,218,856	1,218,856	1,218,856
Cost per journey (€) (95% CI) ^d	17.23 € (10.59 – 32.06)	35.23 € (28.03 - 47.74)	38.74 € (31.56 - 47.74)
Cost per year (€) (95% CI) ^d	21,005,631 € (12,892,315 – 39,155,081)	42,944,299 € (34,171,048 – 58,110,459)	47,219,627 € (38,404,526 – 61,180,688)
Effect per journey ^d Probability of contracting malaria (95% CI) ^d	0.004091 (0.27 – 0.59)	0.003329 (0.0022 – 0.0048)	0.002977 (0.0019 – 0.0043)
Effect per year (95% CI) ^d Number of malaria cases	4,986 (3,244 – 7,252)	4,058 (2,622 – 5,806)	3,629 (2,297 – 5,279)
Incremental effectiveness ^e			
Number of malaria cases prevented	Reference strategy	928	1357
Incremental cost ^e			
Per journey	Reference strategy	18.00 €	21.51 €
Total	Reference strategy	21,938,598€	26,213,996€
ICER ^e			
Per additional malaria cases prevented	Reference strategy	23,640.03 €	19,315.76 €

^a assuming a constant distribution of recourse to CP in the 0% and 65% reimbursement strategy

^b assuming an increased recourse to ATVP in the 65% reimbursement strategy

^c number of departing passenger from France to endemic countries of WCA in 2018

^d 95% CI of 10,000 Monte Carlo simulations with a Beta, Dirichlet and Gamma distributions

^e Results of the CEA using the likeliest estimates

CEA: Cost-Effectiveness Analysis. ICER: Incremental Cost-Effectiveness Ratio. CI: Confidence Interval. CP: Chemoprophylaxis. SSA: Sub-Saharan Africa

This table shows estimates of the effectiveness (i.e., number of malaria cases prevented) of partial reimbursement of CP (65% of the price) by French National Health Insurance, as well as the related costs, per trip and per year. Results are presented under scenarios A and B compared to no reimbursement. The annual costs and effectiveness are calculated with respect to the population targeted by the reimbursement strategy, i.e., the estimated number of travelers who visited WCA in 2018. Values in brackets represent the 95% CI calculated in the probabilistic sensitivity analysis. The second part of the table presents the estimates of incremental effectiveness and costs, i.e. the difference in effectiveness and cost between the reimbursement strategy and no reimbursement, under scenarios A and B. Under scenario A, reimbursing 65% of the cost of CP to SSA travelers could prevent 928 malaria cases per year, nonetheless creating an additional cost of approximately € 21 million to the National Health Insurance, compared to the strategy of no reimbursement. The ICER synthesizes this information by providing the cost per additional malaria case prevented; it is calculated as the cost difference between strategy 3 and the current strategy then divided by the difference in effectiveness ($ICER_{S_0 \rightarrow S_3} = \frac{\Delta C_{0 \rightarrow 3}}{\Delta E_{0 \rightarrow 3}} = \frac{C_0 - C_3}{E_0 - E_3}$). Under scenario A, each additional malaria case prevented would cost around € 26,000 to French National Health Insurance.

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